

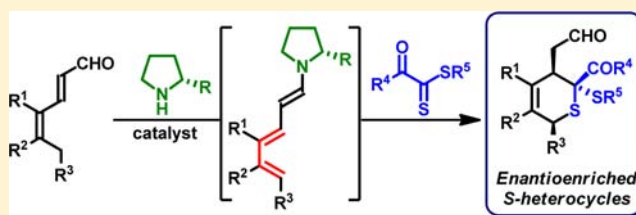
Asymmetric Organocatalytic Thio-Diels–Alder Reactions via Trienamine Catalysis

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S Supporting Information

ABSTRACT: We report a new process to access highly enantioenriched sulfur-based heterocycles by an asymmetric catalytic thio-Diels–Alder reaction. Thiocarbonyls are challenging heterodienophiles in enantioselective Diels–Alder reactions, due to their inherent high reactivity and their poor ability to coordinate to chiral catalysts. We successfully circumvented these problems by employing a different strategy, which explores the use of *in situ* generated catalyst-bound dienes. Synthetically useful dihydrothiopyrans as well as other bi- and tricyclic sulfur-containing heterocycles are formed in high yields and high to excellent selectivities. DFT calculations were performed to examine the mechanism of the developed reaction. Furthermore, a series of synthetic transformations of the optically active sulfur-based heterocycles are presented.



INTRODUCTION

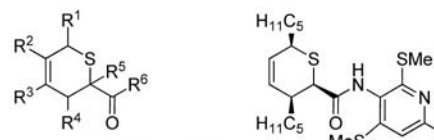
The asymmetric hetero-Diels–Alder reactions provide simple and direct access to a variety of important, chiral, heterocyclic compounds.¹ Driven by the growing demand of these structures in contemporary synthesis, great efforts have been devoted to continually develop new and improved reactions and protocols. One of the central agendas of current research in asymmetric hetero-Diels–Alder reactions is the elaboration of efficient and reliable enantioselective catalytic methods, thereby maximizing the atom economy of the chemical synthesis.² In this regard, the research in oxo- and aza-Diels–Alder reactions has been very fruitful, giving rise to a broad range of complementary methods to, catalytically, furnish O- or N-centered heterocycles in high enantioselectivities (Figure 1, top left).³

On the contrary, the closely related, and equally useful, catalytic asymmetric thio-Diels–Alder reaction, which leads to the formation of sulfur-based heterocycles, has been the object of much less attention (Figure 1, top right).⁴ It is noteworthy that several sulfur-based cycloadducts are known to possess interesting biological activity (Figure 1, bottom).⁵ For example, a series of acetyl CoA cholesterol acyltransferase inhibitors was developed as lead targets for potent oral therapeutic agents against the onset of atherosclerosis. More importantly, it was shown that the absolute configuration of the sulfur-containing heterocycles had a decisive effect on the activities and bioavailability of these compounds, thus emphasizing the need for efficient enantioselective thio-Diels–Alder reactions.

Despite the well-known high dienophilicity of thiocarbonyls, the engagement of sulfur-based dienophiles in asymmetric [4 + 2]-cycloadditions has proven to be difficult. In fact, only few isolated and elusive attempts have been made toward the development of general catalytic enantioselective thio-Diels–Alder reactions to access sulfur heterocycles.⁴ One of the

Heteroatom centered dienophiles in [4+2]-cycloadditions

<ul style="list-style-type: none"> usually requires activation to react with dienes can be targeted with chiral LA or BA catalysts frequently employed in asymmetric catalysis 	<ul style="list-style-type: none"> often reacts uncatalyzed at rt or below difficult to target with chiral catalysts rarely employed in asymmetric catalysis
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General structure of ACAT inhibitors based on sulfur-containing cycloadduct XP767

Figure 1. Diels–Alder reactions with different heteroatom centered dienophiles and the challenges of the enantioselective thio-Diels–Alder reaction. ACAT: acetyl CoA cholesterol acyltransferase.

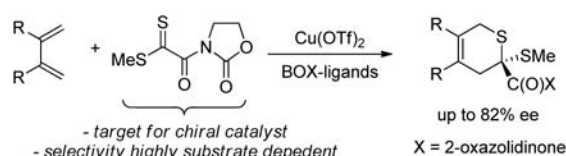
central challenges lies within the inherent high reactivity of the thiocarbonyls toward simple dienes, which complicates the design of general catalytic systems for enantioselective thio-Diels–Alder reaction.⁶ Moreover, in contrary to the O- or N-based analogues, the thiocarbonyl groups are typically unsuitable for activation (and coordination) by Lewis and Brønsted acids, thus, significantly reducing the number of applicable catalysts. The most promising result achieved, up to date, in this reaction was reported by Gulea et al. in 2010,

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where a thiocarbonyl compound was transformed with an enantioselectivity of up to 82% ee using an organometallic catalyst (Figure 2, top).^{4a} However, a specific side-chain

Previous work: Targeting the dienophile (Gulea *et al.*)



This work: Targeting the diene

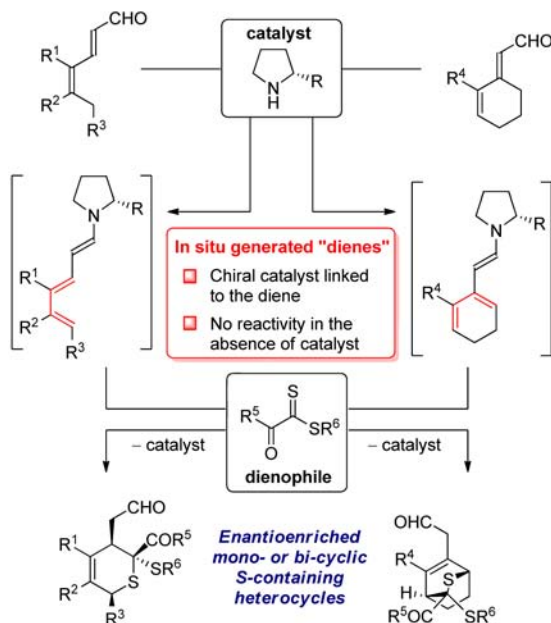


Figure 2. Summary of previous work and the design plan of this work.

containing a functional group, which enabled strong bidentate coordination to the metal center, was shown to be crucial for the selectivity. Any derivation from this catalyst recognizing motif in the thio-dienophile led to a significant reduction in the enantioselectivity of the catalytic enantioselective thio-Diels–Alder reaction.

The lack of more general and effective protocols triggered us to seek alternative strategies, which do not rely on catalyst coordination to thiocarbonyl compounds as a mean to achieve good enantiocontrol. Instead, we questioned the possibility of using a chiral catalyst to *in situ* generate activated diene species from reactants otherwise inert to the thio-Diels–Alder reaction (Figure 2). As such, the presence of any nonstereoselective background reactions can be minimized, and only in its catalyst-bound state, the diene fragment is available for reaction. Optimal influence of the chiral catalyst is thereby warranted, as the active diene is always covalently linked to the catalyst, which may govern the facial approaches of the dienophile.

In recent years, aminocatalysis has evolved to become a useful tool to promote enantioselective Diels–Alder reactions.⁷ In particular, we have been fascinated by the ability of an aminocatalyst to *in situ* generate trienamine species, which subsequently were able to engage as catalyst-bound dienes in asymmetric Diels–Alder reactions.⁸ At the outset of the current study, we hypothesized that this organocatalytic remote functionalization strategy might be a viable approach to address

the challenges of developing an efficient catalytic enantioselective thio-Diels–Alder reaction. The fact that the two success criteria of the design plan (chiral catalyst targeting the diene and *in situ* generation of the diene) are fulfilled encouraged us to further evaluate this hypothesis. However, it shall be noted that aminocatalyzed hetero-Diels–Alder reactions using heteroatom-centered dienophiles have only in few cases been achieved with good enantioselectivity. Moreover, up to date, all reported trienamine-based organocatalytic Diels–Alder reactions have been limited to the use of carbon-centered dienophiles. The engagement of a heterodienophile in such trienamine-mediated reaction pathways has not yet been successful.

RESULTS AND DISCUSSION

Screening and Optimization of the Thio-Diels–Alder Reaction. In order to validate the synthetic design, we chose to study the [4 + 2]-cycloaddition between dienal **1a** and dithioester **2a** as the model reaction (Table 1). Encouragingly,

Table 1. Screening of the Aminocatalytic thio-Diels–Alder Reaction^a

entry	3 (mol %)	additive (mol %)	T (°C)	t (h)	conv (%) ^b	dr ^c	ee (%) ^d
1	20	PhCO ₂ H (20)	rt	1	>95 (85)	94:6	89
2	20	D-MA (20)	rt	1	>95	94:6	89
3	20	NaOAc (20)	rt	48	>95	94:6	89
4	20	None	rt	48	>95	94:6	89
5	10	PhCO ₂ H (20)	rt	3	>95	94:6	89
6	10	PhCO ₂ H (20)	4	24	>95	94:6	92
7	5	PhCO ₂ H (20)	4	72	>95 (89)	94:6	92

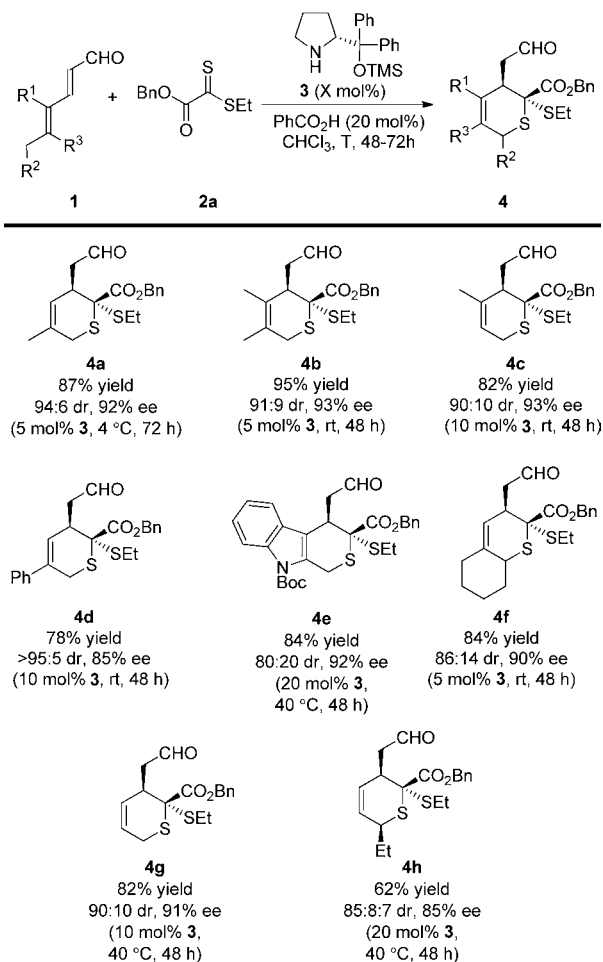
^aReactions were performed with 0.1 mmol **1a** and 0.12 mmol **2a** in the presence of catalyst **3** and the given additives in CHCl₃. ^bDetermined by ¹H NMR on the crude reaction mixture. The values in parentheses are yields of isolated product. ^cDetermined by ¹H NMR on the crude reaction mixture. ^dDetermined by chiral ultraperformance convergence chromatography (UPC²). D-MA = D-mandelic acid.

in the presence of 20 mol % of catalyst **3** and benzoic acid in CHCl₃, the dienal **1a** successfully reacted, via a catalyst-bound trienamine intermediate, to form the corresponding dihydrothiopyrane **4a** in 85% yield, 94:6 dr and 89% ee (Table 1, entry 1). While the presence of a weak base or no additive led to longer reaction times, the use of D-mandelic acid resulted in similar results compared to that of benzoic acid. A small increase of the enantioselectivity to 92% ee could be achieved by performing the reaction at lower temperatures (compare entries 5,6). Furthermore, the catalyst loading could be reduced to 5 mol %, while maintaining the high yield and selectivities obtained (entry 7). However, longer reaction times were required to provide full conversion to the product.

Scope of the Diene Precursors in the Thio-Diels–Alder Reaction. Next, a series of aldehydes **1** was evaluated as

diene precursors in the developed thio-Diels–Alder reaction. Due to small differences in reactivity toward the dithioester **2a**, the reaction conditions were adjusted for each of the substrates with the aim to obtain the best result with minimum catalyst loading (Scheme 1). High to excellent selectivities were

Scheme 1. Scope of the Asymmetric Aminocatalytic thio-Diels–Alder Reaction



achieved in all evaluated cases affording highly enantioenriched heterocyclic products in high yields. Both alkyl and aryl substituents were well-tolerated at the γ - and δ -positions of **1** as demonstrated for the formation of **4a–d** in 78–95% yield, 90:10 to >95:5 dr and 85–93% ee. Bi- and tricyclic products, such as **4e,f**, could also be formed in excellent enantioselectivities. Slightly lower reactivity was observed for trienamines generated from linear dienals such as hexa- and octadienal, which is consistent with previous literature.^{8d} Nevertheless, by increasing the reaction temperature to 40 °C, comparable results could be achieved (see **4g,h**).

Mechanistic Investigations and Rationalization for the Observed Regio-, Diastereo-, and Enantioselectivities. While delighted by the obtained results and successful validation of our hypothesis, we were also intrigued by the observed selectivities of the thio-Diels–Alder reaction. Of particular interest to us was the regioselectivity of the reaction between the unsymmetrical dienes and thiocarbonyl **2a**. Our results demonstrate that such a process proceeds in favor of the pathway involving an initial attack of the catalyst-bound trienamine species at the sulfur atom. Previous reports studying

the reaction of highly polarized dienes with phosphonodithioformate have shown similar site preference.⁴ⁱ A theoretical study of this system was recently reported.^{9b} However, the regioselectivity in these studies proved to be substrate and condition dependent. Moreover, Vedejs and Houk studied the regioselectivity of Diels–Alder reactions involving thioaldehydes using ab initio molecular orbital calculations, suggesting that substituents have a large effect on the regioselectivity of the reaction.^{9a} In order to obtain a better understanding of the reactivity of dithioesters in the developed aminocatalyzed Diels–Alder reactions, a computational study employing DFT calculations was undertaken. All calculations were performed at wB97xd/tzvp¹⁰ level of theory and basis set at 298.15 K and 1.0 atm pressure using Gaussian 09.¹¹ The solvent effects were simulated by the integral equation formalism polarizable continuum model (IEFPCM, CHCl₃).¹² All listed energies are Gibbs free energies. The zero-point energies (ZPEs) and thermochemical corrections were obtained by frequency calculations, which also validated all stationary points as either local minima or first-order saddle points.

In Figure 3, the LUMO and the charge distribution (chelpg)¹³ of methyl 2-(methylthio)-2-thioacetate **2b** are

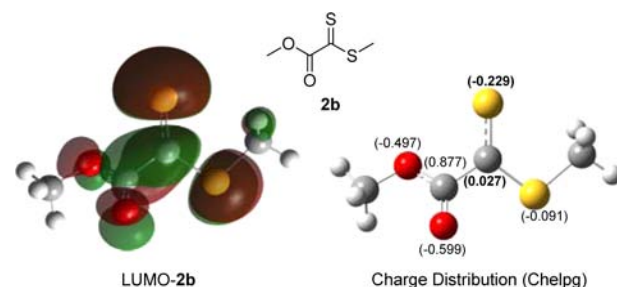


Figure 3. LUMO and charge distribution (chelpg) of a simple thio-dienophile **2b**.

depicted. We see that the LUMO is only slightly larger on the sulfur-atom when compared to the carbon-atom of the thiocarbonyl group. In addition, a relatively small charge separation of 0.256 is observed across the C=S bond, with the sulfur atom being slightly more negatively charged.

In order to understand the experimentally observed regioselectivity, the energy profiles of the two aforementioned reaction pathways (with either the sulfur or the carbon atom as the electrophilic site) were examined. In Figure 4, the free energy profile of the observed thio-Diels–Alder reaction leading to the formation of dihydrothiopyranes **4** is outlined. The reaction between dithioester **2b** and trienamine **A** was chosen as the model system. In this reaction, **2b** has two possible ways to approach the trienamine **A**, namely path I (ester group *endo*) or path II (ester group *exo*). These pathways should lead to the formation of two diastereomers, **C_I** and **C_{II}**, as the final products. **TS_{I-I}** and **TS_{I-II}** of the initial intermolecular reactions were identified as the highest energy transition states, located at 13.9 and 15.0 kcal/mol. Intrinsic reaction path (IRC)¹⁴ calculations connected **TS_{I-I}** and **TS_{I-II}** to two high-energy zwitterionic intermediates **B_I** and **B_{II}**. The final intramolecular cyclization involves very low barriers for both pathways. Both reactions are exothermic; however, the *exo* product **C_{II}** was identified to be slightly more stable (by 0.6 kcal/mol). Nevertheless, due to the large energetic barriers of the backward reactions (>20 kcal/mol), the final product distribution is most likely to be kinetically controlled. In this

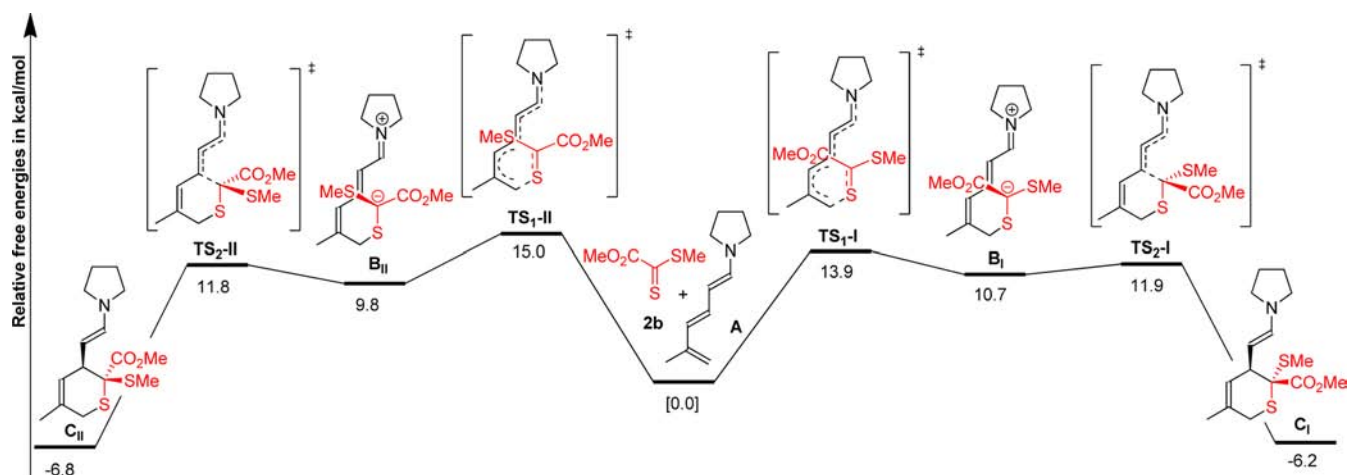


Figure 4. Energy profile for reaction path I–II: reaction via an initial attack at the sulfur atom. The values are Gibbs free energies in kcal/mol, relative to **A** + **2b** [wB97xd/tzvp/IEFPCM].

regard, the anticipated *endo* product **C**_I is favored by 1.0 kcal/mol over its diastereomer **C**_{II}. According to the Boltzmann equation, such an energy difference should correlate to a 85:15 (*endo/exo*) product distribution, which is in agreement with experimental observations (79:21 dr). It should also be noted that interconversion between intermediates **B**_I and **B**_{II} via a rotation around the C–S single bond is not possible due to steric reasons.

Next, the alternative and experimentally not observed cycloaddition reactions involving an initial attack at the carbon center was investigated (Figure 5). The transition states **TS-III** and **TS-IV** involving the two possible approaches (*endo* or *exo*, respectively) of **2b** to **A** were identified. IRC calculations show a distinct shoulder on the path to the products **D**. However, no intermediate could be located,

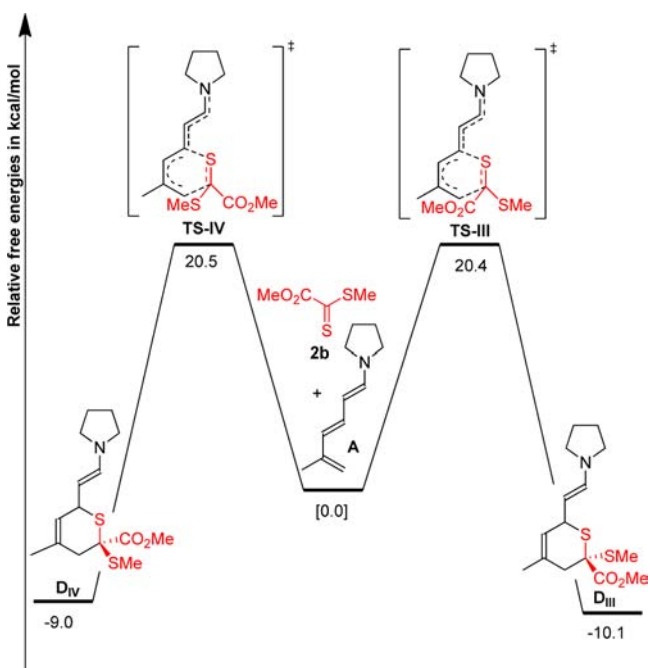


Figure 5. Energy profile for reaction path III–IV: reaction via an initial attack at the carbon atom. The values are Gibbs free energies in kcal/mol, relative to **A** + **2b** [wB97xd/tzvp/IEFPCM].

suggesting an asynchronous concerted mechanism. In terms of thermodynamic stability, the products **D** are favored over their regioisomers **C**. However, the calculated transition states (**TS-III** and **TS-IV**) leading to these cycloadducts (**D**_{III} and **D**_{IV}) were found to be >5.5 kcal/mol higher in energy than **TS-I** and **TS-II**. This large discrepancy in activation barriers is in good agreement with experimental results, in which the regioisomers arising from path III–IV were not detected.¹⁵

The transition-state structures for the initial intermolecular reactions for path I–IV are depicted in Figure 6. Important bond lengths in the dithioester (C=S, C–C, C=O) as well as the distances of the forming bonds have been compared (numbers in *italic*). In **TS**_I-I and **TS**_I-II, the initial attack of the trienamine on the sulfur atom leads to increasing conjugation in the thio-dienophile, which is shown by the shortening of the C–C bonds, while the C=O bonds are lengthened (compared

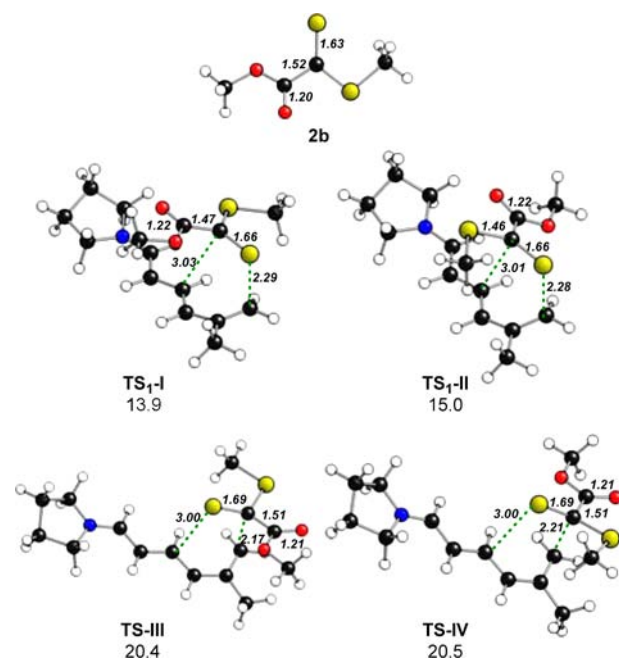


Figure 6. Transition-state geometries for path I–IV. The numbers in *italic* are bond distances in angstroms. The nonitalic values are free energies in kcal/mol, relative to **A** + **2b** [wB97xd/tzvp/IEFPCM].

to the distances in the parent **2b**). The negative charge, which is built up, in the transition state is stabilized by delocalization. In contrast, the intermolecular C–C bond formation in **TS-III** and **TS-IV** localizes the negative charge solely on the sulfur atom. Compared to **TS₁-I** and **TS₁-II**, the C–C and C=S bond distances in **TS-III** and **TS-IV** are longer by 0.05 and 0.03 Å, respectively. Evidently, the charge buildup in **TS-III** and **TS-IV** is much less stabilized, resulting in the apparent higher activation energies in these transition states.

By computationally investigating the reaction of trienamine **A** with three different thio-dienophiles (**E**, **F** and **G**) via the two alternating pathways (initial S- or C-attack), the influence of the substituents on the “S versus C” regioselectivity was examined (Figure 7). In the case of compound **E**, in which the

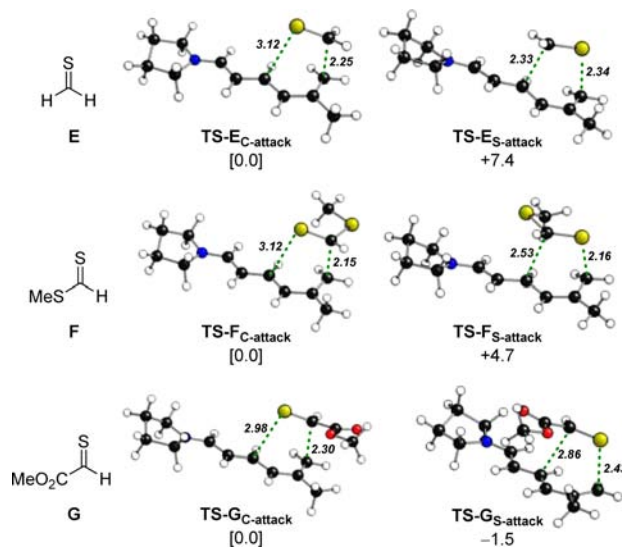


Figure 7. Transition-state geometries for the reaction of trienamine **A** and thiocarbonyl **E/F/G** via two possible pathways. The numbers in italic are bond distances in angstroms. The nonitalic values are free energies in kcal/mol, relative to **A** + **E/F/G** [wB97xd/tzvp/IEFPCM].

thiocarbonyl is only flanked by hydrogen atoms, an initial attack of **A** at the carbon atom is strongly favored ($\Delta\Delta G^\ddagger = 7.4$ kcal/mol). Substituting one of the hydrogen atoms with a SMe group increases the relative preference of the S-attack pathway, although **TS-F_C-attack** is still 4.7 kcal/mol lower in energy than **TS-F_S-attack**. The incorporation of the CO₂Me-substituent proved to have a decisive effect on the regioselectivity. When the approach of **G** to the trienamine intermediate **A** was studied, reaction via the S-attack pathway was found to be the lowest energy pathway. Presumably, a thiocarbonyl compound carrying an adjacent ester group (such as **G** and **2b**) can be regarded as the sulfur equivalent of a Michael acceptor. Similarly, the attack of a nucleophilic species on the electrophilic sulfur atom in these thiocarbonyls may resemble a 1,4-addition, in which the electron-withdrawing ester group assists in delocalizing the negative charge buildup in the transition state (and product). In summary, electronic factors are responsible of the regioselectivity of the trienamine mediated thio-Diels–Alder reaction. The ester group plays a major role in directing the reaction toward an initial attack of the trienamine at the sulfur atom, while the SMe group provides a minor contribution. The effects of the substituents are not additive; however, the combination of the two groups

(an ester and a SMe group) warrants complete selectivity for the experimentally observed reaction pathway.

The obtained high enantioselectivities of the thio-Diels–Alder reaction reflect the ability of the chiral TMS-protected diphenylprolinol to provide facial differentiation when engaged as the catalyst-bound trienamine intermediate. The approaches of dienophile **2b** to both faces of this trienamine (formed from **1a** and **3**) were studied. The structures were optimized employing wB97xd and the 6-31G(d) basis set in CHCl₃ (IEFPCM) (Figure 8). Activation energies were obtained

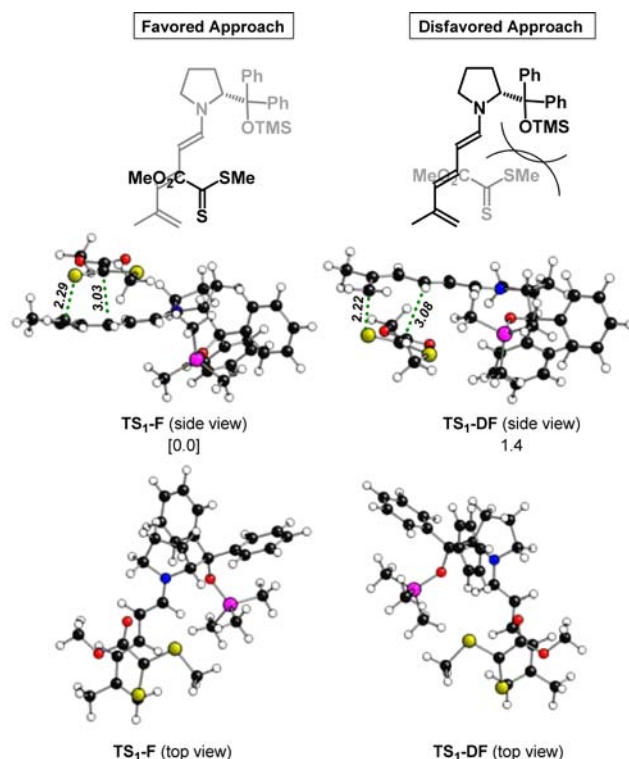
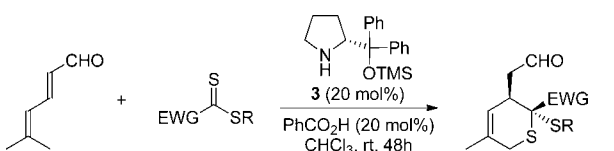


Figure 8. Transition-state geometries for the favored and the disfavored approaches of **2b** to the catalyst-bound trienamine intermediate. The values in italic are bond distances in angstroms. The nonitalic numbers are free energies in kcal/mol [wB97xd/cc-pVDZ/IEFPCM//wB97xd/6-31G(d)/IEFPCM].

with wB97xd/cc-pVDZ¹⁶ single points.¹⁷ The favored approach of **2b** to the trienamine species results in an activation energy, which is 1.4 kcal/mol lower than that of the disfavored approach (**TS₁-F** vs **TS₁-DF**). This energy difference corresponds to a calculated enantioselectivity of 83% ee, which is in good agreement with the experimental value (79% ee).

Experimental Investigation on the Influence of Substituents and Extended Reaction Scope. The obtained computational insights on substituent effects in the regioselectivity of the reaction were experimentally validated by employing methyl benzodithioate as thiodienophile in the developed organocatalytic thio-Diels–Alder reaction. Exchanging the ester group with the phenyl ring completely shut down the reaction, hence confirming the importance of the EWG in **2**. Furthermore, the influence of substituent size (in **2**) on the reactivity and selectivity of the thio-Diels–Alder reaction was examined (Table 2). It was anticipated that the gained knowledge could lead to further development of this reaction, i.e., improving the reaction diastereo- and enantioselectivity. Several thiodienophiles carrying different EWG and R groups

Table 2. Experimental Variation of Substituents on the Thiodienophile and the Influence of the Stereoselectivities^a


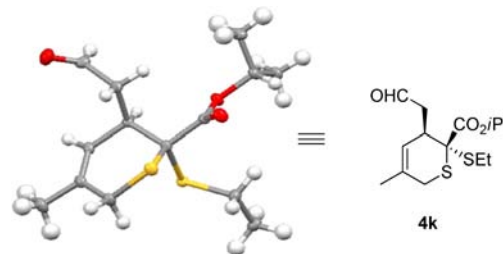
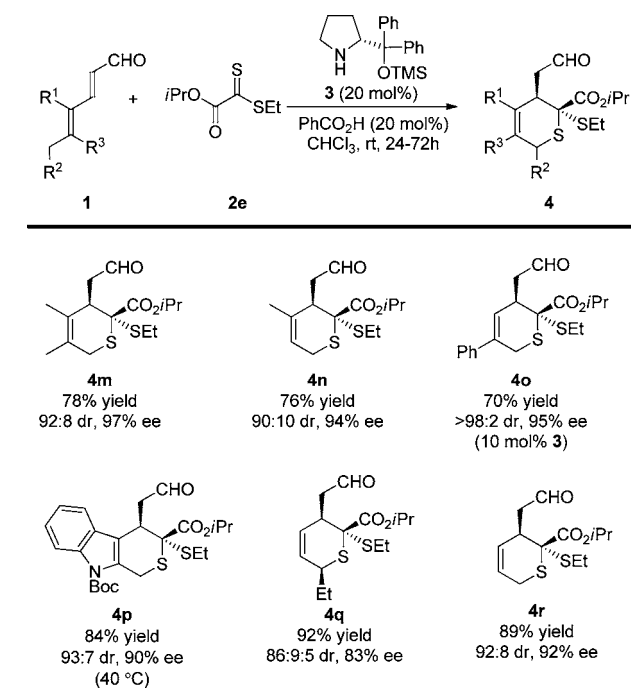
entry	2	EWG	R	yield (%) ^b	dr ^c	ee (%) ^d
1	2a	CO ₂ Bn	Et	4a – 93	94:6	89
2	2c	CO ₂ Bn	Me	4i – 73	92:8	84
3	2d	CO ₂ Bn	Bn	4j – 73	90:10	87
4	2e	CO ₂ iPr	Et	4k – 96	97:3	94
5	2f	COPh	Et	4l – 87	65:35	6/53

^aReactions were performed with 0.1 mmol **1a**, 0.12 mmol **2**, 0.02 mmol **3**, and 0.02 mmol PhCO₂H in CHCl₃. ^bYields of isolated products. ^cDetermined by ¹H NMR on the crude reaction mixture. ^dDetermined by chiral UPC².

were tested and the results are summarized in Table 2. Altering the size of R substituent on the thioester affected the enantioselectivity of the reaction (compare entries 1–3). This effect is anticipated, since the R group clashes with the OTMS group of the catalyst when the thiocarbonyl approaches from the disfavored face (see **TS₁-DF**). By exchanging the ethyl group with a smaller methyl group, a 5% loss of enantioselectivity was observed, while substituting with a larger Bn group only had minor effects. To our delight, further improvement of the selectivities could be achieved by employing a more bulky *i*Pr-ester as the EWG. As result, the cycloadduct **4k** was formed in 97:3 dr and 94% ee at rt. Surprisingly, by exchanging the ester moiety on the dithioester with an phenyl ketone a disappointing 65:35 dr was obtained. More importantly, the formation of **4l** proceeded with almost no (or poor) enantioselectivities for the diastereomeric pair. This dramatic decrease in selectivities can presumably be rationalized by the conformation adopted by **2f**. In order to minimize steric clashes between the Ar–H with the sulfur atoms, the C=O and S=O groups are forced to be oriented close to perpendicularity. The resulting O–C–S dihedral angle is significantly different from those estimated for **2a–e**, which may influence the approach of **2f** to the catalyst-bound trienamine. Finally, the optimized dithioester **2e** was evaluated under standard reaction conditions with several dienals. In all except one case (**4q**), a general trend of similar or improved selectivities was observed (compared to the use of **2a**). The results are summarized in Scheme 2.

The absolute configuration of the dihydrothiopyrane **4k** was unambiguously established to be (2*S*,3*R*) by X-ray crystallography (Figure 9).¹⁸ The configurations of the remaining products **4** were assigned by analogy.

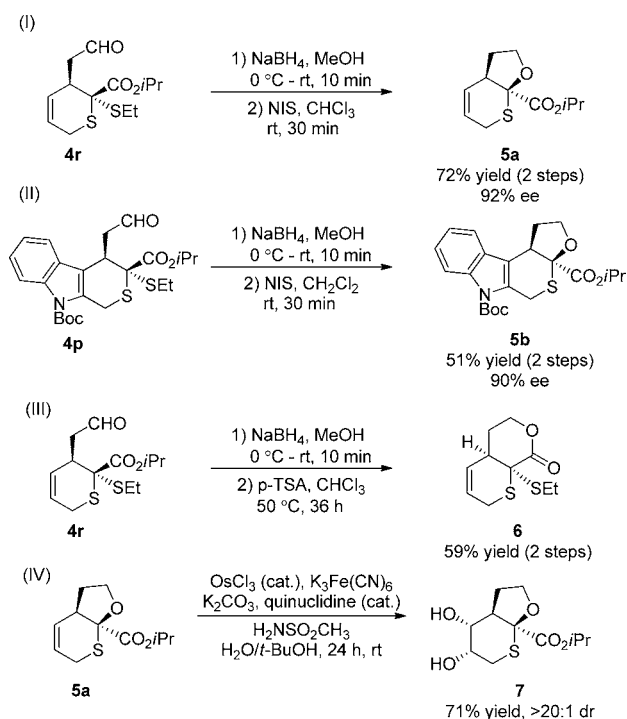
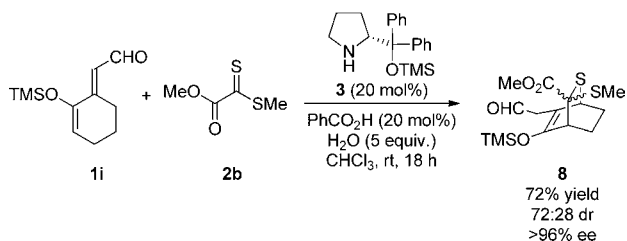
Synthetic Transformations of the Chiral Products. The obtained highly enantioenriched thioheterocycles readily engage in straightforward synthetic manipulations, which allow the access to more complex sulfur-containing chiral molecules. Two cyclization strategies affording products of different ring sizes are demonstrated in Scheme 3. Upon reduction of the aldehyde functionality in **4r** to the corresponding alcohol, the subsequent addition of *N*-iodosuccinimide triggered a rapid O-cyclization to furnish the bicycle **5a** in 92% ee as a single diastereomer (Scheme 3, eq I). Using the same setup and by employing the indole-based

Scheme 2. Extended Scope of the Asymmetric Aminocatalytic Thio-Diels-Alder Reaction**Figure 9. X-ray structure of compound 4k.**

compound **4p** as starting material, the tetracyclic compound **5b** could be afforded (Scheme 3, eq II). Alternatively, an intramolecular lactonization can be promoted by treating the corresponding alcohol of **4r** with *p*-TSA. Noticeably, the sterically hindered *i*Pr-esters is readily transesterified at 50 °C in CHCl₃ to give the six-membered fused lactone product **6** in 59% yield over two steps (Scheme 3, eq III). The endocyclic double bonds in the obtained sulfur-based cycloadducts are useful handles for further functionalizations, as demonstrated for the formation of diol **7** by osmium-catalyzed dihydroxylation in 71% yield and >20:1 dr.

In order to access a broader scope of enantioenriched thioheterocycles, other strategies to generate catalyst-bound dienes for the desired asymmetric thio-Diels–Alder reactions were explored. Recently, our laboratory revealed that cyclic dienals, such as **1i**, were able to selectively react via catalyst-bound cross-trienamine species. We envisioned that this complementary aminocatalyzed cross-trienamine pathway might be compatible with the thio-Diels–Alder reaction. To our delight, such a strategy can be realized providing a facile route to sulfur-containing bridged bicycles. This was exemplified by the cycloaddition of **1i** with **2b** to form compound **8** in 72% yield, 72:28 dr, and >96% ee (Scheme 4). It should be noted that the addition of water had a decisive effect on the conversion of the reaction. Lower substrate

Scheme 3. Synthetic Transformations of the Enantioenriched Sulfur-Based Heterocycles

Scheme 4. Asymmetric thio-Diels-Alder reaction via a *in-situ* generated cross-conjugated trienamine

turnover was observed in the absence of additional water, presumably due to the collapse of a possible zwitterionic species on the iminium ion leading to catalyst inhibition.

CONCLUSIONS

In conclusion, we have reported a new route to access highly enantioenriched sulfur-based heterocycles by asymmetric catalysis. Thiocarbonyls have been challenging substrates in enantioselective Diels–Alder reactions, due to their inherent high reactivity and their lack of ability to coordinate to chiral catalysts. We successfully circumvented these problems by employing a different strategy, which is based on the use of *in situ* generated catalyst-bound dienes. In the presence of a chiral aminocatalyst, otherwise inert substrates are transformed into active reactants, which readily undergo stereocontrolled thio-Diels–Alder reactions with the reactive thiocarbonyls. Synthetically useful dihydrothiopyrans as well as other bi- and tricyclic sulfur-containing heterocycles are formed in high yields and high to excellent selectivities with up to 97% ee. DFT calculations were performed to examine the mechanism of the developed reaction, which is believed to proceed via a stepwise mechanism involving zwitterionic intermediates. The regio- and the diastereoselectivity of the reaction were also

explained based on the findings of our computational study. Finally, several synthetic transformations of the optically active sulfur-based heterocycles are presented affording complex sulfur-containing chiral molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, computational details, NMR spectra, chiral UPC² traces, and complete ref 11. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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