CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002384

# Interplay of Direct Stereocontrol and Dynamic Kinetic Resolution in a Bifunctional Amine Thiourea Catalyzed Highly Enantioselective Cascade Michael–Michael Reaction

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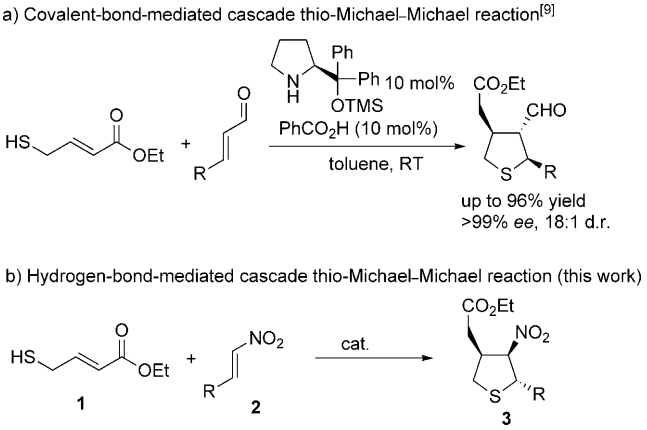
The success of organocatalysis is perhaps attributed to the unique activation modes, which render both single- and multistep cascade reactions to proceed with high efficiency in terms of reaction yields and selectivity.[1,2] Impressively, capitalizing on the reversible iminium–enamine catalysis, chemists have developed a number of synthetically efficient, catalytic, enantioselective cascade processes for the quick construction of complex molecular scaffolds.[2] In contrast, despite the fact that the noncovalent activation modes have been widely used in single-step asymmetric transformations,[3] their potential in cascade catalysis remains to be demonstrated and such examples are relatively rare.[4,5]

Facile assembly of molecular architectures spanning large tracts of biologically relevant chemical space is a significant, but challenging task in diversity-oriented synthesis (DOS).[6] Molecules with highly structural (e.g., functional, stereochemical, and/or scaffold) diversity, a prerequisite for broad biological activity, are highly valuable in the fields of chemical biology and drug discovery. Chiral tetrahydrothiophenes display such an important framework with a wide spectrum of biological activities.[7] Accordingly, it is highly valuable to develop efficient methods to create the chiral scaffold with functional and stereochemical diversities.

Although chiral tetrahydrothiophenes exhibit attractive biological properties, very few asymmetric synthesis methods have been reported.[8] Recently, we have disclosed an organocatalytic, enantioselective thio-Michael–Michel cascade, affording the functionalized chiral tetrahydrothiophenes from readily available compounds in an "one-pot" manner (Scheme 1a).[9] The cascade strategy relies on the use of




Scheme 1. Generation of structurally diverse chiral tetrahydrothiophenes by organocatalytic thio-Michael–Michael cascade reactions.

chiral amine as a catalyst through a covalent bond activation mode, which, in general, leads to highly enantioenriched products. In our continuing effort on the construction of the valuable synthetic target, we disclose herein an alternative catalytic noncovalent activation strategy to construct the framework. The "one-pot" thio-Michael–Michael cascade process was achieved with high enantio- and diastereoselectivity. Notably, the products posses the functional ($NO_2$ group) and stereochemical (*trans* and *cis* configuration) di-

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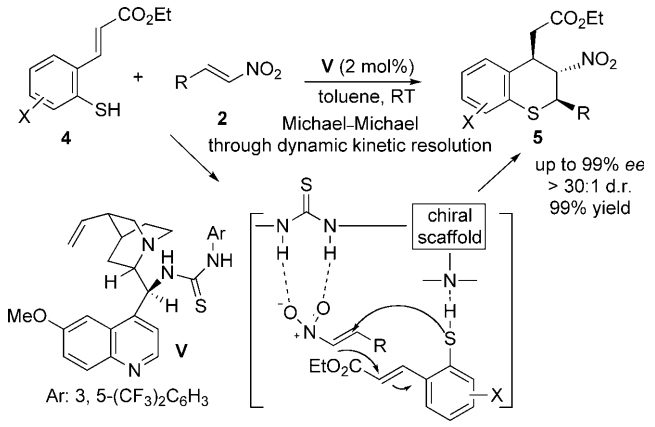
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002384.

versities (Scheme 1b), which are different from those (CHO group and *trans* and *trans* configuration, Scheme 1a) obtained in the covalent-bond-mediated catalysis. Furthermore, a distinct stereocontrol mode (i.e., direct stereocontrol of substrates by a bifunctional chiral catalyst and dynamic kinetic resolution in a cooperative manner) was found to be responsible for high enantioselectivities.[10]

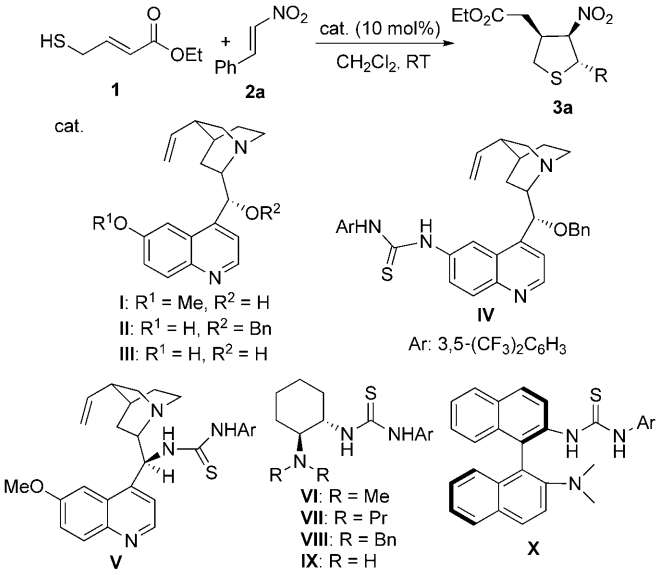
Because a nitro group can be readily transformed into an amine, a nitrile oxide, a ketone, a carboxylic acid, a hydrogen, and so on,[11] nitroolefins, as one of the most active Michael acceptors, have been intensively investigated in oganocatalytic, asymmetric reactions. It is noted that in these transformations, the general observation is that high enantioselectivity is obtained with asymmetric aminocatalysis.[12] Nevertheless, the use of a noncovalent hydrogen bonding activation strategy for an enantioselective thio-Michael addition to nitroolefins has been elusive. Generally poor enantioselectivities are observed in an organocatalytic, asymmetric thio-Michael process with nitroolefins as a result of a high background reaction that results from the inherent, highly active, nucleophilic thiols and electrophilic nitroolefins.[13] However, recently we have discovered a highly enantioselective thio-Michael–Michael reaction between nitroolefins and the 2-thiol-α, β-unsaturated ester **4** (Scheme 2).[5d] The high enantioselectivities attribute to the unprecedented dynamic kinetic resolution process. With this in mind, we decided to apply the novel powerful strategy for the synthesis of biologically significant chiral tetrahydrothiophenes.




Scheme 2. Hydrogen-bond-mediated highly stereoselective cascade Michael–Michael process through dynamic kinetic resolution.[5d]

The proof of concept of the proposed cascade reaction was carried out by a reaction of *trans*-ethyl 4-mercapto-2-butenoate (**1**) with *trans*-β-nitrostyrene (**2a**) in $CH_2Cl_2$ at room temperature in the presence of 10 mol% of an organocatalyst (Table 1). In light of the fact that bifunctional organocatalysts have the capacity of activation of an electrophile and a nucleophile in a cooperative manner, commonly used organocatalysts were explored for the process.[3–6,14] The results revealed that the orientation of the acidic and basic

Table 1. Exploration of organocatalyzed enantioselective the thio-Michael–Michael reaction of *trans*-ethyl 4-mercapto-2-butenoate (**1**) with *trans*-β-nitrostyrene (**2a**).[a]




| Entry | Catalyst | *t* [h] | Yield [%][b] | *ee* [%][c] | d.r.[d] |
|---|---|---|---|---|---|
| 1 | **I** | 4 | 58 | −21 | >30:1 |
| 2 | **II** | 4 | 54 | −30 | 5:1 |
| 3 | **III** | 4 | 54 | 60 | >30:1 |
| 4 | **IV** | 4 | 52 | −14 | >30:1 |
| 5 | **V** | 4 | 86 | −66 | 8:1 |
| 6 | **VI** | 4 | 66 | 84 | 6:1 |
| 7 | **VII** | 28 | 54 | 70 | 3:1 |
| 8 | **VIII** | 56 | 36 | ND[e] | 5:1 |
| 9 | **IX** | 4 | 64 | 3 | 22:1 |
| 10 | **X** | 4 | 81 | 40 | >30:1 |

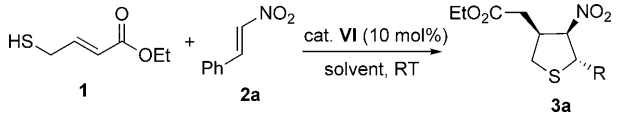
[a] Unless specified, see the Experimental Section. [b] Yield of isolated product. [c] *ee* = enantiomeric excess; determined by chiral HPLC analysis (Chiralcel OD-H). [d] d.r. = diastereomeric ration; determined by $^1$H NMR spectroscopy. [e] Not determined.

groups and the strength of the hydrogen donor moiety in the cinchona alkaloid scaffolds had a significant impact on the enantio- and diasteroselectivity. The Soós cinchona alkaloid thiourea catalyst **V**[15] (Table 1, entry 5) was found to be the best catalyst in this series. The Takemoto amine thiourea **VI**[16] was also an impressive promoter. In this instance, a good yield (66%) and very encouraging enantio- (84% *ee*) and diastereoselectivity (6:1) were achieved. The catalyst structure–product enantioselectivity relationship study showed that the dimethyl group in these analogues was optimal for the catalytic activity and the achieved enantioselectivity (Table 1, entries 6–9). Interestingly, the hydrogen-bond-mediated cascade catalysis gave rise to the product **3a** with *cis* and *trans* configuration. Although a good yield (81%) and excellent d.r. (>30:1) were observed, a poor *ee* (40%) (Table 1, entry 10) was obtained with the chiral binaphthyl derived amine thiourea **X**.

We then selected the Takemoto catalyst to probe the effects of the reaction media and the temperature on the cascade process (Table 2). It is known that in the noncovalent

Table 2. Screening of the solvent and the reaction conditions for a cascade thio-Michael–Michael reaction.[a]




| Entry | Solvent | $t$ [h] | Yield [%][b] | *ee* [%][c] | d.r.[d] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 4 | 66 | 84 | 6:1 |
| 2 | $Cl(CH_2)_2Cl$ | 4 | 64 | 84 | 6:1 |
| 3 | $CHCl_3$ | 4 | 60 | 87 | 9:1 |
| 4[e] | $CHCl_3$ | 4 | 77 | 85 | 12:1 |
| 5[e,f] | $CHCl_3$ | 10 | 78 | 88 | 12:1 |
| 6[e,g] | $CHCl_3$ | 72 | 79 | 93 | 12:1 |
| 7 | toluene | 4 | 79 | 77 | 3:1 |
| 8 | xylenes | 4 | 71 | 84 | 5:1 |
| 9 | $CH_3CN$ | 4 | 74 | 65 | 1:1 |
| 10 | hexane | 4 | 48 | 77 | 4:1 |
| 11 | $Et_2O$ | 4 | 56 | 72 | 6:1 |

[a] Unless specified see the Experimental Section. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralcel OD-H). [d] Determined by $^1$H NMR spectroscopy. [e] Catalyst loading 20 mol%. [f] $T=0$°C. [g] $T=-40$°C.

bond catalysis, nonpolar solvents are generally preferred. It was found that chloroform was the optimal solvent (60% yield, 87% *ee* and d.r. = 9:1, Table 2, entry 3). Increasing the catalyst loading to 20 mol% improved the yield (77%) (Table 2, entry 4). However, lowering the reaction temperature (0°C and −40°C) further enhanced the *ee* values (Table 2, entries 5 and 6) without deteriorating the yields.

The established optimal reaction conditions were explored for examining the scope of the powerful enantioselective thio-Michael–Michael cascade reaction. As revealed in Table 3, the synthetic strategy serves as a general approach to the highly functionalized, chiral tetrahydrothiophenes with a broad substrate scope. Notably, one C–S and one C–C bond and three stereogenic centers are formed in a "one-pot" fashion with high enantioselectivity (92–97% *ee*) and good diasteriomeric ratios (6:1 to >30:1). Moreover, the versatile and densely functionalized, chiral scaffold has a *cis–trans* configuration as determined by X-ray crystal structure analysis of the product (**3j**) (Figure 1),[17] which is complementary to the configuration of the scaffold obtained by the chiral amine catalyzed process (i.e., *trans—trans*). The electronic effect on the enantioselectivity of the cascade reaction appears limited. Aromatic nitroolefins bearing electron-neutral (Table 3, entry 1), electron-withdrawing (Table 3, entries 2–7), and electron-donating groups (Table 3, entries 8–12) were well tolerated. In all cases, high *ee* values were obtained. The steric effect has a certain impact on the diastereoselectivity. The more hindered substrates (Table 3, entries 4 and 7) resulted in a decrease of the diastereoselectivity. The heteroaromatic and less reactive alkyl *trans*-β-nitroolefins (Table 3, entries 13 and 14) are applicable to the processes as well.

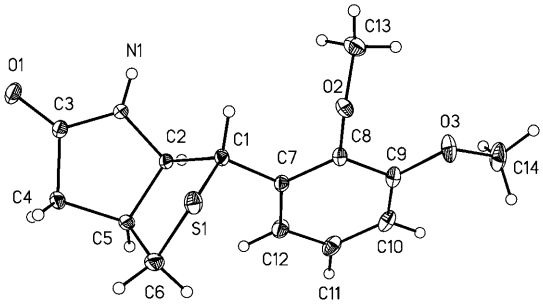
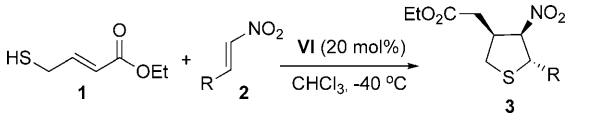



Figure 1. X-ray structure of **3j**.

Table 3. Cascade thio-Michael–Michael reaction of *trans*-ethyl 4-mercapto-2-butenoate (**1**) with *trans*-β-nitrostyrene (**2**) promoted by catalyst **VI**.[a]

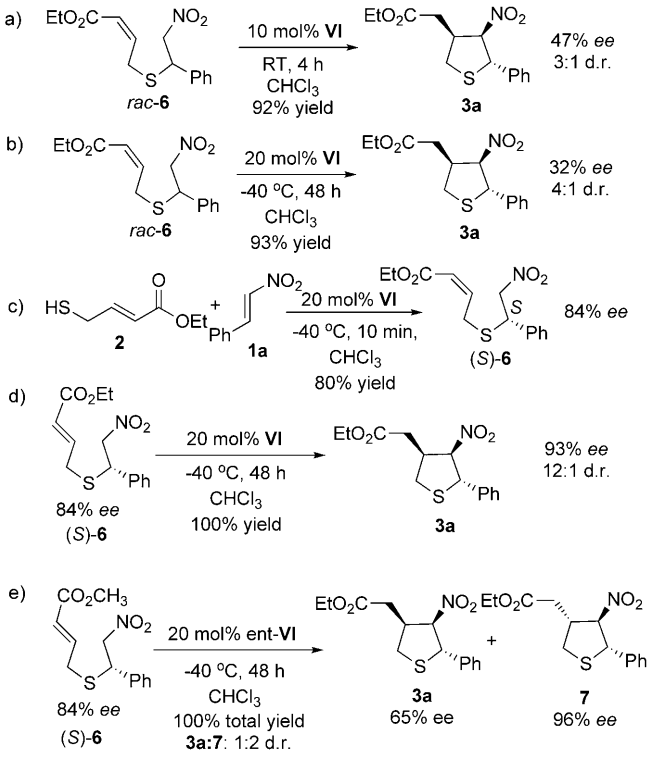



| Entry | R | Product | $t$ [h] | Yield [%][b] | *ee* [%][c] | d.r.[d] |
|---|---|---|---|---|---|---|
| 1 | Ph | **3a** | 72 | 82 | 93 | 12:1 |
| 2 | 4-$FC_6H_4$ | **3b** | 72 | 93 | 96 | 14:1 |
| 3 | 4-$ClC_6H_4$ | **3c** | 96 | 73 | 96 | 13:1 |
| 4 | 2-$ClC_6H_4$ | **3d** | 96 | 75 | 96 | 7:1 |
| 5 | 2,5-$Cl_2C_6H_3$ | **3e** | 120 | 50 | 93 | 16:1 |
| 6 | 3-$BrC_6H_4$ | **3f** | 96 | 62 | 97 | 15:1 |
| 7 | 2-$CF_3C_6H_4$ | **3g** | 96 | 52 | 93 | 6:1 |
| 8 | 4-$MeC_6H_4$ | **3h** | 72 | 76 | 95 | 15:1 |
| 9 | 3-$MeOC_6H_4$ | **3i** | 72 | 60 | 96 | 26:1 |
| 10 | 4-$MeOC_6H_4$ | **3j** | 72 | 66 | 95 | 9:1 |
| 11 | 2,3-$(MeO)_2C_6H_3$ | **3k** | 120 | 59 | 96 | 9:1 |
| 12 | 2,4-$(MeO)_2C_6H_3$ | **3l** | 120 | 51 | 92 | 10:1 |
| 13 | thienyl | **3m** | 96 | 84 | 96 | 18:1 |
| 14 | furanyl | **3n** | 96 | 75 | 94 | >30:1 |
| 15 | *i*Pr | **3o** | 120 | 51 | 95 | 9:1 |

[a] Unless specified, see the Experimental Section. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (Chiralcel OD-H or Chiralpak AS-H). [d] Determined by $^1$H NMR spectroscopy of the crude reaction mixture.

With respect to the mechanism of the asymmetric thio-Michael–Michael cascade reaction, we initially assumed that, as we observed in our early studies (Scheme 2),[5d,18] a dynamic kinetic resolution (DKR) process to achieve high enantioselectivity takes place. To verify the hypothesis, we prepared the racemic form of product of the first Michael addition *rac*-**6.** Treatment of *rac*-**6** in the presence of 10 mol% **VI** under the same reaction conditions as described above gave the desired product **3a** in 92% yield. Nonetheless, lower *ee* (47%) and d.r. (3:1) (Scheme 3a) were obtained in comparison with the results that were achieved by performing the reaction in a cascade manner (84% *ee*, d.r. = 6:1, Table 1, entry 6). When the reaction was performed at −40°C, an even lower *ee* (32%, d.r. = 4:1, Scheme 3b) was observed. The studies indicated that a DKR was involved in the asymmetric cascade process. However, the *ee* value and the diastereomeric ratio (84%, Scheme 3c) were lower than that observed by performing the reaction in a cascade fashion (Table 2, entry 6, 93% *ee*, d.r. = 12:1). The results suggested that in addition to the




Scheme 3. Preliminary mechanistic studies of the **VI**-catalyzed cascade Michael–Michael reaction.

DKR effect, the chiral amine thiourea catalyst **VI** played an important role in direct controlling the stereoselectivity of the cascade process. As shown experimentally (Scheme 3c), an *ee* value of 84% was obtained at −40°C under the same reaction conditions for the first Michael addition reaction. Furthermore, an enhancement of the *ee* value (93%, Scheme 3d) and the diastereomeric ratio (12:1) was observed when (*S*)-**6** with 84% *ee* was treated with **VI** at −40°C.[5d] The discoveries are significant. An interplay of stereocontrol and DKR in an organocatalytic cascade process to govern stereoselectivity is observed.[10] This is a direct contrast to what we observed in our previously described thio-Michael–Michael cascade reaction (Scheme 2), where DKR is the sole source for governing the stereoselectivity.[5d] Finally, interestingly the treatment of (*S*)-**6** (84% *ee*) with ent-**VI** at −40°C gave rise to two diastereomers (**3a** and **7**, Scheme 3e). Product **3a** was the minor isomer with lower *ee* (65%), whereas **7** with a *trans–trans* configuration was the major one and an excellent enantioselectivity (96%) was observed.[19]

In summary, we have developed a novel bifunctional amine thiourea catalyzed cascade thio-Michael–Michael reaction to form biologically significant trisubstituted tetrahydrothiophenes with high enantio- and diastereoselectivity. This transformation efficiently creates one C–S and one C–C bond and three stereogenic centers in a "one-pot" operation. The reaction provides structurally diverse tetrahydrothiophenes, which are highly valuable in chemical biology and medicinal chemistry. More significantly, an unprecedented activation mode of cooperative direct stereocontrol and dynamic kinetic resolution is identified. Because noncovalent bond mediated asymmetric cascade reactions belong to a much less explored field, the activation mode holds great potential in developing new synthetically efficient cascade processes with unexpected discoveries. This represents our future endeavor.

## Experimental Section

**General procedure (Table 3 entry 1 as an example)**: Unless specifically stated, a mixture of *trans*-ethyl 4-mercapto-2-butenoate (**1**) (15.7 μL, 0.12 mmol), *trans*-β-nitrostyrene (**2a**) (14.9 mg, 0.1 mmol), and catalyst **VI** (8.3 mg, 0.02 mmol) in chloroform (0.5 mL) was stirred at −40°C for 72 h. The reaction mixture was directly purified by silica gel chromatography (hexane/EtOAc 30:1) to afford the desired product as a colorless oil (24.3 mg, 82%, 93% *ee*). HPLC (Daicel CHIRALCEL OD-H column, hexane/*i*PrOH 90:10, 0.6 mL min$^{-1}$, $\lambda$ = 210 nm): $t_{minor}$ = 16.50, $t_{major}$ = 17.02 min; $[\alpha]_D^{26.5} = -48.2$ ($c$ = 1.06, $CHCl_3$).

## Acknowledgements

Financial support provided by the National Science Foundation (CHE-0704015, W.W.), the China "111" project (Grant B07023, W.W.) and the Chinese Scholarship Council (C.-G.Y.) is gratefully acknowledged.

**Keywords:** amine thioureas · cascade catalysis · dynamic kinetic resolution · organocatalysis · tetrahydrothiophenes

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Received: August 18, 2010
Published online: December 15, 2010

  