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Hydrogen-Bond-Mediated Asymmetric Cascade Reaction of Stable Sulfur Ylides with Nitroolefins: Scope, Application and Mechanism

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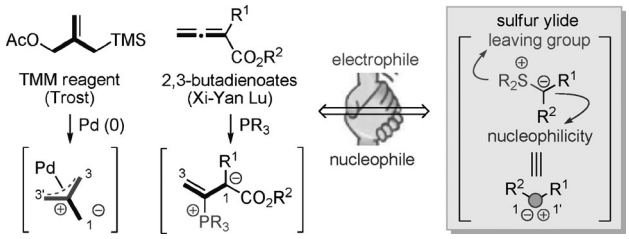
Abstract: A hydrogen-bond-mediated asymmetric [4+1] annulation/rearrangement cascade of stable sulfur ylides and nitroolefins was developed. This reaction provides a facile route to enantioenriched 4,5-substituted oxazolidinones in moderate to excellent isolated yields (65–96%) with excellent stereocontrol (up to more than 95:5 d.r. and 97:3 e.r.). This methodology was successfully applied to the concise synthesis of two bioactive molecules. The stereocontrolled modes and mechanism have been proposed to explain the origin of this stereochemistry.

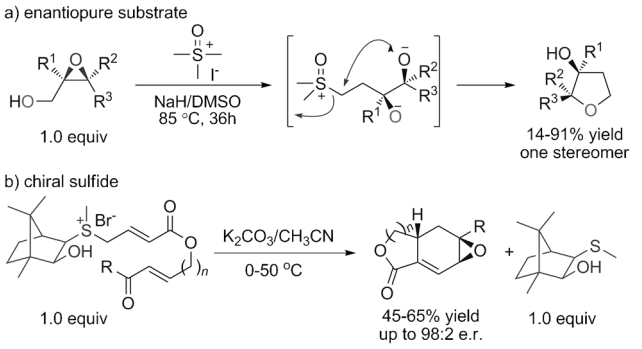
Keywords: annulation · asymmetric synthesis · hydrogen bonds · rearrangement · sulfur · ylides

Introduction

Over the last decade, cascade reactions, particularly those including dipole-type intermediates, have been identified as one of the most powerful tools available to access a variety of functional cyclic compounds.[1,2] For example, 1,3-dipole intermediates generated in situ, trimethylenemethane (TMM) reagents,[2c] and 2,3-butadienoates[2d] have been widely used as versatile building blocks to construct five- to seven-membered or even larger cyclic compounds (Scheme 1). These key zwitterionic intermediates, which couple nucleophilic and electrophilic components, can react with other reaction partners consecutively. From this standpoint, sulfur ylides were believed to possess similar characteristics[3] and thus many unprecedented cascade reactions involving this active intermediate have been developed.[4–7] For instance, the groups of Borhan,[5a,b] Aggarwal[5c–e] and Tang[4b,6a,b] have recently performed elegant studies on cascade reactions with active or semistable sulfur ylides as the key intermediates that can be used to efficiently construct complex cyclic molecules. In this field, we are interested in the design and implementation of novel cascade reactions involving stable sulfur ylides that provide new routes to oxazolidinones, pyrrolines, and some other important heterocycles.[7] At the same time, asymmetric processes that take place in cascade reactions and involve sulfur ylides is another research topic of importance. However, to the best of our knowledge, most studies have largely relied on the use of stoichiometric chiral sources, that is, enantiopure substrates (e.g., Scheme 2a)[5a,b] or chiral sulfides (e.g., Scheme 2b).[5c–f,7c,d] Therefore, the development of asymmetric cascade reactions involving sulfur ylides that use simpler and more economical substoichiometric stereocontrol elements, is still highly desirable.[8] Moreover, the asymmetric construction of chiral oxazolidinones has attracted remarkable research interest due to the biological and synthetic significance of such heterocyclic motifs.[9,10]



Scheme 1. Typical character of dipole-type intermediates: the electrophile and nucleophile coexist in one molecule.



Scheme 2. Traditional methods applied to asymmetric cascade reactions of sulfur ylides: stoichiometric chiral sources, such as a) enantiopure substrates or b) chiral sulfides.

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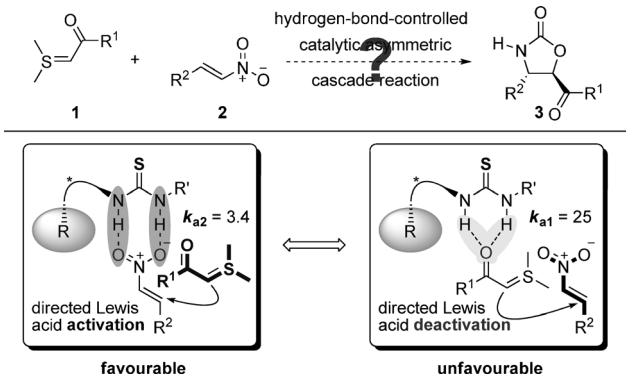
Based on one of our previous reports, referring to the [4+1] annulation/rearrangement cascade of stable sulfur ylides with nitroolefins,[7a,d] we further developed an asymmetric process that allows facile synthesis of chiral 4,5-substituted oxazolidinones with good chemoselectivity (65–96% yield) and good stereoselectivity (up to 95:5 d.r. and 97:3 e.r.). This study features 1) the use of inexpensive and recoverable C_2-symmetric multiple hydrogen-bonding catalysts that can be obtained by a one-step procedure from readily available commercial materials; 2) successful application to the asymmetric synthesis of (+)-*epi*-cytoxazone[11] and valinoctin A;[12] and 3) a rational explanation for the stereochemical course.

Considering the efficiency of hydrogen-bonding donors such as thiourea, urea and amide to direct and activate nitroolefins in their asymmetric Michael addition reactions,[13,14] we proposed that the asymmetric [4+1] annulation/rearrangement cascade of nitroolefins with sulfur ylides might be realised through asymmetric hydrogen-bond control (Scheme 3). However, we also recognised a vital challenge that must be addressed for this proposal to be realised: stable acyl sulfur ylides would coordinate with hydrogen-bonding catalysts, possibly in preference to nitroolefins, due to their zwitterionic character, which would make these catalysts ineffective in the asymmetric cascade reaction. This was indeed confirmed by the results of our hydrogen-bonding titration experiments that were conducted with a thiourea catalyst and sulfur ylide **1a** ($k_{a1}=25$) or nitroolefin **2a** ($k_{a2}=3.4$).[15]



Scheme 3. Proposal and challenge: hydrogen-bonding-mediated asymmetric [4+1] annulation/rearrangement cascade of stable sulfur ylides with nitroolefins.

Results and Discussion

Optimisation of reaction conditions: To validate this proposal, we carried out the cascade reaction of sulfur ylide **1a** and nitroolefin **2a** with 50 mol% of Takemoto's catalyst (**4a**) in xylene at −25 °C for 72 h. The desired oxazolidinone product **3aa** was obtained in moderate yield, but with a very low enantiomeric ratio (Figure 1; 55% yield, 52:48 e.r.). Changing the dimethyl amino group to a primary amino group (**4b**) resulted in the formation of a completely racemic product. We therefore moved our attention to other hydrogen-bonding catalysts, that is, the bis-sulfonamide **4c**, which facilitated excellent stereocontrol in our previous work;[14b] however, in this case, the use of **4c** did not result in any improvement in enantioselectivity. We assumed that if the stronger hydrogen-bonding ability of stable sulfur ylides resulted in this disappointing enantioinducement, the addition of hydrogen-bonding donors would reverse this situation. With this consideration in mind, other multiple hydrogen-bonding catalysts were further examined. We were pleased to find that the use of the triple hydrogen-bonding catalyst **4d** gave product **3aa** with encouraging enantioselectivity (91% yield, 66:34 e.r.); when the quadruplex hydrogen-bonding catalyst **4e** was employed, to our delight, the enantiomeric ratio further increased to 87:13, albeit in reduced yield (37%). Encouraged by this result, we continued to screen a wide array of multiple hydrogen-bonding catalysts to further improve the enantio- and chemoselectivity. As highlighted in Figure 1, we observed that: 1) among the three chiral backbones, for example, cyclohexyl (**4e**: 37% yield and 83:17 e.r.), diphenylethyl (**4k**: 66% yield and 90:10 e.r.) and binaphthyl (**4n**: 22% yield and 53:47 e.r.) units, the second was the best choice; 2) compared with thiourea-type hydrogen-bonding catalysts, urea-type catalysts generally exhibited better stereoinduction abilities (**4e** vs. **4i** and **4k** vs. **4l**); and 3) after examining the effects of electronic factors and steric hindrance on the catalytic activity, we found that the 3,5-bis(trifluoromethyl)benzyl substituent proved to be superior (**4e** vs. **4f–h**, **4i** vs. **4j** and **4l** vs. **4m**). As a result, the C_2-symmetric chiral urea **4l** was found to be the most efficient catalyst for this cascade reaction (**4l**: 81% yield, 93:7 e.r.). Careful evaluation of many other reaction parameters, such as the solvent, concentration and temperature (see the Supporting Information for details) further improved the reaction efficiency in terms of both enantio- and chemoselectivities (88% yield, 95:5 e.r.). However, the catalyst-loading study showed that either a further decrease or an increase in the amount of catalyst **4l** did not have any positive effect on enantioselectivity.

Scope of the reaction: With the optimum conditions in hand, we began to explore the substrate scope of this hydrogen-bond-mediated asymmetric cascade reaction. As highlighted in Scheme 4, this strategy proved to be tolerant of a wide range of nitroolefin partners, and various enantioenriched oxazolidinones were obtained in moderate to excellent yields with high stereoselectivities (65–96% yields, >95:5 d.r., up to 97:3 e.r.). Electronic and steric variation of nitrostyrenes were accommodated with good yields and high enantiomeric ratios (Scheme 4, **3aa–ai**: 74–88% yields, >95:5 d.r. and 90:10–95:5 e.r.). It should be noted that halogen atoms and methoxyl groups on the aryl rings could be easily removed or transformed into other groups through the use of transition-metal catalysts;[17] product **3aj** is an im-

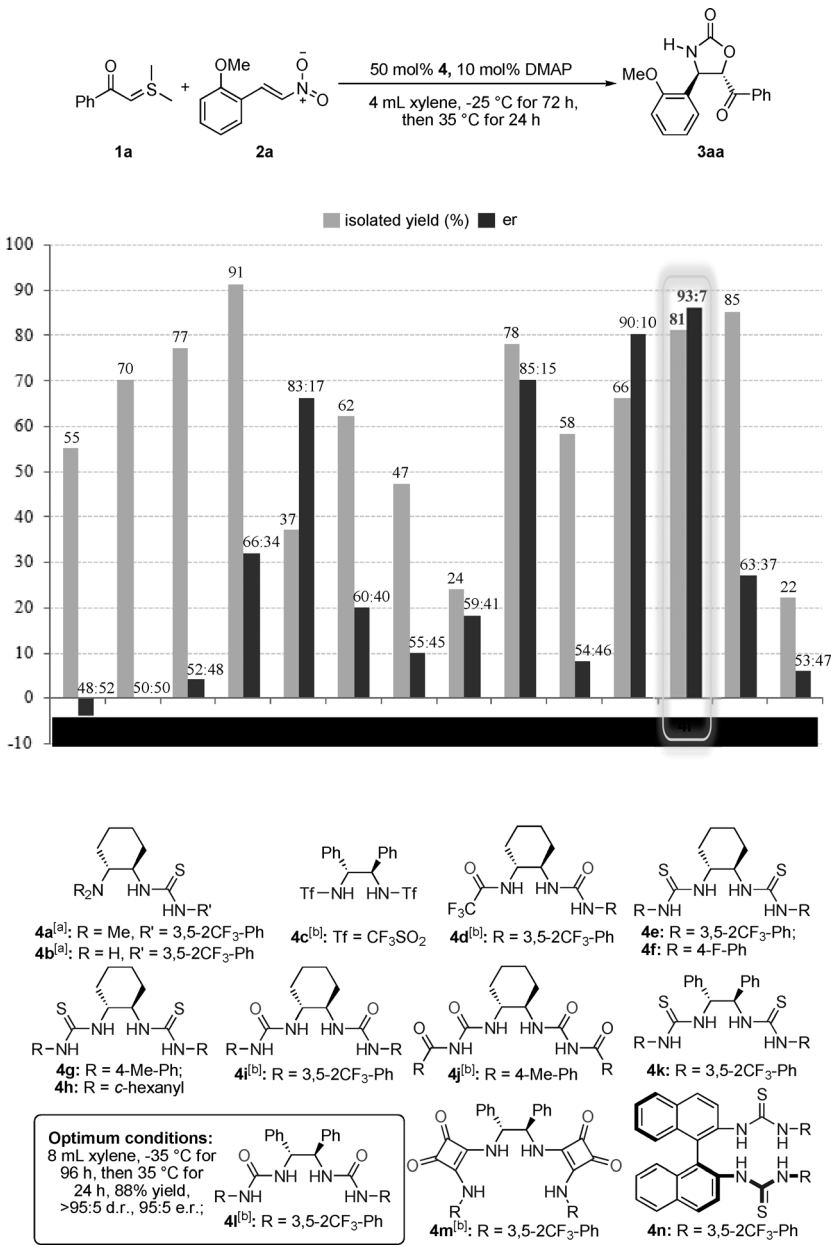
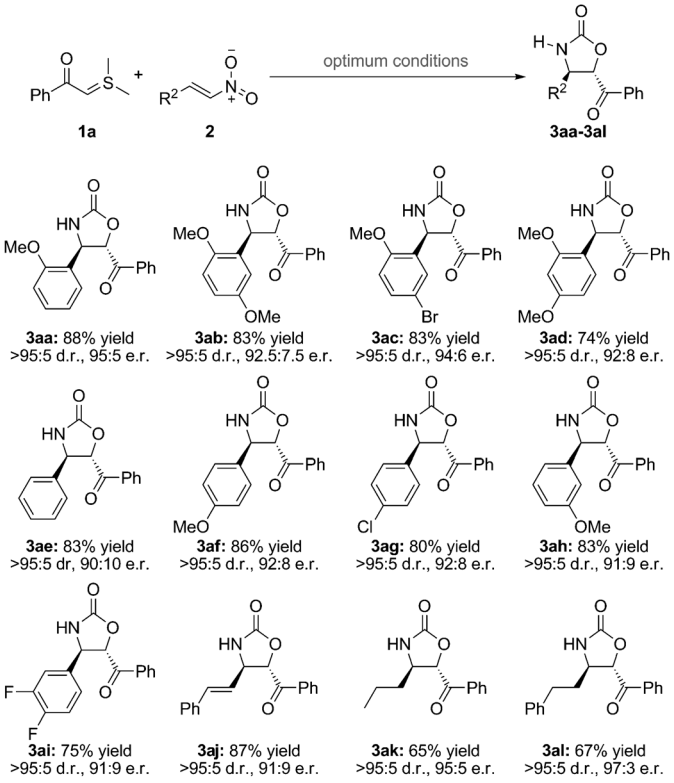


Figure 1. Optimisation of the hydrogen-bond-mediated asymmetric cascade reaction conditions: screening hydrogen-bonding catalysts. Reagents and conditions: **2**a (0.10 mmol, 1.0 equiv) and **1**a (0.11 mmol, 1.1 equiv) were used. Enantiomeric ratios (e.r.) (anti) were determined by chiral HPLC analysis. [a] *N*,*N*-dimethylpyridin-4-amine (DMAP) was not added. [b] 10 mol% 2-chlorophenylthiourea (2-CTU) was added.[16]

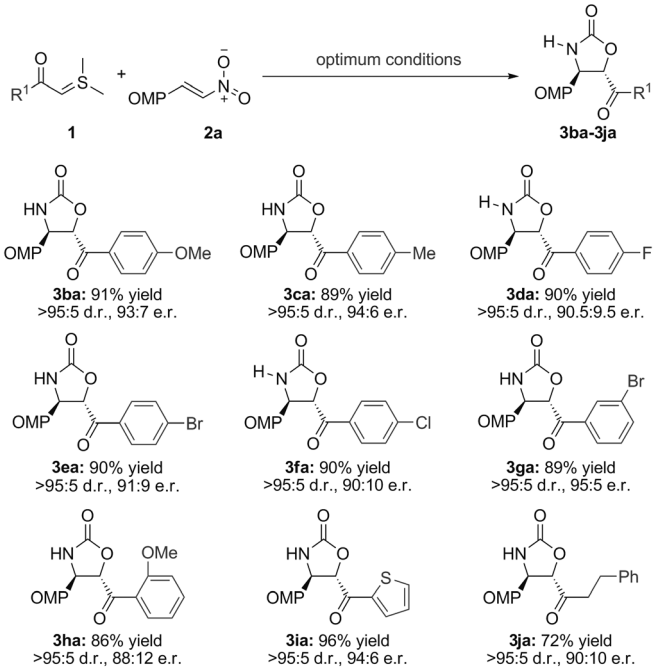
portant intermediate that allows access to a family of potential α-adrenoceptor antagonists.[18] In addition, alkenyl- (Scheme 4, **3aj**: 87% yield, >95:5 d.r. and 91:9 e.r.) and alkyl-substituted nitroolefins (Scheme 4, **3ak**: 65% yield and 95:5 e.r.; **3al**: 67% yield and 97:3 e.r.) could also be successfully used for the enantioselective construction of optically active oxazolidinones.

As outlined in Scheme 5, the same conditions were also compatible with a wide range of stable sulfur ylides. Through the introduction of electron-donating or electron-withdrawing substituents on the benzene ring, this cascade reaction could deliver the desired products with a good level of chemo- and stereoselectivity (Scheme 5, **3ba–fa**: 89–91% yields, >95:5 d.r. and up to 94:6 e.r.). Remarkably, significant variation in the steric demand of the sulfur ylide was also possible. For example, the *meta*-bromo-substituted sulfur ylide **1g** could take part in the reaction efficiently to give the desired product **3ga** in 89% yield with 95:5 d.r. and 95:5 e.r.; for the *ortho*-methoxyl sulfur ylide **1h**, the corresponding oxazolidinone **3ha** could be obtained in good yield with a slight decrease in the enantiomeric ratio (Scheme 5, **3ha**: 86% yield, >95:5 d.r. and 88:12 e.r.). To our delight, heteroaromatic compounds, which are valuable in medicinal chemistry, were also found to be suitable reaction components for this asymmetric cascade reaction. For example, treatment of 2-thiophenyl-substituted sulfur ylide **1i** with nitroolefin **2a** under the optimum reaction conditions generated the heteroarene-containing oxazolidinone **3ia** in 96% yield with 95:5 d.r. and 94:6 e.r. In addition to aryl- and heteroaryl-substituted acyl sulfur ylides, the cascade reaction of alkyl-substituted sulfur ylides also proved to be feasible (Scheme 5, **3ja**: 72% yield, 95:5 d.r. and 90:10 e.r.).

Synthetic applications of the reaction: To illustrate the synthetic utility of this asymmetric cascade reaction, we performed two reactions on millimolar scales (Scheme 6). The corresponding aryl- or alkyl-substituted chiral products were provided efficiently with good enantiocontrol (**3bf**: 80% yield, >95:5 d.r. and 94:6 e.r.; **3bm**: 66% yield, >95:5 d.r. and 92:8 e.r.). It is worth noting that the stereocontroller, chiral urea **4l**, could be easily recovered during the purification of the product. Moreover, starting from these oxazolidinones, (+)-*epi*-cytoxazone and a vital intermediate of the natural dipeptide valinoctin A, which respectively possess significant bioactivities in terms of selectively modulating Th2 cytokine secretion[11a] and in-



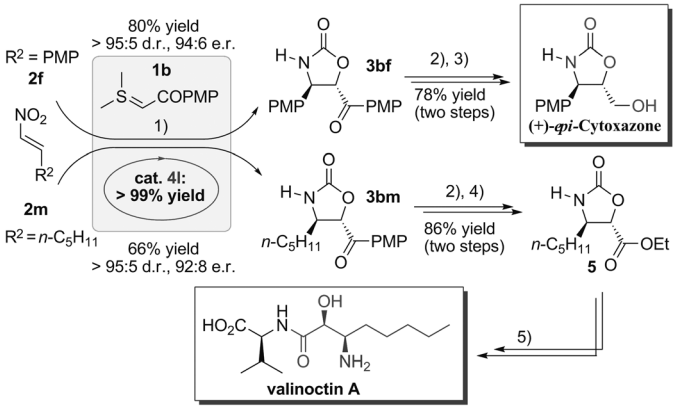
Scheme 4. Scope of the hydrogen-bond-mediated asymmetric [4+1] annulation/rearrangement cascade with respect to nitroolefins. For the optimum conditions: see Figure 1. Yield is given as the isolated yield. Diastereomeric ratios (d.r.) (*anti*/*syn*) were determined by ^{1}H NMR spectroscopic analysis of the reaction mixture and e.r. (*anti*) values were determined by chiral HPLC analysis.



Scheme 5. Scope of the hydrogen-bond-mediated asymmetric [4+1] annulation/rearrangement cascade with respect to stable sulfur ylides. For the optimum conditions: see Figure 1. Yield is given as the isolated yield. Diastereomeric ratios (d.r.) (*anti*/*syn*) values were determined by ^{1}H NMR spectroscopic analysis of the reaction mixture and e.r. (*anti*) values were determined by chiral HPLC analysis. OMP: *o*-methoxyphenyl.

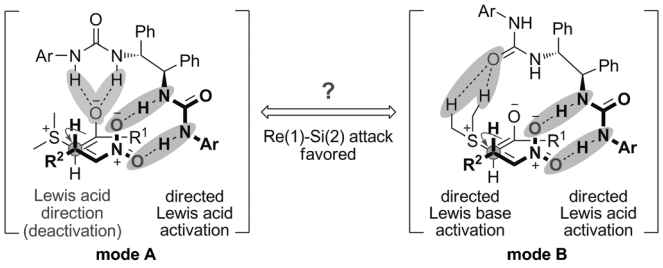
hibiting farnesyl transferase,[12a] could be accessed through a straightforward two-step routine.

Possible stereochemical course of reaction: To address the hydrogen-bond-mediated mechanism, a series of experiments, such as in situ IR experiments, the Job method, and hydrogen bonding titration experiments, were performed (see details in the Supporting Information).[15] As a result, we concluded that: 1) the in situ IR experiment implied that only the [4+1] annulation could be observed at low temperatures and that the subsequent reaction process to generate oxazolidinones occurred only at higher temperature (35 °C); 2) the Job method experiments, not only confirmed the existence of hydrogen-bonding interactions between the starting materials and the nitronate intermediates, but also implied that one molecule of the quadruplex hydrogen-bonding catalyst **4k** could coordinate two molecules of sulfur ylides or nitroolefins, but only one molecule of the nitronate intermediate; and 3) according to the results of hydrogen-bonding titration experiments, we speculated that the thiourea catalyst **4k** exhibited the strongest binding ability with sulfur ylides and the weakest with nitroolefin ($k_{a1}=25$, $k_{a2}=3.2$, $k_{a3}=5.4$, where k_{a1}, k_{a2} and k_{a3} are defined as the binding constants of sulfur ylide **1a**, nitroolefin **2a** and the nitronate analogue Me-**7ae** with the thiourea catalyst **4k**).



Scheme 6. Synthetic application: concise asymmetric synthesis of (+)-*epi*-cytoxazone and valinoctin A. PMP=*p*-methoxyphenyl. Conditions: 1) 1 mmol scale: 50 mol% **4l**, 10 mol% 2-CTU, 10 mol% DMAP, 0.0125 M in xylene, −35 °C, 96 h, then 24 h at 35 °C; 2) $NaH_2PO_4{\cdot}2H_2O$, *meta*-chlorobenzoperoxoic acid (*m*-CPBA), 1,2-dichloroethane (DCE), 60 °C, 6 h; 3) $NaBH_4$, HOAc, THF, 0 °C–RT, 2 h; 4) K_2CO_3, EtOH; 5) See ref. [12b].

In light of previous work on asymmetric multiple hydrogen-bonding catalysis,[19] two efficient modes were established to understand the origin of stereodiscrimination in this asymmetric cascade reaction (Scheme 7): in mode A, two urea segments coordinate to the oxygen atom of the acyl sulfur ylide and nitroolefin, functioning as a Lewis acid



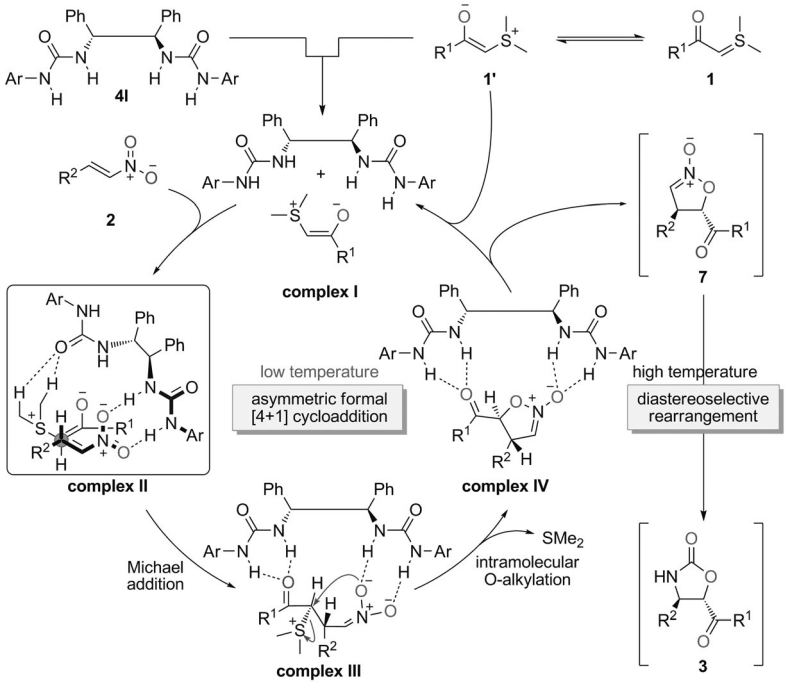
Scheme 7. Rationalising the stereocontrolled course of this hydrogen-bond-mediated asymmetric cascade reaction.

to activate and/or direct the two reactants; in mode B, one urea unit imposed on the nitroolefin functions as a Lewis acid, whereas the other plays the role of a Lewis base to activate and direct the acyl sulfur ylide. The involvement of these two modes was convincingly supported by the above experiments and theoretical calculations;[19b] the absolute configuration deduced from these two modes are in accordance with those obtained in the chemical transformation of **3bf** or **3bm**.[11b,12b] However, at the current stage, Mode B is believed to be favoured, possibly as a result of activation energy.

Based on these results, we also propose a possible catalytic cycle for the hydrogen-bond-mediated asymmetric cascade [4+1] annulation/rearrangement reaction of stable sulfur ylides with nitroolefins. As illustrated in Scheme 8, catalyst **4l** incorporates sulfur ylide **1** with the charge-separated isomer into **complex I** through strong hydrogen-bonding interactions; this complex could further transiently coordinate with another molecule of nitroolefin to form **complex II**. Although the second complexation process is thermodynamically disadvantageous ($k_{a2}' < k_{a1}'$),[20] the cooperative Lewis acid/base activation served by the C_2-symmetric urea catalyst **4l** in mode B would make the asymmetric Michael addition of sulfur ylide to nitroolefin proceed efficiently. Subsequently, the hydrogen-bonding complex of the nitronate intermediate and catalyst **4l** (**complex IV**) gradually forms through an intramolecular chemoselective O-alkylation of the zwitterionic intermediate complex (**complex III**). Finally, presumably because of its stronger binding ability ($k_{a1}' > k_{a3}'$), the unreacted sulfur ylide preferentially coordinates with catalyst **4l**, replacing nitronate intermediate **7** to ensure the turnover of the hydrogen-bonding catalyst and the release of intermediates at low temperature. After most of the starting material was consumed, the reaction system was warmed to promote the rearrangement of chiral nitronate intermediates **7** into the final enantioenriched oxazolidinones **3**. Consequently, stepwise operation at a temperature that ensures the high enantioselectivity of this cascade reaction would be explained by this proposed mechanism. Tentatively, the relatively high catalyst loading in this asymmetric cascade reaction arises either from a competing catalyst-free cascade process or possibly from inhibitory action of intermediates on hydrogen catalysts as depicted in **complex III** and **complex IV**.

Conclusion

In this full paper, we have developed a hydrogen-bond-mediated asymmetric [4+1] annulation/rearrangement cascade of stable sulfur ylides with nitroolefins. A readily available, inexpensive and recoverable C_2-symmetric chiral urea catalyst could efficiently promote this cascade reaction and the optically active oxazolidinones were provided with good reaction efficiency and high stereoselectivities. Moreover, the corresponding products can be applied in the concise synthesis of (+)-*epi*-cytoxazone and valinoctin A, and a possible stereocontrol mode of the hydrogen-bonding cooperative catalysis was proposed on the basis of reliable experiments. Further studies directed toward the application of this strategy to other stable sulfur-ylide-participating cascade reactions for the enantioselective construction of other heterocyclic adducts will be reported in due course.



Scheme 8. Mechanistic proposals for the hydrogen-bond-mediated asymmetric cascade reaction of stable sulfur ylides with nitroolefins.

Experimental Section

Representative procedure: To a 25 mL flask equipped with a magnetic stir bar was added nitroolefin **2a** (0.1 mmol, 1.0 equiv, 17.9 mg), 2-CTU (0.01 mmol, 10 mol%, 1.87 mg), DMAP (0.01 mmol, 10 mol%, 1.22 mg), catalyst **4l** (0.05 mmol, 50 mol%, 36.13 mg) and xylene (8.0 mL), and the mixture was stirred at −35 °C for 30 min. Sulfur ylide **1a** (0.11 mmol, 1.1 equiv, 20.5 mg) was added directly to the above system. After 96 h, the reaction mixture was slowly warmed to 35 °C and stirring was continued for 24 h. The desired chiral product **3aa** was obtained in 88% yield by flash chromatography (silica: 200–300; petroleum ether/CH_2Cl_2/acetone). The diastereomeric ratio and enantiomeric ratio were determined by ^{1}H NMR spectroscopic analysis and chiral stationary phase HPLC analysis of the reaction mixture, respectively. White solid; diastereomeric ratio: >95:5, enantiomeric ratio: 95:5 (Daicel Chirapak OD-H; hexane/isopropanol = 80:20; flow rate: 0.7 mL min^{-1}; T = 25 °C; 254 nm; t_R = 17.79 (minor), 22.25 min (major)). $[\alpha]_D^{27} = +108$ (c = 1.3 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 (d, J = 7.5 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.42–7.29 (m, 2H), 7.04 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.59 (d, J = 4.5 Hz, 1H), 5.52 (d, J = 4.3 Hz, 2H), 3.64 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 192.6, 157.7, 155.4, 133.6, 133.4, 128.9, 128.3, 128.1, 127.1, 125.7, 120.1, 109.9, 79.8, 54.2, 52.5 ppm; MS: m/z: 297.6 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{15}NO_4$: C 68.68, H 5.09, N 4.71; found: C 68.57, H 5.02, N 4.62.

Acknowledgements

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