CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Lewis Base/Brønsted Acid Co-catalyzed Asymmetric Thiolation of Alkenes with Acid-Controlled Divergent Regioselectivity

Authors: Hui-Yun Luo, Jia-Wei Dong, Yu-Yang Xie, Xu-Feng Song, Deng Zhu, Tong-Mei Ding, Yuanyuan Liu, and Zhi-Min Chen

To be cited as: *Chem. Eur. J.* 10.1002/chem.201904028

Link to VoR: http://dx.doi.org/10.1002/chem.201904028

Supported by
ACES

WILEY-VCH

10.1002/chem.201904028

WILEY-VCH

Lewis Base/Brønsted Acid Co-catalyzed Asymmetric Thiolation of Alkenes with Acid-Controlled Divergent Regioselectivity

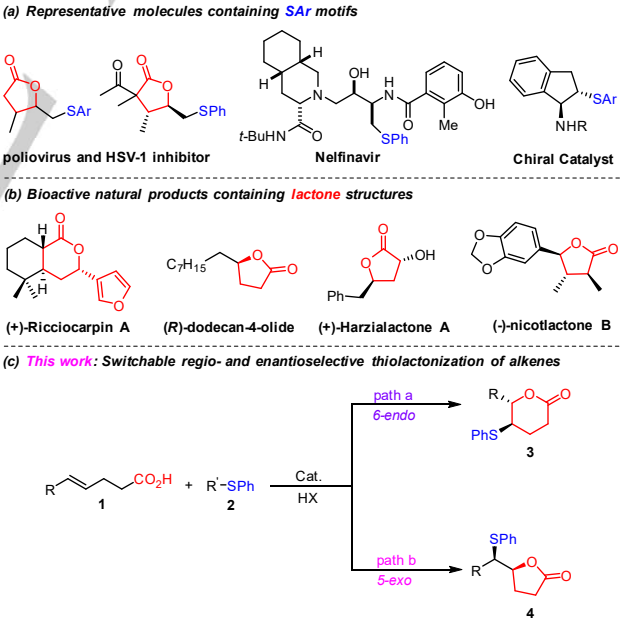
Hui-Yun Luo,[a] Jia-Wei Dong,[a] Yu-Yang Xie,[a] Xu-Feng Song,[a] Deng Zhu,[a] Tongmei Ding,[a] Yuanyuan Liu,*[b] and Zhi-Min Chen*[a]

Abstract: A divergent strategy for the facile preparation of various enantioenriched phenylthio-substituted lactones was developed based on Lewis base/Brønsted acid co-catalyzed thiolation of homoallylic acids. The acid-controlled regiodivergent cyclization (6-*endo* vs 5-*exo*) and acid-mediated stereoselective rearrangement of phenylthio-substituted lactones were explored. Experimental and computational studies were performed to clarify the origins of the regioselectivity and enantioselectivity. The calculation results suggest that C–O and C–S bond formation might occur simultaneously, without formation of a commonly supposed catalyst-coordianted thiiranium ion intermediate and the potential *π–π* stacking between substrate and SPh as an important factor in the enantiodetermining step. Finally, this methodology was applied in the rapid syntheses of bioactive natural products (+)-ricciocarpin A and (*R*)-dodecan-4-olide.

Introduction

The development of a modular and convenient method for the formation of structurally and selectively (chemo, regio, diastereo, and enantio) divergent compounds (divergent synthesis strategy) is a major goal in modern organic synthesis.[1] Various efforts to develop this strategy have been made and a number of successful examples have been reported, mainly catalyst-controlled, ligand-controlled, solvent-controlled, additive-controlled, and temperature-controlled processes.[2] Despite these advances, catalytic asymmetric versions are relatively rare and further development of enantioselective divergent synthesis strategies for the synthesis of a library of biologically relevant isomers is still highly desirable and challenging.[3,4]

Cyclization reactions are direct and powerful tools for accessing complex and divergent compounds.[5] For example, there are two possible pathways (6-*endo* vs 5-*exo*) for the SAr electrophile-promoted cyclization of homoallylic acid **1**, which could produce functionalized δ-valerolactone **3** and γ-butyrolactone **4**, respectively (Scheme 1c). SAr groups are a ubiquitous scaffold in many natural products, medicines, catalysts, and functional materials[6,7], which are readily transformed into useful sulfide and sulfone groups (Scheme 1a). Additionally, chiral lactones are important and useful compounds. They are not only widely present in natural products and drug molecules but are also a common and valuable class of synthetic intermediates (Scheme 1b).[8] However, to the best of our knowledge, no example of divergent enantioselective synthesis of the two products has been reported, although a series of studies of enantioselective electrophilic lactonizations[9] and sulfenylations of alkenes have been documented.[10,11] Our aim was therefore to achieve the divergent synthesis of the two products with excellent regio- and enantio-selectivities by changing some of the reaction parameters, and to clarify the origins of the regio- and enantio-selectivities.



Scheme 1. Divergent Enantioselective Synthesis of Chiral Functionalized Lactones.

Herein, we report the successful development of catalytic regio- and enantio-selective thiolactonizations of a variety of homoallylic acid derivatives with different electrophilic SAr reagents (Scheme 1c). This method offers a versatile approach to divergent synthesis of enantiomerically enriched phenylthio-substituted lactones. The regiodivergent catalytic production of

[a] H. Y. Luo,+ J. W. Dong, Y. Y. Xie, X. F. Song, D. Zhu, T. Ding, Prof. Dr. Z. M. Chen*
Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240, (P. R. China)
E-mail: chenzhimin221@sjtu.edu.cn
[b] Prof. Dr. Y. Y. Liu*
School of Chemistry and Molecular Engineering
East China Normal University
500 Dongchuan Road, Shanghai 200241, (P. R. China)
E-mail: yyliu@chem.ecnu.edu.cn
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:

6-*endo* or 5-*exo* cyclization products was achieved by changing the amount of Brønsted acid. Furthermore, the origins of the regio- and enantio-selectivities were explored by additional controlling experiments and density functional theory calculations. The practicality of this transformation was demonstrated by the concise synthesis of (+)-ricciocarpin A and (*R*)-dodecan-4-olide.

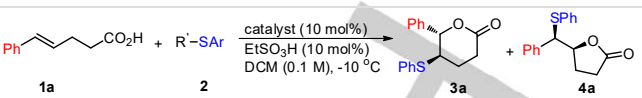
Results and Discussion

Optimization Studies

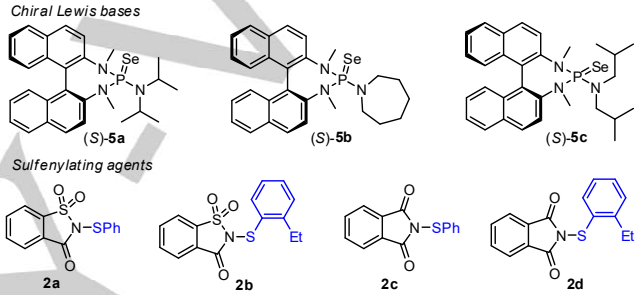
Initially, (*E*)-5-phenylpent-4-enoic acid (**1a**) was selected as the model substrate. After preliminary screening, the 6-*endo* cyclization product **3a** was obtained in 92% yield with excellent regio- and enantio-selectivities by using highly active N-phenylthiosaccharin (**2a**) as the sulfenylating agent, chiral BINOL-derived selenide (*S*)-**5a** as the Lewis base, $EtSO_3H$ (0.1 equiv) as the Brønsted acid, and CH_2Cl_2 as the solvent at −10 °C (Table 1, entry 1). Replacing Lewis base **5a** with **5b** led to reduction in the yield and enantioselectivity, whereas using **5c** slightly affected the result (entries 2 and 3). Almost no reaction occurred when N-phenylthiophthalimide (**2c**) was used instead of **2a** (entry 4). It was found that Lewis base and Brønsted acid are indispensable in this reaction. Without adding an acid, the 6-*endo* product was only obtained in 21% yield with 76% ee (entry 5). The mixture of **3a** and **4a** (**3a**:**4a** = 2.5:1, 39% yield) was observed when chiral Lewis base was not performed (entry 6). Use of the chiral selenide (*S*)-**5a** and $EtSO_3H$ (0.1 equiv) gave the best enantioselectivity, with excellent regioselectivity (dr > 99:1), and a good yield. The conditions in entry 1 were therefore identified as the optimum conditions for 6-*endo* cyclization.

We then identified suitable conditions for the preparation of enantiomerically enriched 5-*exo* cyclization products. Considering Brønsted acid as an important element, we first used CF_3SO_3H instead of $EtSO_3H$ as the acid with **2a** and **2c**, respectively. To our delight, the 5-*exo* cyclization product **4a** was generated in 78% yield with 84% ee using **2c** as the sulfenylating agent. However, **3a** was still obtained using **2a** (entries 7 and 8). The results indicate that the regioselectivity may be controlled by the acidity of system or sulfenylating agent. Next, 1.0 equiv of $EtSO_3H$ was used. It was found that the use of **2c** afforded the desired 5-*exo* cyclization product **4a** with 86% ee (entry 9). Meanwhile, the racemic 5-*exo* cyclization product **4a** was generated in quantitative yield using **2a** (entry 10). We reasoned that the racemic back-ground reaction was clearly promoted but the catalytic asymmetric process was completely suppressed in the presence of stoichiometric amounts of $EtSO_3H$ and N-phenylthiosaccharin (**2a**). Hence, the acidity of system is a controlling element. With the aim of improving the enantioselectivity and controlling regioselectivity, a careful survey of other chiral selenide catalysts for this cyclization process was conducted, but no better outcome was obtained (entries 11 and 12). To our satisfaction, the enantioselectivity increased to 92% ee when the sulfenylating agent **2d**, which has lower activity and greater steric hindrance, was used (entry 13).

Table 1. Optimization Studies[a].



entry	catalyst	*SAr agent	product	% yield	er
1	***(S)*-5a**	**2a**	**3a:4a>99:1**	**92**	**96:4**
2	*(S)*-**5b**	**2a**	**3a**:**4a**>99:1	11	84:16
3	*(S)*-**5c**	**2a**	**3a**:**4a**>99:1	92	96:4
4	*(S)*-**5a**	**2c**	-	-	-
5[b]	*(S)*-**5a**	**2a**	**3a**:**4a**>99:1	21	88:12
6		**2a**	**3a**:**4a**=2.5:1	39	50:50
7[c]	*(S)*-**5a**	**2a**	**3a**:**4a**>99:1	82	93:7
8[c]	*(S)*-**5a**	**2c**	**3a**:**4a**=1:28	78	92:8
9[d]	*(S)*-**5a**	**2c**	**3a**:**4a**=1:86	92	93:7
10[d]	*(S)*-**5a**	**2a**	**3a**:**4a**<1:99	99	50:50
11[d]	*(S)*-**5b**	**2c**	**3a**:**4a**=1:61	92	89:11
12[d]	*(S)*-**5c**	**2c**	**3a**:**4a**<1:99	97	88:12
13[d]	***(S)*-5a**	**2d**	**3aa:4aa<1:99**	**90**	**96:4**



[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.12 mmol), Lewis base (10 mol%), and acid (10 mol%) in CH_2Cl_2 (1.0 mL); stirred for 24 h at −10 °C under Ar; all yields are isolated yields. Chiral HPLC was used to determine ee values. [b] Without adding $EtSO_3H$. [c] CF_3SO_3H (0.1 equiv) was added instead of $EtSO_3H$. [d] $EtSO_3H$ (1.0 equiv) was added and the reaction was conducted at −5 °C.

Substrate Scope of 6-*endo* Cyclization

With the optimized conditions in hand, the scope of the 6-*endo* cyclization was investigated with a broad range of alkene derivatives. In general, the desired phenylthio-substituted δ-valerolactones were obtained with excellent enantiomeric excesses and moderate to excellent yields (Table 2). The 6-*endo* to 5-*exo* selectivity was greater than 99:1 when styrene-based carboxylic acids were used as the substrates. Electron-withdrawing substituents at the para position of the phenyl group (**3e**, **3f**) decreased the reactivity and enantioselectivity compared with those achieved with the model substrate **1a**. The absolute configuration of **3e** was confirmed by X-ray crystallography.[12] The substituent position affected the enantiomeric excess. A fluorine group at the para position was well tolerated, but a fluorine substituent at the *meta* or *ortho* position decreased the enantioselectivity (**3d**, **3g**, **3h**). Multi-substituted styrene was successfully transformed and provided the desired product **3i** in 87% yield and with 88% ee. 2-Naphthyl, 2-thienyl and 3-furyl derivatives all reacted well and gave the corresponding products with 95%, 94%, and 94% ee, respectively (**3j–l**). An ethynylbenzene-substituted alkene was also used as the substrate in this protocol, and the desired product **3m** was obtained with good enantioselectivity, although the yield was relatively low (42%). Various unbiased alkyl-substituted alkenes

were also subjected to this reaction. The yields and enantioselectivities were excellent but the regioselectivities were unsatisfactory (**3n–r**). As expected, only the 5-*exo* cyclization product was obtained, in 99% yield and with 96% ee, when a terminal alkene reacted with a sulfenylating agent with a bulky substituent (**4q**). Finally, the reaction of **1a** with **2d** under the standard reaction conditions gave the corresponding product **3aa** in 80% yield and with 92% ee. The practicability of this method was evaluated by performing 6-*endo* lactonization of **1a** on a 1 g scale. Product **3a** was delivered in 92% yield and with 90% ee.

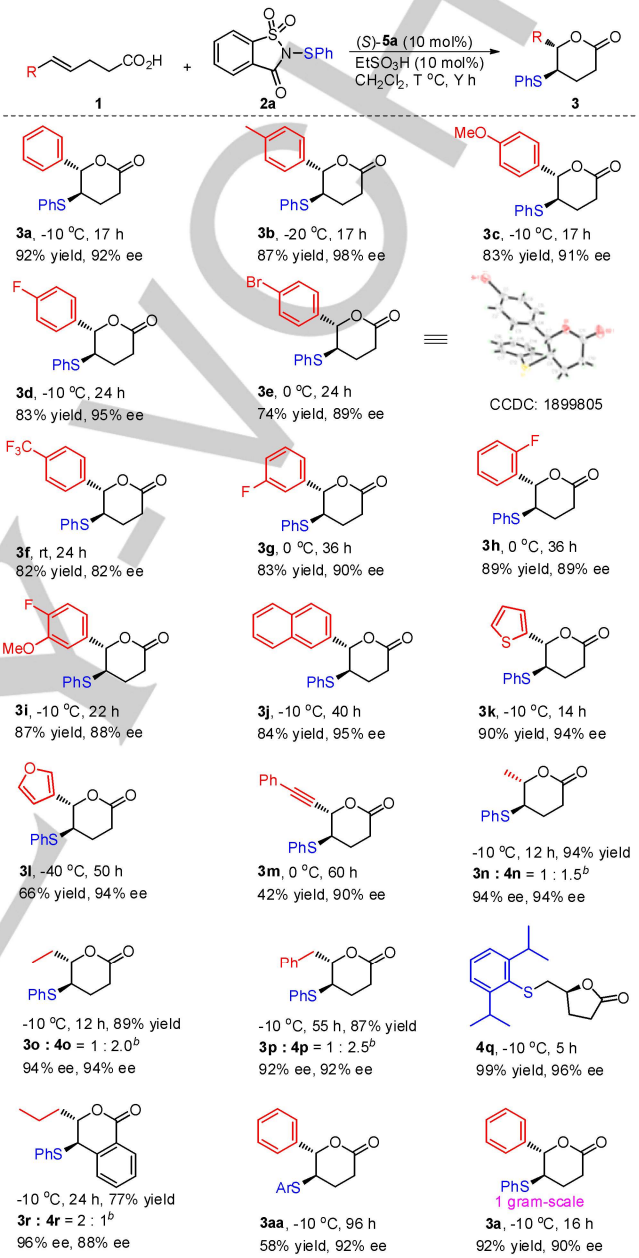
Substrate Scope of 5-*exo* Cyclization

Next, we used the optimum reaction conditions for 5-*exo* cyclization for exploring the use of a number of unsaturated carboxylic acids and different sulfenylating agents to evaluate the generality of this method. In all cases, the desired products were obtained with excellent regioselectivities and good to excellent enantioselectivities. The data in Table 3 show that styrenes with methyl and fluorine groups at any position were all incorporated, and yielded the phenylthio-substituted γ-butyrolactones in good yields and with high levels of enantioselectivity. However, a methoxy substituent at the *para* position of the aryl group decreased the ee value (**4aa–hh**). A multi-substituted substrate and a 2-naphthyl-substituted substrate also reacted smoothly to give products with 89% ee and 86% ee, respectively (**4ii** and **jj**). An ethynylbenzene-substituted alkene was not well tolerated and afforded the corresponding product **4mm** in 30% yield with 80% ee. Unbiased alkyl-substituted alkenes were suitable for this transformation and the desired products were obtained with excellent enantioselectivities. Inspired by these results, we used **2c** as the sulfenylating agent for alkyl-substituted substrates and the corresponding products were also obtained with high efficiency and ee values. A methyl substituent at the *ortho* position of the aryl ring of the sulfenylating agent was a viable choice for this reaction (see the Supporting Information). The absolute configuration of the 5-*exo* products was determined by X-ray crystallographic analysis of the sulfone derivative of **4dd**.[12]

DFT Calculations

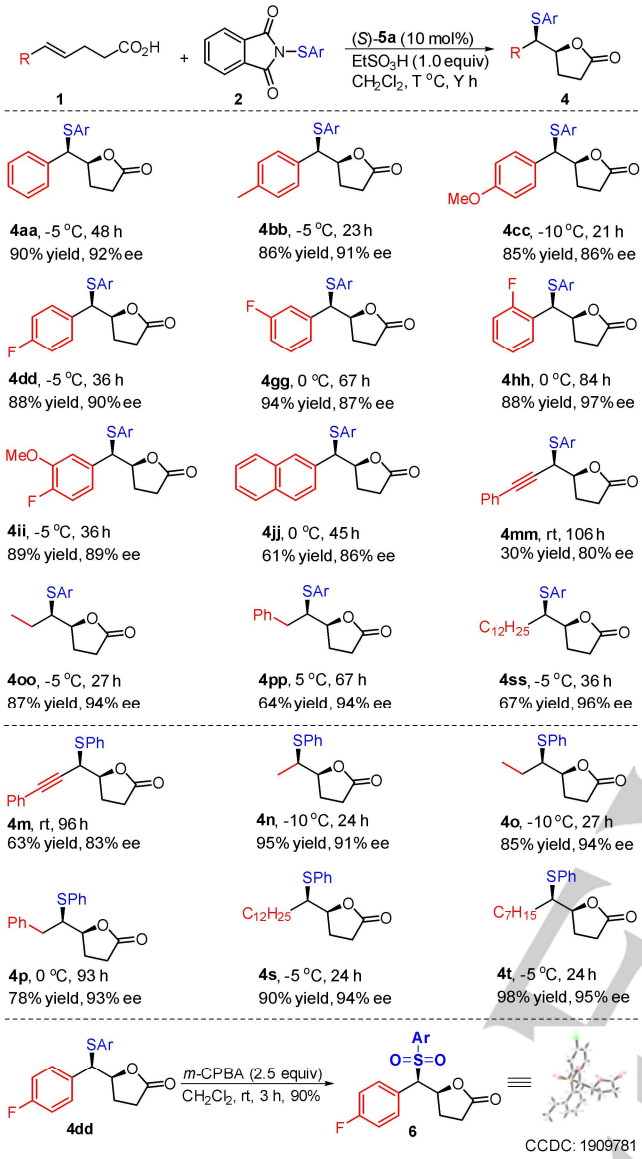
With the above experimental results in hand, DFT calculations were performed (see the Supporting Information for details) to clarify the mechanisms of enantioselectivity and regioselectivity. Substrate **1a** with a phenyl group and **1n** with a methyl group were used as model substrates. All the structures were fully optimized at the MN15/6-31G(d)+DCM (IEF-PCM) // MN15/6-311G(d,p)+DCM (IEF-PCM) level. The accurecy of computational results was valued by comparing with the free energies of M06-2x and M06-2x-d3 functional for SP correction. Though M06-2x-d3 functional is better in the case of **1a**, it works far from satisfaction in the case of **1n**. Thus, MN15 functional was used to study this reaction system for the good compatibility of both aryl and alkyl substituted substrates. Relative energies are expressed in terms of free energy. Energies are given in kilocalories per mole and distances are given in angstroms.

Table 2. Substrate Scope of Enantioselective 6-*endo* Thiolactonization[a].

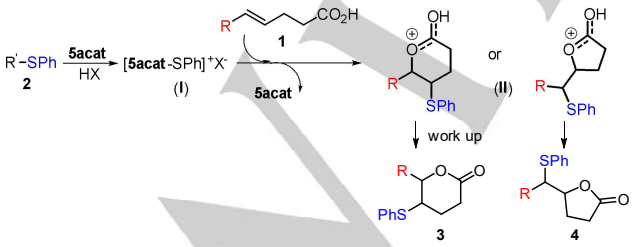


[a] Reaction conditions: alkene acid (0.1 mmol), **2a** (0.12 mmol), (*S*)-**5a** (10 mol%), and $EtSO_3H$ (10 mol%) in CH_2Cl_2 (1.0 mL) under Ar; the isolated yields obtained at specified reaction time and temperature are given. Chiral HPLC and SFC were used to determine ee values. [b]The ratio was determined by crude ^1H NMR spectroscopy. [c] Ar = 2-EtC_6H_4.

Table 3. Substrate Scope of Enantioselective 5-*exo* Thiolactonizationa[a].



[a] Reaction conditions: alkene acid (0.1 mmol), **2c** or **2d** (0.12 mmol), (*S*)-**5a** (10 mol%), and $EtSO_3H$ (1.0 equiv) in CH_2Cl_2 (1.0 mL) under Ar; isolated yields obtained at specified reaction time and temperature are shown. Chiral HPLC and SFC were used to determine ee values. Ar = 2-EtC_6H_4.



Scheme 2. Proposed Catalytic Pathways.

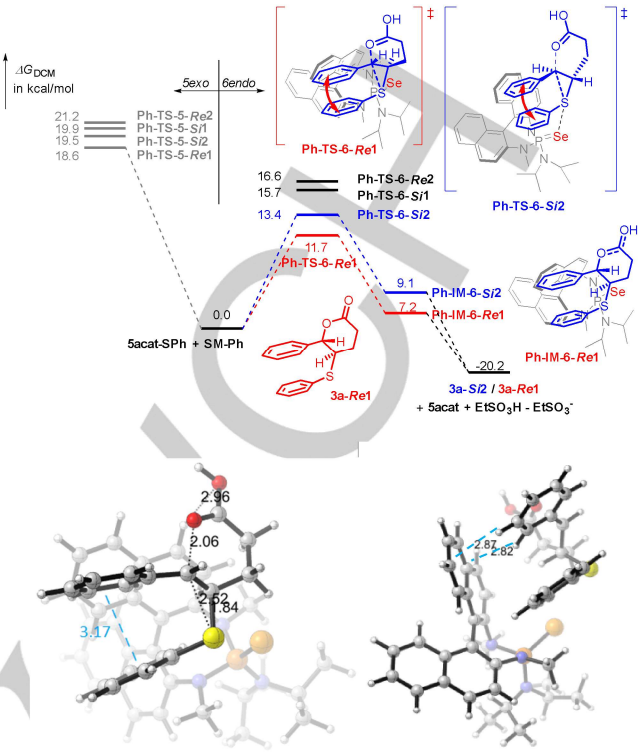


Figure 1. Possible pathways for generating **3a** and computed structure of **Ph-TS-6-*Re*1**.

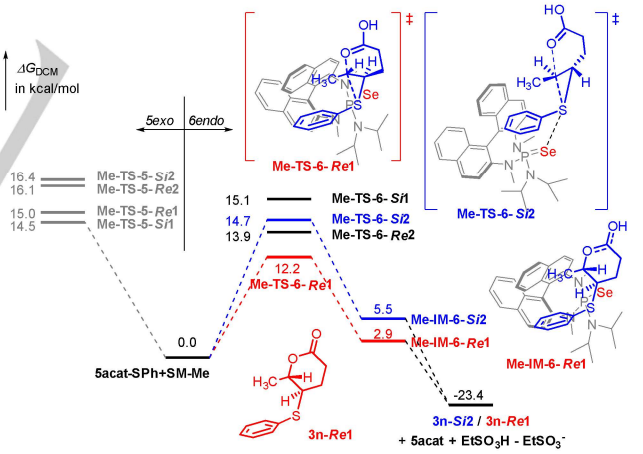


Figure 2. Possible pathways for generating **3n**.

There are eight possible pathways. Four of these create six-membered-ring products **3** (the C1-symmetric prochiral **1** can attack the complex **5acat-SPh** via both the Re face and *Si* faces, and the phenyl group of **1** can be distant from or near the complex **5acat-SPh**). The other four possible pathways give the five-membered-ring products **4**. Consideration of the proposed catalytic pathway for Lewis base-catalyzed thiolactonization of alkenes to give sulfenylated lactones suggests that the activated catalytic complex **[5acat-SPh]$^+$X$^-$ (I)** is generated initially and

subsequent reaction with **1** forms oxocarbenium ion (**II**) (Scheme 2).

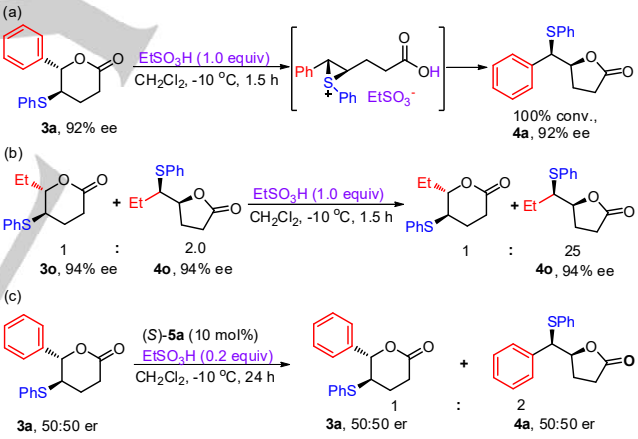
The possible pathways for generating the 6-*endo* product **3a** and the computed structure of **Ph-TS-6-*Re*1** are shown in Figure 1. The free energy of the transition state involved in generation of the 5-*exo* product **4a** and that involved in generation of the 6-*endo* product **3a** were compared. The energy of **Ph-TS-5-*Re*1** (18.6 kcal/mol), the lowest transition state for 5-*exo* product formation, was calculated to be near 7 kcal/mol higher than that of **Ph-TS-6-*Re*1** (11.7 kcal/mol) in the pathways that give the 6-*endo* product **3a**. In chemical terms, this means that construction of the 6-*endo* product in the reaction system is easier than construction of the 5-*exo* product in this catalytic system. The high barrier of 7 kcal/mol blocks the pathways that yield the 5-*exo* product and the reaction proceeds in a highly regioselective manner to afford the corresponding 6-*endo* product **3a**. This is supported by the results of experimental investigations. The enantioselectivity for the 6-*endo* product **3a** was explored for all four transition states with highly asymmetric structures. The transition states **Ph-TS-6-*Re*1** and **Ph-TS-6-*Re*2** would lead to product (5*R*,6*S*)-**3a**, whereas **Ph-TS-6-Si1** and **Ph-TS-6-*Si*2** would lead to (5*S*,6*R*)-**3a**. In this transformation, the two most stable transition states (**Ph-TS-6-*Re*1** and **Ph-TS-6-*Si*2**) show *π*–*π* stacking between alkene **1a** and SPh,[13] but such interactions are not present in the other two transition states (**Ph-TS-6-*Si*1** and **Ph-TS-6-*Re*2**). The difference between the calculated free energies of the most stable transition states (**Ph-TS-6-*Re*1** and **Ph-TS-6-*Si*2**) is 1.7 kcal/mol, which agrees with the experimental enantioselective outcome (92% ee, $\Delta\Delta G^{exp}$ = 1.9 kcal/mol). In the transition state **Ph-TS-6-*Re*1**, alkene **1a** finds the right configuration to fit the catalyst hole, and interacts weakly via O•••H–C and C(phenyl)–H•••*π* bonding with the naphthalene C–H and naphthalene ring of catalyst **5a**. This assists discrimination between the two transition states, which leads to high stereoselectivity. Our calculation results suggest that C–O and C–S bond formation might occur simultaneously, without formation of a stable **5a**-coordianted thiiranium ion intermediate, similarly to the case of sulfenylation of ketone-derived enoxysilanes, which was reported by Denmark.[10e]

Similarly to **1a**, the possible pathways for generating the 6-*endo* product **3n** and 5-*exo* product **4n** were computed; the results are shown in Figure 2. The enantioselectivity (94% ee, $\Delta\Delta G^{exp}$ = 2.0 kcal/mol) for the 6-*endo* product **3n** was determined from the difference between the free energies of transition states **Me-TS-6-*Re*1** and **Me-TS-6-*Si*2**, which is 2.5 kcal/mol. As in the case of **1a**, the calculated results with alkene **1n** for the corresponding pathways that generate **4n** during the reactions with catalyst (*S*)-**5a** have energy barriers 2.3 kcal/mol higher than those of the transition states that generate **3n** (Figure 2). This means that the 5-*exo* product **4n** could not be obtained directly via these pathways, and **4n** is generated via other pathways.

Kinetic Control Experiments

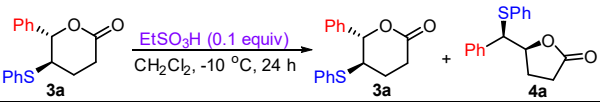
Based on the above results and previous works,[14] we assumed that the two cyclization products can isomerize and the kinetically favored cyclization product could rearrange to the corresponding thermodynamically favored product under suitable reaction conditions. Preliminary kinetic control experiments were therefore performed to acquire mechanistic information on this reaction. When the isolated chiral 6-*endo* product **3a** (92% ee) was treated with 1.0 equiv of $EtSO_3H$ at −10 °C, the corresponding 5-*exo* product **4a** was obtained; it retained its enantioselectivity after 1.5 h (Scheme 3a). A mixture of **3o** and **4o** (1:2.0) was also subjected to the above conditions. The 5-*exo* product **4o** was obtained with retained ee (Scheme 3b). These results indicate that the 6-*endo* product can isomerize to the 5-*exo* product, which is a thermodynamic product, through a configurationally stable thiiranium intermediate under strongly acidic conditions. As shown in Scheme 3c, the outcome suggests that the catalyst (*S*)-**5a** will not participate in the formation of a thiiranium intermediate.

The isomerization process was studied in more detail to gain further insights into the reaction mechanisms (Tables 4 and 5). The ratio of the isomerization products clearly decreased when 0.1 equiv of $EtSO_3H$ was used instead of 1.0 equiv (Table 4, entry 1). The isomerization process was further inhibited by the presence of saccharin (entry 2). The 6-*endo* product **3a** could not be converted to the 5-*exo* product **4a** when 1.2 equiv of saccharin and 0.1 equiv of **5a** were added to the system (entry 3). δ-Valerolactone **3a** was also subjected to the simulated 6-*endo* cyclization conditions and was still stable after 24 h (entry 4). The results of these control experiments indicate that saccharin, N-phenylthiosaccharin, and catalyst **5a** can function as Brønsted bases and inhibit acid-catalyzed isomerization. In contrast, **3a** can be fully converted to **4a** under the simulated 5-*exo* cyclization conditions (entry 5). We also found that **3a** was fully isomerized to **4a** when 0.1 equiv of CF_3SO_3H was used (entry 6). Next, a mixture of **3o** and **4o** (in a 1:2 ratio) was treated with $EtSO_3H$ (0.1 equiv) at −10 °C; **3o** slowly isomerized to **4o** (Table 5, entry 1). The ratio remained unchanged under the simulated 6-*endo* reaction conditions (entry 2). Finally, 5-*exo* product **4o** was also treated with 0.1 equiv of $EtSO_3H$ at −10 °C; **4o** was stable after 24 h.



Scheme 3. Isomerization Process.

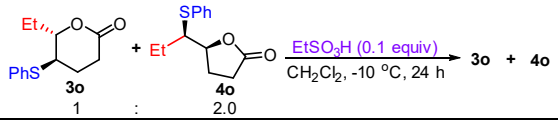
Table 4. Study of Isomerization of Product **3a** [a].

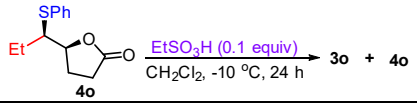


entry	variation from above conditions	3a:4a
1	none	1:3.2
2	adding 1.2 equiv saccharin	1:0.7
3	adding 1.2 equiv saccharin + 0.1 equiv (*S*)-**5a**	>99:1
4	adding 0.6 equiv saccharin and **2a** + 0.1 equiv (*S*)-**5a**	>99:1
5[b]	adding 0.6 equiv phthalimide and **2c** + 0.1 equiv (*S*)-**5a**	<1:99
6	0.1 equiv CF_3SO_3H instead of $EtSO_3H$	<1:99

[a] Each entry shows the ratio of two products, which were determined by crude ^{1}H NMR spectroscopy. [b]1.0 equiv of $EtSO_3H$ was added.

Table 5. Study of Isomerization of Product **3o** [a].



entry	variation from above conditions	3o:4o
1	none	1:3.0
2	adding 1.2 equiv saccharin + 0.1 equiv (*S*)-**5a**	1:2.0
3		0:100

[a] Each entry shows the ratio of the two products, which was determined by crude ^{1}H NMR spectroscopy.

In DFT studies, 5-*exo* product 4 was calculated more stable than 6-*endo* product **3** in both enthalpy and free energy. For instance, **4a-*Re*1** was calculated 2.2 kcal/mol more stable than **3a-*Re*1** in enthalpy and 3.3 kcal/mol in free energy. Similarly, **4n-*Re*1** was calculated 3.4 kcal/mol more stable than **3n-*Re*1** in enthalpy and 3.5 kcal/mol in free energy. The above results of kinetic control experiments, and the observation that the same ee values were obtained for products **3** and **4** when an additional quantity of $EtSO_3H$ was added, assume that the two cyclization products isomerize via an intermediate thiiranium ion and the kinetically favored cyclization product **3** can rearrange to the corresponding thermodynamically favored product **4** under suitable reaction conditions, with retention of configuration. Next, the pathways that generate the 6-*endo* product **3** and 5-*exo* product **4** from the intermediate thiiranium ion were calculated, with **1a** and **1n** as model substrates and *Re*-face attack (Figures 3 and 4). In the case of **1a**, the transition state for forming the 6-*endo* product **3a** (**TS-oniumS-6-Ph**) is 2.1 kcal/mol more stable than that for forming the 5-*exo* product **4a** (**TS-oniumS-5-Ph**). The free energy of the transition state for forming the 5-*exo* product **4n** (**TS-oniumS-5-Me**) is 2.2 kcal/mol lower than that for forming the 6-*endo* product **3n** (**TS-oniumS-6-Me**). These results suggest that if the thiiranium ion **oniumS-Ph-*Re*1** was formed under the 6-*endo* thiolactonization conditions by dissociation of catalyst **5a** from transition state **Ph-TS-6-*Re*1**, it would form **IM-oniumS-6-Ph** kinetically, followed by irreversible and immediate deprotonation by Brønsted bases in the catalytic system. This would make the thiolactonization irreversible and generate the 6-*endo* product **3a** as the kinetically favored product. Regardless of whether or not catalyst **5a** dissociates from **Ph-TS-6-*Re*1**, it will therefore always generate product **3a** rather than **4a**. However, if the thiiranium ion **oniumS-Me-*Re*1** was formed under the 6-*endo* thiolactonization conditions in a similar manner, this would irreversibly lead to the kinetic product **4n** via **IM-oniumS-5-Me**. The two pathways following transition state **Me-TS-6-*Re*1** will therefore result in two different regioselective thiolactonization products, i.e., **3n** and **4n**. However, if 1.0 equiv of $EtSO_3H$ is added under the thiolactonization conditions, an excess of strong acid can reversibly protonate products **3** and **4** to the intermediates **IM-oniumS-6** and **IM-oniumS-5**; as a result, all the 6-*endo* product **3** would rearrange to the thermodynamically favored product **4**.

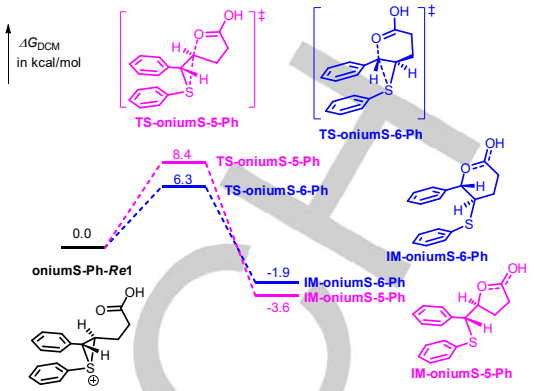


Figure 3. Possible pathways for rearrangement of **3a** to **4a** without catalyst **5a**.

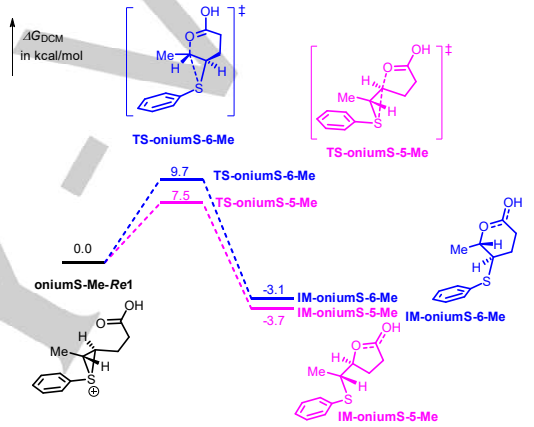
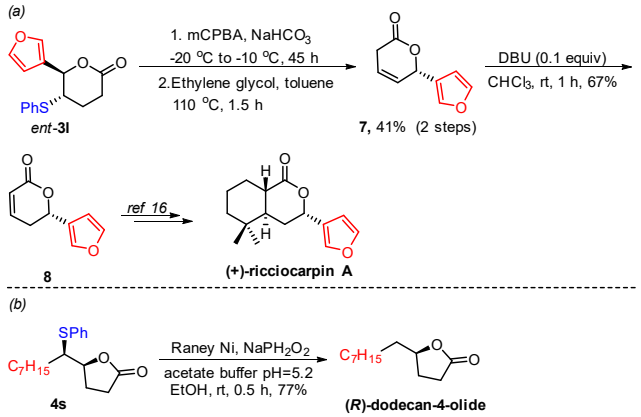


Figure 4. Possible pathways for rearrangement of **3n** to **4n** without catalyst **5a**.

Application to Synthesis of Natural Products

We achieved enantioselective synthesis of (+)-ricciocarpin A and (*R*)-Dodecan-4-olide from chiral phenylthio-substituted lactones to further demonstrate the synthetic utility of this method. Ricciocarpin A, which isolated from the liverwort *ricciocarpos natans*, shows good molluscicidal activity against the water snail biomphalaria glabrata.[15] The first enantioselective total synthesis of ricciocarpin A was reported by Metz group and compound **8** is the key intermediate.[16] We found that compound **8** could be readily prepared from product *ent*-**3l**. First, *ent*-**3l** which was obtained with 93% ee under standard conditions was oxidized to sulfoxide under 1.0 equiv of *m*-CPBA, which could be transformed to unsaturated ester **7** under thermal elimination reaction. Isomerization of **7** could afford the key intermediate **8** in 67% yield (Scheme 4a). (*R*)-Dodecan-4-olide has been isolated from a range of natural sources and plays an important role in a number of biological processes.[17] The reaction of product **4s** with Raney Ni and $NaPH_2O_2$ led to the formation of (*R*)-dodecan-4-olide in 77% yield and with ee retention (Scheme 4b).



Scheme 4. Synthetic Applications of Enantioenriched Sulfenylated Products.

Conclusion

In summary, we have developed a switchable, versatile, and modular method for the catalytic asymmetric thiolactonization of homoallylic acids with a chiral Lewis basic selenide and a Brønsted acid as the co-catalyst. This strategy enabled rapid formation of a broad range of enantioenriched γ-butyrolactones and δ-valerolactones with phenylthio groups. Switchable acid-controlled 6-*endo* and 5-*exo* regioselectivite processes were developed. The calculation results suggest that C–O and C–S bond formation might occur simultaneously, without formation of a stable **5a**-coordianted thiiranium ion intermediate. The acid-mediated stereoselective rearrangement of phenylthio-substituted lactones were explored. Finally, two bioactive natural products were obtained from the corresponding phenylthio-substituted lactones, which shows that these reactions are synthetically useful and valuable. Other divergent enantioselective synthesis strategies are under investigation by our group.

Computational methods

All DFT calculations were performed with the Gaussian 16 (Revision A.03) package[18] using the density functional theory method. Solution-phase relaxed PES scans and geometry optimizations of all the minima and transition states involved were carried out at the MN15[19]/6-31G(d)+DCM (IEF-PCM)[20] // MN15/6-311G(d,p)+DCM (IEF-PCM) level. The keyword "5D" was used to specify that five d-type orbitals were used for all elements in the calculations. Frequency calculations at the same level were performed to validate each structure as either a minimum or a transition state and to evaluate its zero-point energy and thermal corrections at 298 K. All discussed energies were Gibbs free energies unless otherwise specified. Enthalpies were also given for reference. 3D structure was prepared with CYLview.[21]

Experimental Section

Experimental details and spectra can be found in the Supporting Information. CCDC 1899805 and 1909781 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgements

This work was supported by NSFC (21871178, 21702135 and 21871088), and sponsored by "Chenguang Program" (16CG22) supported by Shanghai Education Development Foundation and Shanghai Municipal Education Commission. The computation was performed at ECNU Public Platform for Innovation (001). We gratefully thank Prof. Yong-Qiang Tu (Shanghai Jiao Tong University) for helpful suggestions and comments on this manuscript.

Conflict of interest

The authors declare no conflict of interest.

Keywords: Thiolation • Divergent synthesis • Functionalized lactone • Rearrangement • Computational study

[1] B. M. Trost, *Science*. **1983**, *219*, 245-250.
[2] For selected recent examples of stereodivergent synthesis, see: a) L.-Y. Mei, Y. Wei, X.-Y. Tang, M. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8131-8137; b) J.-Y. Liao, P.-L. Shao, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 628-631. c) J.-J. Feng, T.-Y. Lin, C.-Z. Zhu, H. Wang, H.-H. Wu, J. Zhang, *J. Am. Chem. Soc.* **2015**, *138*, 2178-2181; d) M. Wang, X. Zhang, Y.-X. Zhuang, Y.-H. Xu, T.-P. Loh, *J. Am. Chem. Soc.* **2015**, *137*, 1341-1347; e) X. Liu, X. Ye, F. Bureš, H. Liu, Z. Jiang, *Angew. Chem.* **2015**, *127*, 11605– 11609; *Angew. Chem. Int. Ed.* **2015**, *54*, 11443-11447; f) T.-R. Li, B.-Y. Cheng, Y.-N. Wang, M.-M. Zhang, L.-Q. Lu, W.-J. Xiao, *Angew. Chem.* **2016**, *128*, 12610– 12614; *Angew. Chem. Int. Ed.* **2016**, *55*, 12422-12426; g) H. Wang, Q. Lu, C. Qian, C. Liu, W. Liu, K. Chen, A. Lei, *Angew. Chem.* **2016**, *128*, 1106-1109; *Angew. Chem. Int. Ed.* **2016**, *55*, 1094-1097; h) M. Chaitanya, P. Anbarasan, *Org. Lett.* **2018**, *20*, 3362-3366.
[3] The reviews on divergent asymmetric synthesis, see: a) G. Zhan, W. Du, Y.-C. Chen, *Chem. Soc. Rev.* **2017**, *46*, 1675-1692; (b) L. L. Lin, X. M. Feng, *Chem.-Eur. J.* **2017**, *23*, 6464-6482.
[4] For selected recent examples, see: a) J. Lv, L. Zhang, Y. Zhou, Z. Nie, S. Luo, J.-P. Cheng, *Angew. Chem. Int. Ed.* **2011**, *50*, 6610-6614; b) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc.* **2014**, *136*, 11107-11114; c) B. Zhu, R. Lee, J. Li, X. Ye, S.-N. Hong, S. Qiu, M. L. Coote, Z. Jiang, *Angew. Chem.* **2016**, *128*, 1321– 1325; *Angew. Chem. Int. Ed.* **2016**, *55*, 1299-1303; d) Z. Zhou, Z.-X. Wang, Y.-C. Zhou, W. Xiao, Q. Ouyang, W. Du, Y.-C. Chen, *Nat. Chem.* **2017**, *9*, 590-594; e) C. Ma, T. Zhang, J.-Y. Zhou, G.-J. Mei, F. Shi, *Chem. Commun.* **2017**, *53*, 12124-12127; f) Y. Xu, Fe. Chang, W. Cao, X. Liu, X. Feng, *ACS Catal.* **2018**, *8*, 10261-10266; g) H.-K. Liu, S. R. Wang, X.-Y. Song, L.-P. Zhao, L. Wang, Y. Tang, *Angew. Chem.* **2019**, *131*, 4389– 4393; *Angew. Chem. Int. Ed.* **2019**, *58*, 4345-4349.
[5] A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703-4832.
[6] a) N. Gouault, M. David, J. F. Cupif, A. Sauleau, M. Amoros, *Pharm. Pharmacol. Commun.* **1999**, *5*, 159-163; b) O. Yonemitsu, J. Uenishi, N. Kobayashi, T. Sasaki, Y. Yamada, *Heterocycles*. **1997**, *44*, 277-287; c) J. A. Tobert, *Nat. Rev. Drug Discovery* **2003**, *2*, 517-526; d) R. Bandichhor, B. Nosse, O. Reiser, *Top. Curr. Chem.* **2005**, *243*, 43-72; e) T. Janecki, E. Błaszczyk, K. Studzian, A. Janecka, U. Krajewska, M. Różalski, *J. Med. Chem.* **2005**, *48*, 3516-3521; f) A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Álvarez, *Chem. Rev.* **2013**, *113*, 4567-4610; g) B.-F. Yan, S.-T. Fang, W.-Z. Li, S.-J. Liu, J.-H. Wang, C.-H. Xia, *Nat. Prod. Res.* **2015**, *29*, 2013-2017.
[7] a) L. A. Damani, *Sulphur-Containing Drugs and Related Organic Compounds*; Wiley: New York, 1989; b) M. R. Prinsep, *Stud. Nat. Prod. Chem.* **2003**, *28*, 617-715; c) M. Mellah, A. Voituriez, E. Schulz, *Chem. Rev.* **2007**, *107*, 5133-5209; d) M. Feng, B. Tang, S. H. Liang, X. Jiang, *Curr. Top. Med. Chemi.* **2016**, *16*, 1200-1216; e) S. Otocka, M. Kwiatkowska, L. Madalińska, P. Kiełbasiński, *Chem. Rev.* **2017**, *117*, 4147-4181.
[8] For selected recent other methods for constructing chiral organosulfur compounds, see: a) Z. Wang, F. K. Sheong, H. H. Y. Sung, I. D. Williams, Z. Lin, J. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 5895-5898; b) D. Qian, L. Wu, Z. Lin, J. Sun, *Nat. Comm.* **2017**, *8*, 567-576; c) D. Qian, M. Chen, A. C. Bissember, J. Sun, *Angew. Chem.* **2018**, *130*, 3825– 3828; *Angew. Chem. Int. Ed.* **2018**, *57*, 3763-3766; d) K. J. Hock, R. M. Koenigs, *Angew. Chem.*

2017, *129*, 13752– 13754; *Angew. Chem. Int. Ed.* **2017**, *56*, 13566-13568; e) X. Lin, Y. Tang, W. Yang, F. Tan, L. Lin, X. Liu, X. Feng, *J. Am. Chem. Soc.* **2018**, *140*, 3299-3305; f) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807-8864.

[9] S. E. Denmark, D. J. P. Kornfilt, T. Vogler, *J. Am. Chem. Soc.* **2011**, *133*, 15308-15311. In this paper, one substrate was shown and they got *5-exo* product with 82% ee.

[10] For selected recent examples, see: a) D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298-3300; b) X. Liu, R. An, X. Zhang, J. Luo, X. Zhao, *Angew. Chem. Int. Ed.* **2016**, *55*, 5846-5850; c) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 8069-8077.

[11] a) S. E. Denmark, A. Jaunet, *J. Am. Chem. Soc.* **2013**, *135*, 6419-6422; b) S. E. Denmark, H. M. Chi, *J. Am. Chem. Soc.* **2014**, *136*, 3655-3663; c) S. E. Denmark, S. Rossi, M. P. Webster, H. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 13016-13028; d) S. E. Denmark, H. M. Chi, *J. Am. Chem. Soc.* **2014**, *136*, 8915-8918; e) S. E. Denmark, E. Hartmann, D. J. P. Kornfilt, H. Wang, *Nat. Chem.* **2014**, *6*, 1056-1064; f) S. E. Denmark, A. Jaunet, *J. Org. Chem.* **2014**, *79*, 140-171; g) E. Hartmann, S. E. Denmark, *Helv. Chim. Acta.* **2017**, *100*, e1700158; h) S. E. Denmark, D. J. P. Kornfilt, *J. Org. Chem.* **2017**, *82*, 3192-3222; i) Z. Tao, K. A. Robb, K. Zhao, S. E. Denmark, *J. Am. Chem. Soc.* **2018**, *140*, 3569-3573; j) Z. Tao, K. A. Robb, J. L. Panger, S. E. Denmark, *J. Am. Chem. Soc.* **2018**, *140*, 15621-15625.

[12] a) N. J. Archer, C. M. Rayner, D. Bell, D. Miller, *Synlett* **1994**, *8*, 617-619; b) V. A. Soloshonok, D. J. Nelson, *Beilstein J. Org. Chem.* **2011**, *7*, 744-758; c) L. Li, Z. Li, D. Huang, H. Wang, Y. Shi, *RSC Adv.* **2013**, *3*, 4523-4525; d) J.-J. Wang, H. Yang, B.-B. Gou, L. Zhou, J. Chen, *J. Org. Chem.* **2018**, *83*, 4730-4738.

[13] CCDC 1899805 (**3e**) and 1909781 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] a) A. J. Neel, M. J. Hilton, M. S. Sigman, F. D. Toste, *Nature* **2017**, *543*, 637-646; b) M. Orlandi, J. A. S. Coelho, M. J. Hilton, F. D. Toste, M. S. Sigman, *J. Am. Chem. Soc.* **2017**, *139*, 6803-6806.

[15] a) H. Wang, D. Huang, D. Cheng, L. Li, Y. Shi, *Org. Lett.* **2011**, *13*, 1650-1653; b) H. Guan, H. Wang, D. Huang, Y. Shi, *Tetrahedron.* **2012**, *68*, 2728-2735.

[16] a) J. A. Tobert, *Nat. Rev. Drug Discovery* **2003**, *2*, 517-526; b) R. Bandichhor, B. Nosse, O. Reiser, *Top. Curr. Chem.* **2005**, *243*, 43-72; c) T. Janecki, E. Błaszczyk, K. Studzian, A. Janecka, U. Krajewska, M. Różalski, *J. Med. Chem.* **2005**, *48*, 3516-3521; d) A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Álvarez, *Chem. Rev.* **2013**, *113*, 4567-4610; e) B.-F. Yan, S.-T. Fang, W.-Z. Li, S.-J. Liu, J.-H. Wang, C.-H. Xia, *Nat. Prod. Res.* **2015**, *29*, 2013-2017.

[17] H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Lett.* **2013**, *15*, 4838-4841.

[18] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Jr. Montgomery, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, *Gaussian 16*, Revision A.03; Gaussian, Inc.: Wallingford CT, 2016.

[19] H. S. Yu, X. He, S. L. Li, D. G. Truhlar, *Chem. Sci.* **2016**, *7*, 5032-5051.

[20] a) B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *106*, 5151-5158; b) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995-2001.

[21] C. Y. Legault, *CYLview*, 1.0b; Université de Sherbrooke, **2009**. http://www.cylview.org.

10.1002/chem.201904028

WILEY-VCH

FULL PAPER

H. Y. Luo, J. W. Dong, Y. Y. Xie, X. F. Song, D. Zhu, T. M. Ding, Y. Y. Liu, and Z. M. Chen**

Lewis Base/Brønsted Acid Co-catalyzed Asymmetric Thiolation of Alkenes with Acid-Controlled Divergent Regioselectivity