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Lewis Base/Brønsted Acid Co-catalyzed Enantioselective Sulfenylation/Semipinacol Rearrangement of Di- and Tri-substituted Allylic Alcohols

Yu-Yang Xie,[a] Zhi-Min Chen,*[a] Hui-Yun Luo,[a] Hui Shao,[a] Yong-Qiang Tu,*[a,b] Xiaoguang Bao,*[c] Ren-Fei Cao,[a] Shu-Yu Zhang,[a] and Jin-Miao Tian[a]

Abstract: An enantioselective sulfenylation/semipinacol rearrangement of 1,1-disubstituted and tri-substituted allylic alcohols was accomplished under the co-catalysis of chiral Lewis base/chiral Brønsted acid, to generate various β-phenylthio ketones bearing an all-carbon quaternary center in moderate to excellent yields and excellent enantioselectivities. These chiral phenylthio ketone products are common intermediates with many applications, including the design of new chiral catalysts/ligands and the total synthesis of natural products. Computational studies (DFT calculations) were carried out to explain the origin of enantioselectivity and the role of chiral Brønsted acid. Additionally, the synthetic utility of this methodology was exemplified by an enantioselective total synthesis of (-)-herbertene and a one-pot synthesis of a chiral sulfoxide and sulfone.

Chiral organosulfur compounds are not only widely present in bioactive natural products and medicines,[1] but also play an important role in asymmetric catalysis as chiral catalysts/ligands, as well as in material science (Figure 1). [2] They are also versatile synthetic intermediates that are useful for numerous transformations in synthetic chemistry.[3] Accordingly, the development of synthetic methods to prepare such organosulfur compounds has attracted much attention and some enantioselective methodologies have been developed,[4] mainly including sulfur-nucleophile additions,[5] 2,3-sigmatropic rearrangements of sulfonium ylides,[6] and sulfenylation reactions[7]. Among them, catalytic enantioselective sulfenylation of alkenes provides a direct and indispensable strategy for the preparation of these compounds. In contrast to the comprehensive and intensive development of enantioselective

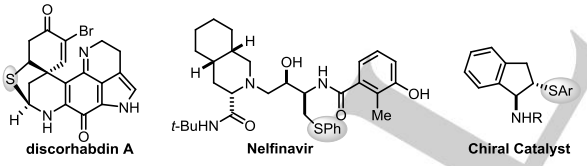

Figure 1. Representative examples of bioactive natural products, medicines and chiral catalysts containing sulfur group.

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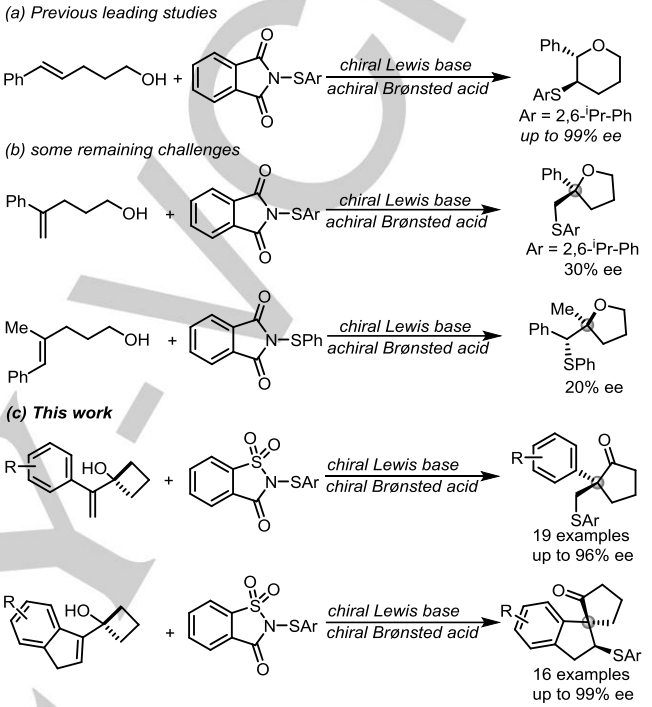
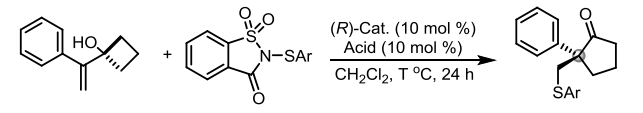


Scheme 1. Design of a catalytic enantioselective sulfenylation/semipinacol rearrangement of di- and tri-substituted allyl alcohols.

halogenations of alkenes during last decade,[8] there are few examples of catalytic asymmetric sulfenylations of alkenes and further development is necessary. Recently, some pioneering studies were reported by Denmark[9], Shi[10] and others[11]. Among them, the Denmark group reported the seminal studies on enantioselective sulfenylation of olefins, using a chiral Lewis base and an achiral Brønsted acid as co-catalysts (Scheme 1a). The Shi group made some noteworthy efforts on the catalytic asymmetric sulfenylation of alkenes using a chiral Brønsted acid as a catalyst. Despite these advances, catalytic enantioselective variants for constructing chiral sulfur-containing compounds are still limited in terms of reaction types and substrate scope. For example, because of the difficulty in discriminating between enantiotopic faces of 1,1-disubstituted and tri-substituted alkenes, sulfenylations of these two substrates to form quaternary stereocenters, which are prevalent in pharmaceuticals and natural products, give low enantioselectivity and remain synthetically challenging (Scheme 1b).[9a,h] The lack of development in this area inspired us to try and address these challenges with our sulfenylation/semipinacol rearrangement reaction.

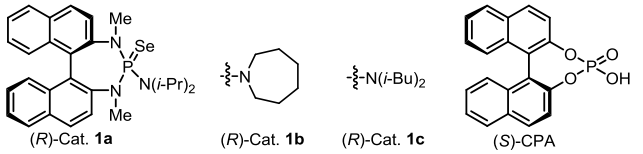
The semipinacol rearrangement of allylic alcohols has become a powerful strategy for the formation of a variety of β-functionalized carbonyl compounds with an α-quaternary carbon center.[12] Although numerous catalytic enantioselective variants have been documented,[13] to the best of our knowledge, no example of a catalytic asymmetric sulfenylation/semipinacol rearrangement reaction of allylic alcohols has been reported.[14]

Table 1. Optimization of the enantioselective reaction.[a]



3a **2a:** Ar = Ph **2b:** Ar = 2-Me-C_6H_4 **4**

entry	Cat.	$^+$SAr	acid	T (°C)	yield (%)[b]	ee (%)[c]
1	**1a**	**2a**	-	r.t	15	9
2	**1a**	**2a**	MeSO3H	-5	53	69
3	**1a**	**2a**	EtSO3H	-5	58	71
4	**1a**	**2a**	(*S*)-CPA	-5	70	85
5	**1a**	**2a**	(*R*)-CPA	-5	76	74
6	**1b**	**2a**	(*S*)-CPA	-5	65	57
7	**1c**	**2a**	(*S*)-CPA	-5	64	85
8	-	**2a**	(*S*)-CPA	-5	5	3
9	**1a**	**2b**	(*S*)-CPA	-5	73	94
10	**1a**	**2b**	**(*S*)-CPA**	**0**	**80**	**94**
11[d]	**1a**	**2b**	(*S*)-CPA	0	57	89



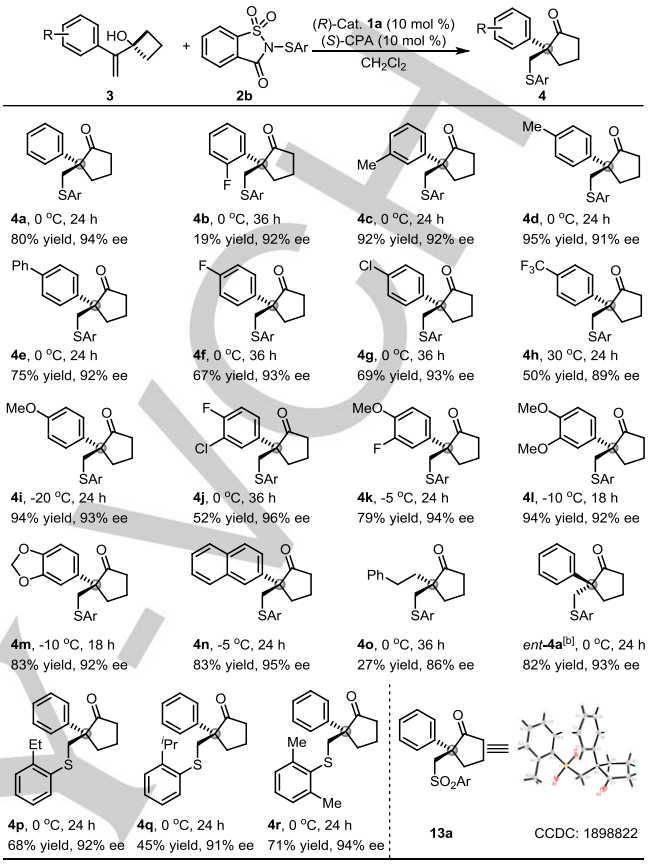
(*R*)-Cat. **1a** (*R*)-Cat. **1b** (*R*)-Cat. **1c** (*S*)-CPA

[a] Reaction conditions: compound **3a** (0.1 mmol), **2** (0.12 mmol), (*R*)-Cat. (10 mol%) and acid (10 mol%) in CH_2Cl_2 (1.0 mL) stirred 24 h under argon. [b] Isolated yield. [c] Determined by chiral HPLC. [d] (*R*)-Cat. (5 mol%) and (*S*)-CPA (5 mol%) were used as co-catalyst.

Herein, we are pleased to present the development of a successful catalytic asymmetric sulfenylation/semipinacol rearrangement reaction of 1,1-disubstituted and tri-substituted allylic alcohols. This process enables a straightforward and efficient method to synthesize a wide range of β-phenylthio ketones containing an all-carbon quaternary center (Scheme 1c). To realize this reaction, a catalytic system containing a chiral Lewis base and chiral Brønsted acid is required to activate the sulfenylating agent for the enantioenriched formation of thiiranium ion intermediates.

In our initial study, 1,1-disubstituted allylic alcohol **3a** was selected as a model substrate with *N*-phenylthiosaccharin **2a** as sulfenylating agent, and chiral Lewis base selenide **1a** as the catalyst with CH_2Cl_2 as the solvent. Disappointingly, the reaction yielded the product in 15% yield and 9% ee at room temperature after 24 h (Table 1, entry 1). On the basis of previous work,[9] and the proposed catalytic cycle, a catalytic amount of $MeSO_3H$ was used as a co-catalyst to promote the reaction; this resulted in the desired rearrangement product being afforded in 53% yield with a moderate 69% ee at -5 ºC (entry 2). Using $EtSO_3H$ instead of $MeSO_3H$ slightly affected the enantioselectivity (entry 3). Inspired by the above results and combined our prior successful development of chiral Brønsted acid system for semipinacol rearrangement,[15] we found chiral BINOL-derived phosphoric acid (CPA) was necessary for this reaction. Remarkably, the addition of 10 mol% (*S*)-CPA notably improved the enantioselectivity to 85% ee, whereas 10 mol% of (*R*)-CPA only gave 74% ee (entries 4-5). This outcome suggested the absolute configuration of the acid is an important variable. No further improvement was observed when different Lewis bases were investigated (entries 6-7). It should be noted that the Lewis

Table 2. Scope of 1,1-disubstituted allylic alcohols.[a]



Ar = 2-Me-C_6H_4. [a] Unless otherwise specified, each example represents the isolated yield on a 0.1 mmol scale under the standard reaction conditions and ee values were determined by chiral HPLC. [b] (*S*)-**1a** and (*R*)-CPA were used as co-catalyst.

base played a key role in improving the reaction activity and enantioselectivity; without a Lewis base, barely any reactivity was observed (entry 8). Further optimization of the reaction conditions was performed by varying the sulfenylating agent. To our delight, the use of **2b** as the sulfenylating agent greatly increased the enantioselectivity to 94% ee with 73% yield (entry 9). To our delight, increasing the reaction temperature to 0 ºC afforded the desired product **4a** in 80% yield and 94% ee (entry 10). It was found that either the yield or the enantioselectivity decreased when the amount of Lewis base and acid was reduced (entry 11). Therefore, the conditions of entry 10 gave the best results and were selected as the optimal conditions.

With these optimized conditions established, the scope of this reaction was explored with a variety of 1,1-disubstituted allylic alcohols and some different sulfenylating agents (Table 2). In general, the desired β-phenylthio ketones were obtained with moderate to excellent yields and excellent enantiomeric excess. In contrast to the model substrate (**3a**), substituents at the ortho-position of phenyl group markedly decreased the yield (**4b**),[16] while a methyl group at the meta- or para-position increased the yield and had little effect on the enantioselectivity (**4c**, **4d**). It was found that electron-withdrawing groups at the para-position led to a subtle reduction in yield (**4f**, **4g**, **4h**). Meanwhile, the use of an electron-donating allylic alcohol increased the yield while

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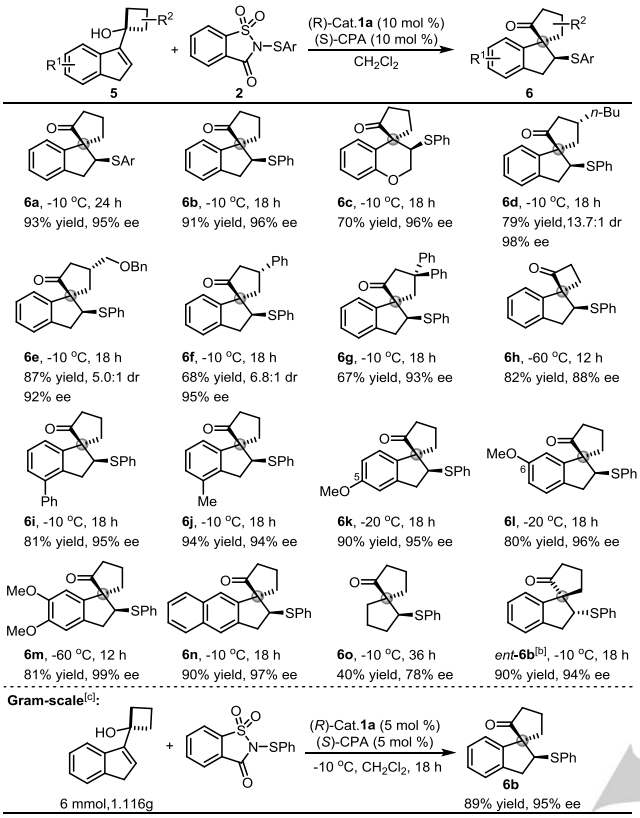
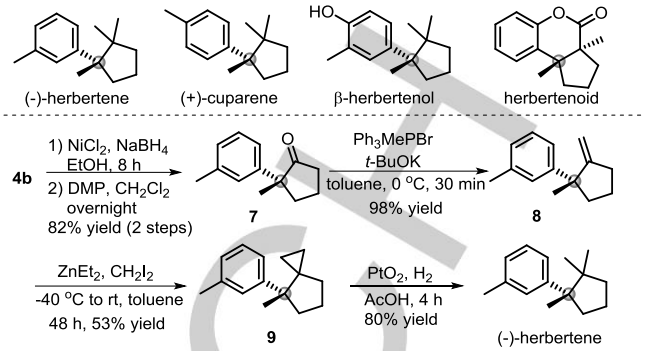
Table 3. Scope of the trisubstituted allylic alcohols.[a]



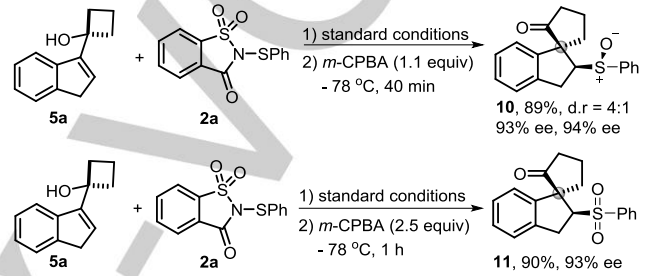
Ar = 2-Me-C_6H_4. [a] Unless otherwise specified, each example represents the isolated yield on 0.1 mmol scale under the standard reaction conditions and ee values were determined by chiral HPLC. [b] (*S*)-**1a** and (*R*)-CPA were used as co-catalyst. [c] Reaction conditions: **5a** (6 mmol), **2a** (7.2 mmol), (*R*)-**1a** (5 mol%) and (*S*)-CPA (5 mol%) in CH_2Cl_2 (30 mL) stirred 18 h at -10 ºC under argon.

maintaining the high enantioselectivity (**4i**). Substrates with multiple substituents on the phenyl moiety were tested in this reaction and they showed excellent enantioselectivity (**4j-m**). Again, the electron-withdrawing substituents produced the lower yields. In particular, using 3-chloro-4-fluorophenyl allylic alcohol afforded the corresponding product **4j** in 52% yield and 96% ee. Furthermore, 2-naphthyl substituted substrate **3n** was also tolerated by this reaction and the desired product was obtained in good yield and excellent ee (**4n**). It was found that the product (**4o**) was also obtained in 86% ee albeit with 27% yield when unbiased alkene compound **3o** was used as a substrate under the standard reaction conditions. The opposite enantiomer of the product (*ent*-**4a**) can be obtained in 82% yield and 93% ee when (*S*)-**1a** and (*R*)-CPA were used as co-catalysts. Finally, sulfenylating agents with different substituents on the phenyl group were also examined; these compounds were successfully incorporated and afforded the corresponding products in moderate yields and good enantioselectivities (**4p-r**). Notably, the absolute configuration of the rearrangement product was assigned by X-ray crystallography analysis of the sulfone derivative of **4a**.[17]

(a) Application to enantioselective total synthesis of (-)-herbertene



(b) Application to enantioselective synthesis of sulfoxide and sulfone *in situ*



[a] Unless otherwise specified, each example represents the isolated yield on 0.1 mmol scale under the standard reaction conditions and ee values were determined by chiral HPLC. DMP = Dess-Martin periodinane, *m*-CPBA = 3-Chloroperbenzoic acid.

Scheme 2. Synthetic applications of the products.[a]

As mentioned above, sulfenylation of tri-substituted alkenes is still challenging. Given the importance of chiral spirocyclic skeletons,[18] we sought to further expand our method to trisubstituted indene-type allylic alcohols. We first examined the feasibility of the above hypothesis with 1-(1H-inden-3-yl)cyclobutan-1-ol **5a** as the model substrate. To our delight, the initial attempt with 10 mol % Lewis basic selenide **1a** and (*S*)-CPA in the presence of **2b** in CH_2Cl_2 at -10 ºC successfully gave the corresponding product **6a** in 93% yield and 95% ee (Table 3). This reaction was also tested with N-phenylthiosaccharin **2a**, which led to the enantioselectivity slightly increasing to 96% ee with negligible impact on the yield (91%, **6b**). And the ^{1}H-NMR results for crude product **6b** indicated that the diastereoselectivity of the reaction was excellent and another product was not observed.[19] Accordingly, **2a** was selected as the sulfenylating agent and a broad range of substrates were evaluated under the reaction conditions. Generally, the desired β-phenylthio spirocyclic ketones were obtained with good yields and excellent enantioselectivities.

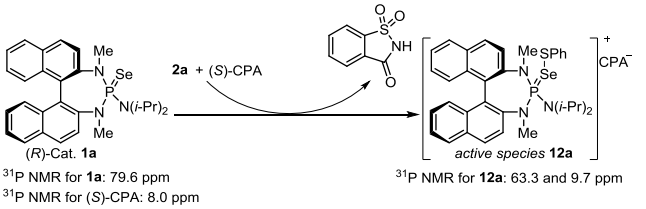


Figure 2. Proposed catalytically active species **12a.**

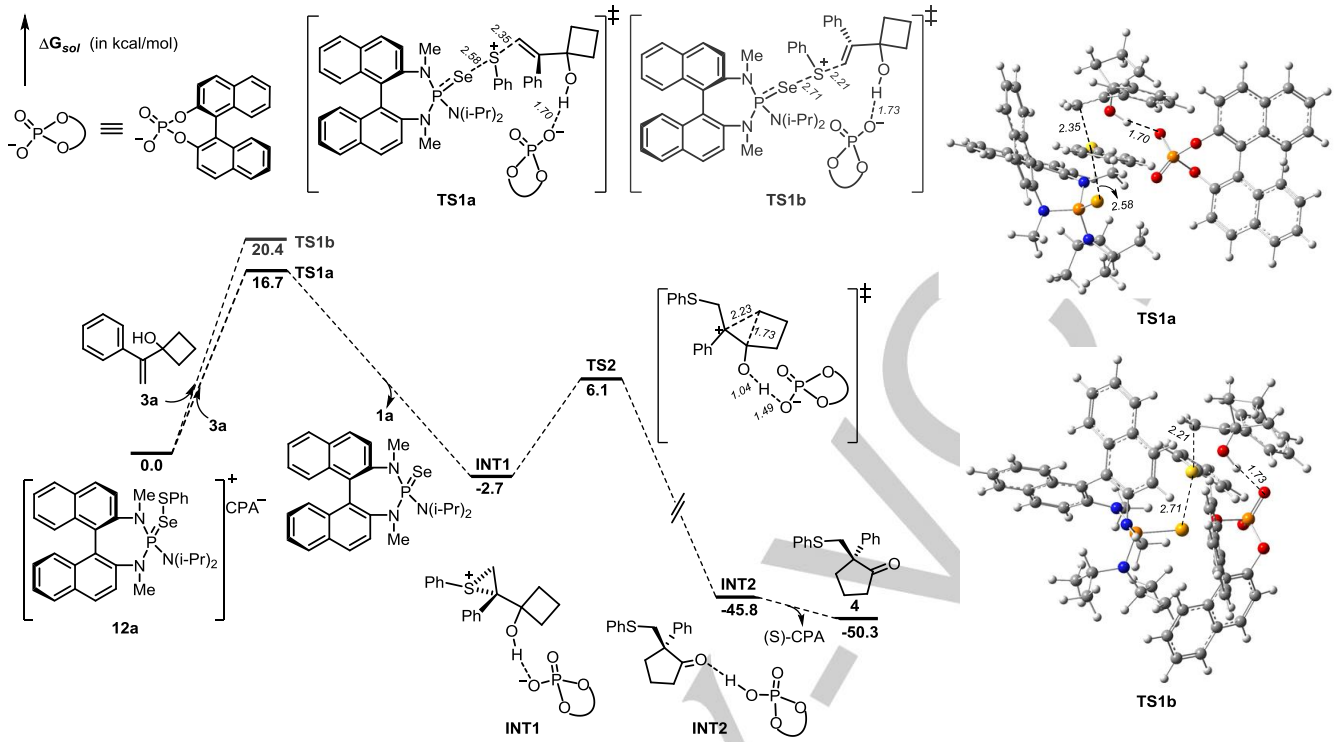


Figure 3. Energy profiles for the enantioselective sulfenylation/semipinacol rearrangement of 1,1-disubstituted allylic alcohol (**3a**) after the formation of **12a**. Bond distances are given in Å.

First, the derivative of chromene **5c** was well tolerated delivering product **6c** in 70% yield and 96% ee. Subsequently, various substrates containing different substituents at the cyclobutanol moiety were subjected to the standard reactionconditions to afford products in good yields with satisfying d.r values and excellent enantiomeric excess (**6d-f**).[20] The cyclopropanol substrate only gave 88% ee at -60 °C (**6h**). The substituent effects on the phenyl ring were also carefully investigated (**6i-m**), which indicated that electron-rich groups led to a higher enantioselectivity. It is noteworthy that the substrate containing two vicinal methoxy groups furnished the product with the highest, 99% ee (**6m**). It is frustrating that hardly any reaction was observed using 3-(1-hydroxycyclobutyl)-1H-inden-7-yl trifluoromethanesulfonate as an electro-deficient substrate. As expected, the 2-naphthyl substituted substrate afforded the product **6n** in 90% yield and 97% ee. Finally, unactivated 1-(cyclopent-1-en-1-yl)cyclobutan-1-ol was also tested in this catalytic system, affording the desired product **6o** in 40% yield and 78% ee. It was found that opposite enantiomer (*ent*-**6b**) can be obtained in excellent yield and enantioselectivity when (*S*)-**1a** and (*R*)-CPA were employed. To demonstrate the practicality of this catalytic system, a gram-scale reaction of substrate **5a** (6 mmol, 1.116 g) was conducted using the optimized reaction conditions and the desired product **6b** was readily obtained with maintained yield and ee. It is worth mentioning that the loading of catalyst can be decreased to 5 mol %.

As shown in Scheme 2a, chiral (1-methylcyclopentyl)benzene motifs containing an all-carbon quaternary center exist in many natural products.[21] For example, herbertane-type sesquiterpenoids, which were isolated from the liverwort Herberta adunca species and showed efficient anti-lipid peroxidation and anti-fungal activities.[22] However, total synthesis of chiral herbertene is difficult. Most of the enantioselective syntheses either incorporate the chiral stereocenter in the starting substrate or a catalytic asymmetric fashion with low optical purity.[23] To highlight the synthetic utility of this asymmetric transformation, an enantioselective total synthesis of (-)-herbertene was accomplished. First, C-S bond cleavage followed by oxidation smoothly gave product **7** in 82% total yield. Subsequently, compound **7** was subjected to a Wittig reaction to afford methylene compound **8** in near-quantitative yield, **8** could then be converted to cyclopropane **9** by a Simmons-Smith cyclopropanation. Finally, hydrogenation of **9** delivered (-)-herbertene in 80% yield. In addition, a one-pot synthesis of a chiral sulfoxide was also achieved based on this enantioselective reaction, affording the product **10** in excellent yield with acceptable diastereoselectivity and excellent enantioselectivity. The absolute configuration of the main product **10a** was assigned by X-ray crystallography.[17] Meanwhile, the enantioenriched sulfone **11** was only obtained when an excess amount (2.5 equiv.) of *m*-CPBA was used.

Based on previous work,[9] species **12a** would be the most catalytically active intermediate in this transformation when a chiral Brønsted acid was added (Figure 2). To gain further insight into this process, some additional low-temperature ^{31}P-NMR experiments were conducted.[24] The experimental results indicated that species **12a** is formed after the addition of (*S*)-CPA to this catalytic system.

Next, computational studies[25] were carried out to gain mechanistic insights into the enantioselective sulfenylation/semipinacol rearrangement of 1,1-disubstituted allylic alcohol **3a**. After the formation of **12a**, the sulfenyl group transfer *via* electrophilic attack to the terminal alkenyl carbon of **3a** can occur in a S_N2 manner. Two approaching modes of the sulfenyl group from both *Si* and *Re* sides of **3a** were considered and the corresponding transition states were designated as **TS1a** and **TS1b**, respectively. The optimized **TS1a** is characterized by a lengthening of the Se...S distance to 2.58 Å while shortening the S…C distance to 2.35 Å. In addition, a π...π interaction between the phenyl rings of **3a** and the sulfenyl group was found in **TS1a**. The presence of (*S*)-CPA$^-$ anion favors the formation of O—H…O and C—H…O H-bonds with **3a**. Analogous geometrical features are also found in **TS1b** except for the orientation of (*S*)-CPA$^-$ anion. When the sulfenyl group of **12a** approaches the alkenyl carbon from the *Si* side of **3a**, the two bulky groups of **1a** and (*S*)-CPA$^-$ anion stay away from each other. However, when the sulfenyl group attacks from the *Re* side of **3a**, there is steric hindrance between the bulky groups of (*S*)-CPA$^-$ and **1a**. Therefore, the predicted free energy barrier via **TS1a** is 3.7 kcal/mol lower than that of **TS1b**, meaning that the attack from the *Si* side of **3a** is favored (Figure 3). Subsequently, a thiiranium intermediate could be yielded and the catalyst **1a** is regenerated. Afterwards, the ring opening of the *S*-containing three membered ring and the semipinacol rearrangement *via* the 1,2-carbon migration, accompanying with the proton transfer from hydroxyl group of **3a** to (*S*)-CPA$^-$ anion, could take place to produce the desired product (**4**). The computational results suggest that the rate-limiting step from **12a** to the final product is the electrophilic attack of the sulfenyl group to **3a**. The enantioselectivity of product is determined by the favorable attack of sulfenyl group of **12a** from the *Si* side of **3a** to minimize the steric hindrance between the bulky groups of **1a** and (*S*)-CPA$^-$ anion.[26]

In conclusion, we have successfully developed the first example of an enantioselective sulfenylation/semipinacol rearrangement of 1,1-disubstituted and tri-substituted allylic alcohols, using a chiral Lewis base and a chiral Brønsted acid as co-catalysts. This method provides an efficient, direct and facile synthetic access to enantiomerically enriched β-phenylthio ketones. Moreover, a chiral all-carbon quaternary stereocenter was efficiently constructed; in particular, two adjacent stereocenters were also smoothly formed using trisubstituted allylic alcohols. Additionally, a convenient synthesis of the natural product (-)-herbertene and a one-pot synthesis of chiral sulfoxide and sulfone demonstrated the synthetic utility of this methodology. The success of a gram-scale transformation demonstrates that the enantioselective sulfenylation reaction is transferable to a preparative scale. These chiral sulfur-ketone products or their analogs may be useful as chiral auxiliaries or intermediates in asymmetric catalysis and organic synthesis.

Acknowledgements

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Keywords: Semipinacol Rearrangement • Quaternary Center• Sulfur Compound • Spirocyclic Skeleton • Co-catalysis

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[16] Using 1-(1-(o-tolyl)vinyl)cyclobutan-1-ol as a substrate, hardly could any reaction be observed.

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[19] For ^{1}H-NMR results, please see Supporting Information.

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[24] For ^{31}P-NMR experiments, please see Supporting Information.

[25] See Supporting Information for computational details.

[26] To further illustrate the steric effect of the (*S*)-CPA$^-$ anion in accounting for the enantioselective sulfenylation of **3a**, the $MeSO_3^-$ anion assisted sulfenylation of **3a** was also considered computationally. The predicted free energy barrier for attack from the *Si* side of **3a** via **TS1a'** is only 0.9 kcal/mol lower than the competitive attack mode from the *Re* side via **TS1b'** (Figure S1). Computational results suggest that the sulfenylation of **3a** using the $MeSO_3^-$ anion is less enantioselective compared with the (*S*)-CPA$^-$ anion, which is consistent with the experimental observation.

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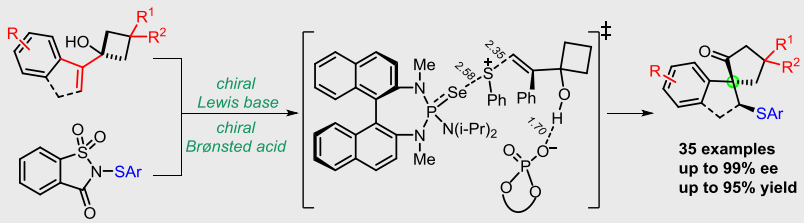

An enantioselective sulfenylation/semipinacol rearrangement of 1,1-disubstituted and tri-substituted allylic alcohols was accomplished under the co-catalysis of chiral Lewis base/chiral Brønsted acid, to generate various β-phenylthio ketones bearing an all-carbon quaternary center in moderate to excellent yields and excellent enantioselectivities. Computational studies were carried out to explain the origin of enantioselectivity and the role of chiral Brønsted acid.

Yu-Yang Xie, Zhi-Min Chen, Hui-Yun Luo, Hui Shao, Yong-Qiang Tu*, Xiaoguang Bao*, Ren-Fei Cao, Shu-Yu Zhang, and Jin-Miao Tian*

Lewis Base/Brønsted Acid Co-catalyzed Enantioselective Sulfenylation/Semipinacol Rearrangement of Di- and Tri-substituted Allylic Alcohols