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Enantioselective Synthesis of Vinylcyclopropanes and Vinylepoxides Mediated by Camphor-Derived Sulfur Ylides: Rationale of Enantioselectivity, Scope, and Limitation

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Abstract: By a sidearm approach, camphor-derived sulfur ylides **1** were designed and synthesized for the cyclopropanation of electron-deficient alkenes and epoxidation of aldehydes. Under the optimal conditions, the exo-type sulfonium salts **4a** and **4b** reacted with β-aryl-α,β-unsaturated esters, amides, ketones, and nitriles to give 1,3-disubstituted-2-vinylcyclopropanes with high diastereoselectivities and enantioselectivities. When the endo-type sulfonium salts **5a** and **5b** were used, the diastereoselectivities were not changed, whereas the absolute configurations of the products became the opposite to those of the reactions of **4a** and **4b**. An ylide cyclopropanation of chalcone derivatives with phenylvinyl bromide in the presence of catalytic amount of chiral sulfonium salts **4b** and **5b** has been developed. The sidearmed hydroxyl group was found to play a key role in the control of enantioselectivity and diastereoselectivity. The origins of the high diastereoselectivity and enantioselectivity were also studied by density functional theory calculations, which reveal the importance of the hydrogen-bonding between the sidearmed hydroxyl group and the substrate in determining the diastereoselectivity and enantioselectivity. The ylides **1** were also successfully applied for the epoxidation of aromatic aldehydes.

Introduction

Vinylcyclopropane derivatives have received considerable attention because of their frequent occurrence in biologically active compounds,[1] as well as their utility as valuable synthetic intermediates.[2] Although many synthetic methods for cyclopropanes[3] such as the Simmons−Smith reaction and transition metal-catalyzed cyclopropanation of electron-rich alkenes with α-diazocarbonyl compounds have been developed, the preparation of multisubstituted vinylcyclopropanes with high selectivity remains challenging due to the difficulty in controlling regioselectivity, diastereoselectivity (cis/trans) and enantioselectivity. Of the methods for the synthesis of vinylcyclopropanes,[4] only a few successful direct asymmetric synthesis has been reported except those related to disubstituted or 1,1,2-trisubstituted ones,[5] involving the use of symmetric dienes[5a−c] or β-phenylvinyldiazoester.[5e−g] For the preparation of other trisubstituted vinylcyclopropanes, Hanessian et al.[6] reported a cycloaddition reaction of chiral chloroallylphosphonic amide to afford 1,2,3-trisubstituted cyclopropanes with excellent diastereoselectivity. Suzuki[7a] and Taylor[7b,7c] found that these kinds of compounds could be prepared from optically pure homoallylic alcohols. Aggarwal

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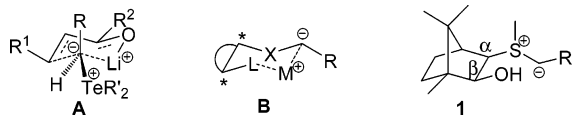
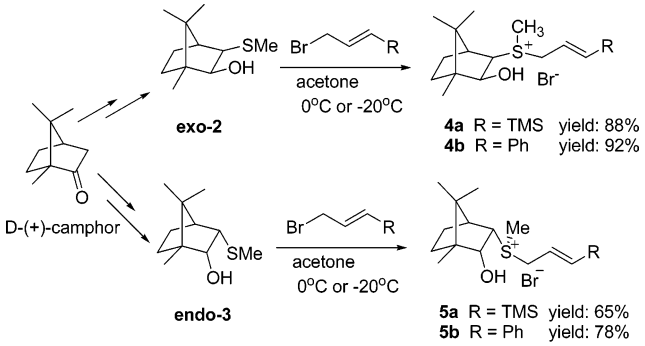
Chart 1



et al.[8] also reported the reaction of a chiral silylated allylic sulfur ylide with α-aminoacrylate to afford the desired vinylcyclopropane with 71% de and 75% ee.

Ylides proved to be efficient reagents not only for constructing carbon−carbon double bonds but also for preparing small ring compounds such as epoxides,[9] aziridines,[9b,9c,10] and cyclopropanes.[9b,9c,11] In a previous study on ylide chemistry,[12] we found that lithium ion could switch the diastereoselectivity of cyclopropanation reaction of telluronium allylides with α,*β*-unsaturated esters or amides. The mechanism for this tuning has been rationalized as the formation of a chelating six-membered ring transition state (**A** in Chart 1) by coordination of lithium ion with carbonyl oxygen and ylidic carbanion simultaneously.[13] On the basis of this mechanistic insight, we designed chiral ylides **1** with a hydroxyl group at the *β*-position of the sulfur atom by a sidearm approach.[14] It is envisaged that ylides of type **1** might form a rigid six-membered ring in the presence of metal ion as shown in Chart 1 (**B** in Chart 1) and thus the chirality of ylidic carbon is fixed, beneficial to the diastereoselectivity and enantioselectivity. On the basis of this strategy, we recently developed a highly enantioselective cyclopropanation reaction and reported that ylide **1a**, generated from the corresponding salt **4a** and *t*-BuOK (3.0 equiv) in situ, could react in a stoichiometric manner with a variety of α,*β*-unsaturated carbonyl compounds in one pot to afford 1,3-disubstituted-2-silylvinylcyclopropanes **10** in high enantiomeric excess (ee) and in good to high yields.[15] The substrates, however, were limited to *β*-aryl-α,*β*-unsaturated esters, amides, ketones, and nitriles. For methyl crotonate, only 20% yield was obtained due to the rearrangement of the sulfur ylide, although the enantioselectivity was high. Very recently, we found that both *exo*-type sulfur salt **4b** and *endo*-type sulfur salt **5b** also worked well in the cyclopropanation of both *β*-aryl- and *β*-alkyl-α,*β*-unsaturated carbonyl compounds and nitriles. Compared with the *exo* ones, remarkably, the *endo* ones gave the opposite enantioselectivity. Thus, the new development provides an easy access to both enantiomers of trisubstituted cyclopropanes. We also extended this reaction successfully to the epoxidation of aromatic aldehydes and catalytic asymmetric ylide cyclopropanation. In this paper, we wish to report the details of these reactions and their applications in organic synthesis, as well as the theoretical studies toward understanding the origins of the diastereo- and enantioselectivities of these reactions.

Scheme 1



Results and Discussion

Synthesis of Sulfonium Salts. Chiral sulfides **2** and **3** were easily prepared from D-(+)-camphor in two steps by a known procedure.[16] The reactions of **2** and **3** with allylic bromides in acetone result in sulfonium salts **4** and **5**, respectively, in good yields (Scheme 1).

Enantioselective Synthesis of Silylvinylcyclopropanes. Initially, we tried the stepwise reaction of sulfonium salt **4a**

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Scheme 2

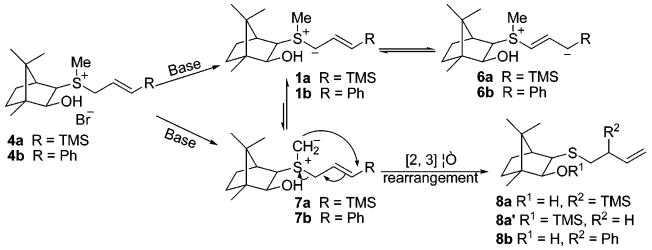
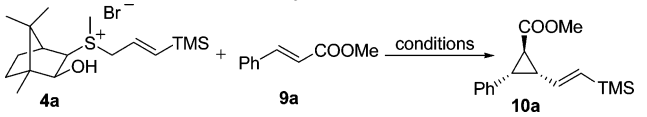


Table 1. Effects of Reaction Conditions on the Cyclopropanation of Sulfonium Salt **4a** with Methyl Cinnamate **9a**[a]



entry	solvent	base	**4a**/**9a**/base	*T*(×c1âC)	yield (%)[b]	ee (%)[c]
1	THF	KOBu^t	1/1.2/2.4	−78	82[d]	96
2	THF	KOBu^t	1/1.2/2.4	−40	23	92
3	THF	KOBu^t	1/1.2/2.4	0	12	91
4	DME	KOBu^t	1/1.2/2.4	−78	74	96
5	DCM	KOBu^t	1/1.2/2.4	−78	22	95
6	ether	KOBu^t	1/1.2/2.4	−78	trace	/
7	hexane	KOBu^t	1/1.2/2.4	−78	trace	/
8	THF	KOBu^t	1/1.2/1.3	−78	25[d]	96
9	THF	KOBu^t	1/1.2/3.6	−78	85[d]	97
10	THF	NaHMDS	1/1.2/2.4	−78	62	95
11	THF	KHMDS	1/1.2/2.4	−78	43	93
12	THF	KOH	1/1.2/3.6	−78	0	/
13	THF	KOBu^t/LiBr	1/1.2/3.6	−78	trace	/
14	THF	NaOMe	1/1.2/3.6	−78	0	/
15	THF	KOBu^t/HMPA	1/1.2/3.6	−78	75	95
16	THF	KOBu^t/$ZnCl_2$	1/1.2/3.6	−78	trace	/
17	THF	KOBu^t/HMPA	1/1.2/3.6	−78	35	96

[a] Unless otherwise noted, the reaction time was 4 h. [b]Isolated yield and only **10a** was observed. [c]Determined by chiral HPLC. [d]The reaction time was 2 h.

with methyl cinnamate. Deprotonation of compounds **4a** by lithium diisopropylamide (LDA) or *n*-butyllithium, followed by treatment with methyl cinnamate, unfortunately, only gave trace amount of the desired product. In this case, sulfide **8a** was isolated as the major product, indicating that the [2,3]-sigmatropic rearrangement[17] of ylide **7a** dominated (Schemes 2 and 3).

We reasoned that a weaker base than LDA would reduce the formation of sulfur ylide **7a** and should be beneficial to the cyclopropanation. Thus, when *t*-BuOK was used instead of LDA, we were pleased to find that vinylcyclopropane **10a** was achieved with 96% ee in 71% yield. Considering that the rearrangement of compound **7a** is an intramolecular reaction, to further improve the yield, we also tried a one-pot reaction by mixing salt **4a** and *t*-BuOK with methyl cinnamate at −78 °C and stirring for several hours. In this case, the yield was increased to 82% and the enantioselectivity remained the same (96% ee) (entry 1, Table 1).

Further studies showed that the yield and enantioselectivity of the cyclopropanation were significantly influenced by the reaction conditions. As shown in Table 1, higher temperature than −78 °C decreased the yield probably due to the rearrangement (entries 2−3, Table 1). Choice of solvents proved crucial for this reaction (entries 4−7, Table 1). In ethylene glycol dimethyl ether (DME), the yield of cyclopropanation was slightly decreased (entry 4, Table 1). In dichloromethane (DCM), only 22% (entry 5, Table 1) yield was obtained. When the solvent was switched to ether or hexane (entries 6, 7, Table 1), only a trace amount of the desired cyclopropane was observed due to the insolubility of both *t*-BuOK and sulfonium salt in these solvents. Increasing the amount of *t*-BuOK also increased the yield of the cyclopropane (entries 1, 8−9, Table 1). When 1.3 equiv of *t*-BuOK were used, the reaction was sluggish and only 25% yield was obtained. However, when 3.6 equiv of the base were added, the reaction rate increased and the yield was also improved to 85%. A significant effect of the base on yield was observed (entries 10−17, Table 1). Strong bases such as NaHMDS and KHMDS lowered the yield. Weak bases such as KOH, NaOMe, and *t*-BuOK /LiBr did not work in this reaction. Interestingly, in all of the reaction conditions screened, the enantioselectivities were higher than 90% and the diastereoselectivities were excellent with only one diastereomer **10a** isolated.

Encouraged by the observed excellent diastereoselectivity and high enantioselectivity, we evaluated a variety of α,*β*-unsaturated carbonyl compounds as substrates to study the generality of this reaction. As shown in Table 2, α,*β*-unsaturated esters, amides, ketones, and nitriles all worked well to give desired products in good yields with excellent enantioselectivities. For *β*-aryl-α,*β*-unsaturated esters and amides (entries 1−7, Table 2), the diastereoselectivities of this reaction were outstanding and only the anti diastereoisomer **10** was isolated for each reaction. When α,*β*-unsaturated ketones (entries 8, 9, Table 2) were employed, the desired cyclopropane products were obtained with high diastereoselectivities and enantioselectivities in moderate to good yields and no epoxides were detected. It is known that simple sulfonium allylides are hard to react with α,*β*-unsaturated nitriles (Scheme 5). In the present case, however, the ylide derived from **4a** reacted with α,*β*-unsaturated nitriles well to give excellent diasteroselectivities and enantioselectivities (entries 10−12, Table 2). Methyl acrylate gave a high yield with excellent ee and diastereoselectivity but methyl crotonate afforded cyclopropane only in 20% yield, although the diastereoselectivity (86/14) and enantioselectivity (92% ee) were good (entries 13, 14, Table 2). Methyl *cis*-cinnamate was inactive in this reaction and only gave a trace amount of the desired product (entry 15, Table 2).

Enantioselectivity-Controllable Synthesis of Phenylvinylcyclopropanes. The camphor-derived *exo*-sulfonium ylide proved to be an excellent reagent for the cyclopropanation of methyl cinnamate. The camphor-derived *endo*-isomer **5a** (eq 1) could also react with methyl cinnamate to afford the corresponding cyclopropanation product with moderate but opposite enantioselectivity. Although the yield and the enantioselectivity are not good, it suggested that both enantiomers might be prepared selectively using the natural camphor as the

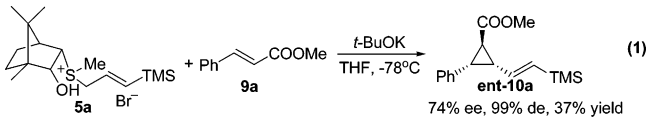


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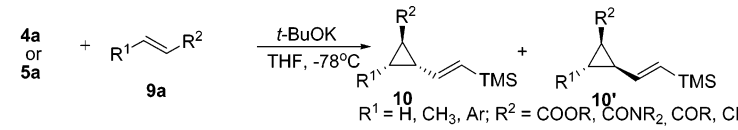
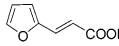
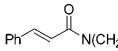
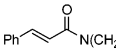
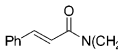
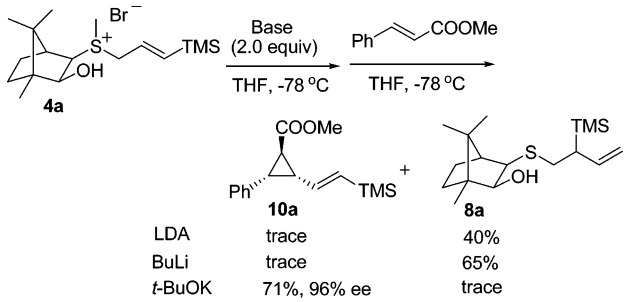
Table 2. Asymmetric Cyclopropanation of Sulfonium Salts **4a** and **5a** with Michael Acceptors[a]



entry	Sulfur salt	substrate	yield (%)[b]	**10**/**10'**[c]	ee (%)[d]
1	**4a**	Ph, COOMe (**9a**)	85	>99/1	97
2	**4a**	Ph, COOEt (**9b**)	75	>99/1	97
3	**4a**	*p*-MeC$_6$H$_4$, COOMe (**9c**)	80	>99/1	97
4	**4a**	*p*-MeOC$_6$H$_4$, COOMe (**9d**)	59	>99/1	96
5	**4a**	 (**9e**)	57	>99/1	97
6	**4a**	 (**9f**)	70	>99/1	97
7	**4a**	 (**9g**)	66	>99/1	97
8	**4a**	Ph, COPh (**9h**)	81	90/10	94[e]
9	**4a**	*p*-ClC$_6$H$_4$, COBu^t (**9i**)	64	92/8	95[e]
10	**4a**	Ph, CN (**9j**)	61	>99/1	94
11	**4a**	*p*-ClC$_6$H$_4$, CN (**9k**)	61	>99/1	96
12	**4a**	*p*-BrC$_6$H$_4$, CN (**9l**)	79	>99/1	99
13	**4a**	COOMe (**9m**)	83[f]	>99/1	95
14	**4a**	COOMe (**9n**)	20[f,g]	86/14	92[d]
15	**4a**	Ph, COOMe (**9o**)	trace[g]	ND[h]	ND[h]
16	**5a**	Ph, COOMe (**9a**)	37	>99/1	-74[i]
17	**5a**	 (**9f**)	72	>99/1	-96[i]
18	**5a**	Ph, COPh (**9h**)	78	>99/1	-96[i]
19	**5a**	*p*-ClC$_6$H$_4$, COBu^t (**9i**)	87	>99/1	-94[i]
20	**5a**	COOMe (**9m**)	55	>99/1	-93[i]

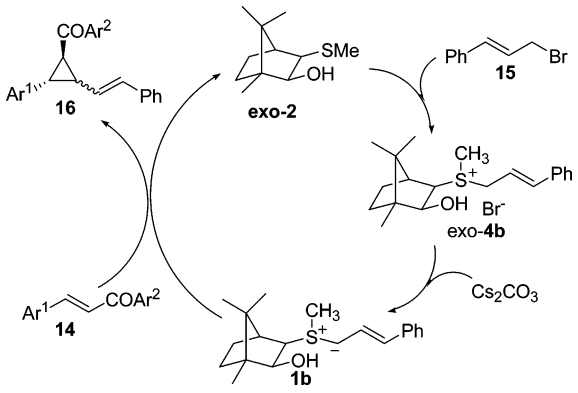
[a] All reactions were carried out in 2−4 h. [b] Isolated yield and sulfide **2** was recovered in 50−70% yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] Ee for **10**. [f] 4 equiv. of **9m** or **9n** were used. [g] The major products were sulfides **8a** and **8a′** (Scheme 2). [h] Not determined. [i] The enantiomer of **10** was obtained.

Scheme 3



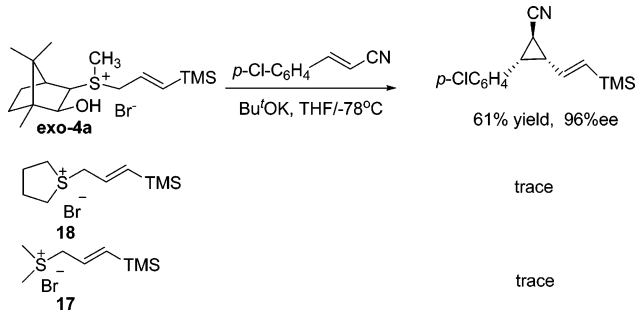
chiral source. The key is to inhibit the [2, 3]-σ-rearrangement reaction of the ylide **7**. To reduce the formation of ylide **7**, we used an electron-withdrawing group instead of trimethylsilyl group to increase the acidity of the allylic hydrogen of sulfonium salts **4** (Scheme 2). As expected, phenyl-substituted sulfonium salt **4b,** which was readily available from the corresponding *exo*-sulfide **2** and phenylallylic bromide as a 9/1 mixture of diastereoisomers, could be used directly to react with methyl cinnamate in the presence of *t*-BuOK to afford vinylcyclopropane **12a** with high diastereoselectivity (>99/1) and excellent enantioselectivity (99% ee) in 77% yield (entry 1, Table 3).

Scheme 4



Encouraged by these results, we studied the generality of this reaction and evaluated a variety of α,β-unsaturated carbonyl compounds with different structures. As shown in Table 3, β-aryl and β-alkyl-α,β-unsaturated esters, ketones, amides, and nitriles were good substrates for this reaction. For β-aryl-α,β-unsaturated substrates, both diastereoselectivities and enantioselectivities were good to excellent (entries 1−6, Table 3). For β-alkyl-α,β-unsaturated substrates, compared with our previous work using sulfonium salt **4a**, the yields were improved

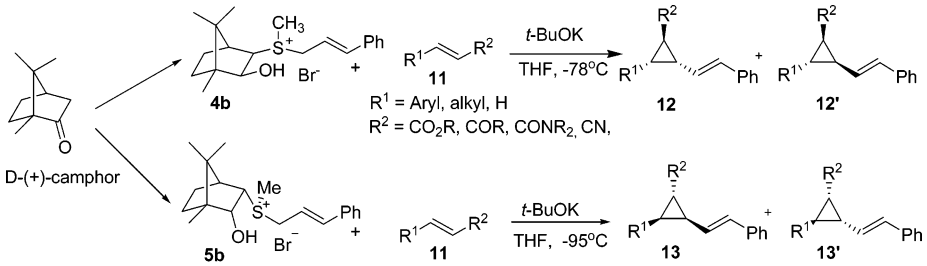
Scheme 5



greatly (entries 10−11, Table 3) and the enantioselectivities were increased slightly. Acrylate, acrylamide, and acrylonitrile[18] gave high to excellent diastereo- and enantioselectivities (entries 7−9, Table 3). Methyl crotonate afforded the cyclopropane with high enantioselectivities of 97% ee (**12j′**) and 95% ee (**12j**) in 98% yield (entry 10, Table 3), but their diastereoselectivities decreased. β-Alkyl-α,β-unsaturated ketone also worked well with high enantioselectivity 99% ee and in 88% yield (entry 12, Table 3) to give cis-diastereomer **12′** as the major product, without epoxide observed. The α-benzyl acrylate also gave the desired 1,1,2-trisubstituted cyclopropane with good diastereoselectivity (91/9) and enantioselectivity (88% ee) and in 83% yield (entry 13, Table 3). Thus, 1,2-disubstituted or 1,2,3-trisubstituted or 1,1,2-trisubstituted cyclopropanes could be synthesized with high to excellent enantioselectivities.

The reaction of silylated *endo*-sulfonium salt **5a** with methyl cinnamate afforded the desired cyclopropane in low yield with moderate enantioselectivities. However, phenyl-substituted *endo*-sulfonium salt **5b** furnished vinylcyclopropane **13** in 86% yield with high diastereoselectivity (>99/1) and excellent but opposite enantioselectivity (98% ee), compared with that using *exo*-sulfonium salt **4b**. As shown in Table 3, a variety of electron deficient alkenes with different structures worked well in this reaction, affording vinylcyclopropanes with high to excellent enantioselectivities (up to 99% ee). Thus, either one of the two enantiomers could be obtained at will just by the choice of *exo*- or *endo*- sulfonium salts, both derived from cheap D-camphor. To the best of our knowledge, these were the best results of enantioselective synthesis of both enantiomers of vinylcyclopropanes via chiral sulfonium ylides.

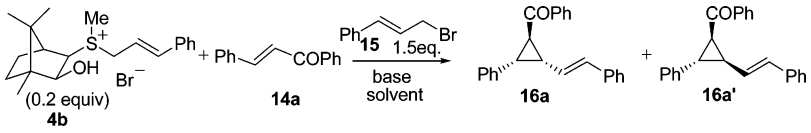
Table 3. Highly Enantioselective Synthesis of Both Enantiomers of Phenylvinylcyclopropane



entry	substrate	4b yield (%)[a]	4b **12**/**12′**[b]	4b ee (%)[c]	5b yield (%)[a]	5b **13**/**13′**[b]	5b ee (%)[c]
1	Ph, CO_2Me (**11a**)	77	>99/1	99	86	>99/1	98
2	Ph, COPh (**11b**)	83	97/3	94	71	92/8	92
3	*p*-Cl-C_6H_4, $COBu^t$ (**11c**)	91	95/5	98	91	99/1	98
4	Ph, $CON(CH_2)_4$ (**11d**)	98	>99/1	98	87	>99/1	96
5	Ph, $CON(CH_2CH_2)_2O$ (**11e**)	99	>99/1	94	97	>99/1	99
6	*p*-BrC_6H_4, CN (**11f**)	83	>99/1	96	75	>99/1	95
7	CO_2Me (**11g**)	90[d]	>99/1	93	60	>99/1	91
8	$CON(CH_2)_4$ (**11h**)	70[d]	93/7	90	78	93/7	98
9	CN (**11i**)	50[d]	93/7	87	42	87/13	84
10	CO_2Me (**11j**)	98[d]	57/43	95(97)[e]	72	78/22	91(95)[e]
11	*n*-C_4H_9, CO_2Me (**11k**)	78	52/48	87(96)[e]	70	73/27	90(98)[e]
12	*n*-C_4H_9, $COBu^t$ (**11l**)	88	29/71	70(99)[e]	81	62/38	90(99)[e]
13	CO_2Me, CH_2Ph (**11m**)	83	91/9	88	78	92/8	97

[a] Isolated yield and the reactions were carried out for 2−4 h. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC. [d] 5 equiv. of α,β-unsaturated compounds were used. [e] The enantioselectivity of the cis product 12′ and 13′.

Table 4. Effects of Reaction Conditions on Catalytic Ylide Cyclopropanation



entry	solvent	base/ additive	*T* (°C)	conversion[a] (%)	**16a/16a'**[b]	ee (%)[c]
1[d]	Bu^{t}OH	Cs_2CO_3	30	77[g,h]	77/23	72
2[e]	Bu^{t}OH	Cs_2CO_3	30	86[g,h]	80/20	74
3[f]	Bu^{t}OH	Cs_2CO_3	30	79[g,h]	75/25	73
4[f]	THF	Cs_2CO_3	30	20[i]	55/45	52
5[f]	CH_3CN	Cs_2CO_3	30	56[i]	50/50	51
6[f]	acetone	Cs_2CO_3	30	40[i]	50/50	54
7[f]	DME	Cs_2CO_3	30	45[i]	50/50	51
8[f]	Bu^{t}OH	K_2CO_3	30	65[i]	82/18	75
9[f]	Bu^{t}OH	*t*-BuOK	30	75[i,l]	60/40	80
10[f]	Bu^{t}OH	NaOH	30	86[i,l]	50/50	65
11[f]	Bu^{t}OH	KOH	30	70[i,l]	50/50	73
12[f]	Bu^{t}OH/ CH_3CN[j]	K_2CO_3/18-crown-6	30	71[i,l]	85/15	81
13[f]	Bu^{t}OH/ CH_3CN[j]	Cs_2CO_3	0	92[g,i]	86/14	82
14[f]	Bu^{t}OH/ CH_3CN[j]	Cs_2CO_3/KI[m]	0	60[g,i]	86/14	81
15[f]	Bu^{t}OH/ CH_3CN[j,k]	Cs_2CO_3	0	86[g,i]	86/14	81

[a] On the basis of the recovered **14a**. [b] Determined by ^{1}H NMR. [c] Determined by Chiral HPLC. [d] Phenyl allylic bromide was added in one pot. [e] Added by syringe pump in 6 h. [f] Added in 3 h. [g] Isolated yield and 100% conversion. [h] 24 h. [i] 36 h. [j] The ratio of Bu^{t}OH/CH_3CN (v/v, 2.5/1). [k] Trace amount of H_2O was added. [l] Disordered reactions and low yields for cyclopropanes. [m] 0.2 equiv. of KI was added.

Catalytic Asymmetric Cyclopropanation. The stoichiometric reaction of camphor-derived sulfonium salts provides a good method for highly enantioselective synthesis of both enantiomers of phenylvinylcyclopropanes. For a more practical application, we tried to develop a catalytic asymmetric ylide cyclopropanation. Fortunately, we found that chalcone could react with phenylallylic bromide to afford cyclopropane with 72% ee and moderate diastereoselectivity in the presence of 20% mol sulfonium salt **4b** in Bu^{t}OH at 30 °C.

To further improve the yield and stereoselectivity, we investigated the effects of the reaction conditions on the cyclopropanation, including solvents, temperature, bases as well as addition sequence of the reactants. Finally, the best result was achieved when a mixture of chalcone **14a** (1.0 equiv), phenyl allylic bromide **15** (1.5 equiv) and sulfonium salt *exo*-**4b** (0.2 equiv) was stirred at 0 °C for 36 h in the mixed solvent of *tert*-butyl alcohol and acetonitrile. In this case, the cyclopropanation product was obtained with a moderate diastereoselectivity (86/14) and a good enantioselectivity (82% ee) in high yield (92%) (entry 13, Table 4). To investigate the generality of this catalytic reaction, a variety of α,β-unsaturated carbonyl compounds were investigated (Table 5). While the silylated sulfonium salts **4a** and **5a** were inert, both *exo*-sulfonium salt **4b** and *endo*-sulfonium salt **5b** were found to catalyze the cyclopropanation of α,β-unsaturated ketones with bromide **15** well, affording the desired cyclopropanes in good to high yields and with good to high enantioselectivities (Table 5). Using chiral sulfide **2** as the catalyst, similar results were achieved (entries 2 and 5, Table 5).[19] It is worth noting that the enantiomer of **16a** could be obtained using **5b** as the catalyst, similar to the results in the case of stoichiometric amount of sulfonium salts employed (entry 11, Table 5). A catalytic cycle is proposed as shown in Scheme 4. First, the sulfide **2** reacts with bromide **15** to afford the salt **4b**, which is deprotonated by Cs_2CO_3 to generate ylide **1b**. Then, the ylide reacts with unsaturated alkenes readily to give the cyclopropanes and regenerate the sulfide **2** to complete the catalytic cycle. Attempts to extend this catalytic reaction to ester **11a** and amide **11d** failed.

Mechanism. The camphor-derived β-hydroxyl-sulfonium ylide proves to be efficient for the cyclopropanation of electron-deficient alkenes. For example, the reaction of salt **4a** with α,β-unsaturated nitrile affords the desired cyclopropane in 66% yield with 96% ee. But the corresponding dimethyl sulfonium salt **17** as well as tetrahydrothiophene-derived sulfonium salt **18** only gave a trace amount of cyclopropane (Scheme 5).

We rationalized that the hydroxyl group in salt **4a** might play a crucial role in this reaction. An attempt to remove the hydroxyl group of the compound **4a** failed.[20] Thus, we tried to protect the free hydroxyl group of **4a** with methyl and prepared the sulfonium salt **19** for study (Scheme 6). It was found that no desired cyclopropane was observed when salt **19** was used instead of **4a** and only rearrangement products **20** were isolated (Scheme 6). These demonstrate that the free sidearmed hydroxyl group strongly influenced the reaction behavior of the ylides in the cyclopropanation reactions.

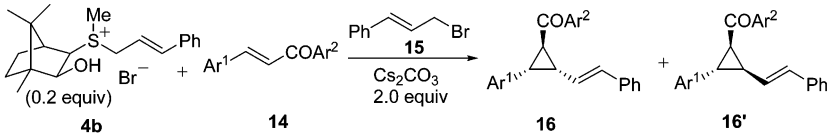
To understand the difference between salts **4a** and **19**, we obtained their crystals. As shown in Figure 1, from the X-ray

(18) Polymerization was observed in this reaction, similar to the cyclopropanation of acrylonitrile using ammonium ylide, see ref 11c.

(19) It is always more convenient to add sulfide rather than to have to make sulfonium salt.

(20) For details please see Supporting Information.

Table 5. Catalytic Asymmetric Cyclopropanation by Chiral Sulfonium Salts[a]



entry		substrate	time (h)	yield (%)[b]	**16/16'**[c]	ee (%)[d]
1	**14a**	Ph, COPh	36	92	86/14	82
2[e]	**14a**	Ph, COPh	40	92	85/15	80
3	**14b**	*p*-Cl-C_6H_4, COPh	30	86	76/24	78
4	**14c**	*p*-Br-C_6H_4, COPh	30	89	75/25	77
5[e]	**14c**	*p*-Br-C_6H_4, COPh	38	80	74/26	78
6	**14d**	*p*-Me-C_6H_4, COPh	54	80	86/14	81
7	**14e**	*p*-MeO-C_6H_4, COPh	80	66(90[f])	86/14	80
8	**14f**	*o*-Br-C_6H_4, COPh	20	90	77/23	88
9	**14g**	*o*-MeO-C_6H_4, COPh	60	86(92[f])	67/33	78
10	**14h**	Ph, CO(*p*-Me-C_6H_4)	57	87	87/13	81
11[g]	**14a**	Ph, COPh	36	85	87/13	78

[a] Sulfonium salt *exo*-**4b** (0.2 equiv), α,β-unsaturated ketone **14** (1.0 equiv.), phenyl allylic bromide **15** (1.5 equiv.), Cs_2CO_3 (2.0 equiv.), Bu^{t}OH/CH_3CN (v/v, 2.5/1.0), 0 °C. [b] Isolated total yield for cis- and trans-isomers. [c] Determined by ^{1}H NMR. [d] Ee for **16** and determined by chiral HPLC. [e] Chiral sulfide **2** was used as a catalyst. [f] Conversion. [g] **5b** was used and the enantiomer of **16a** was isolated.

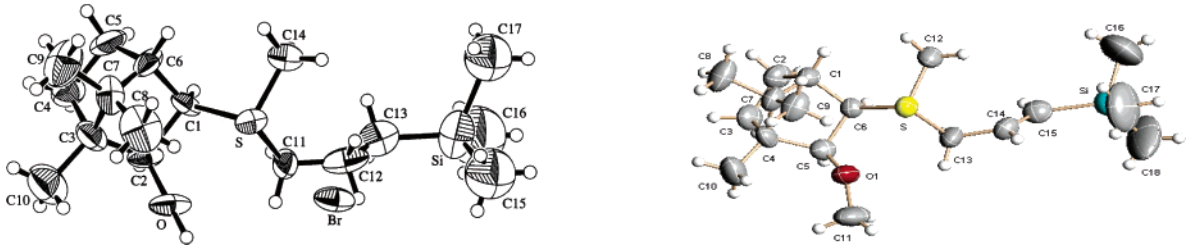
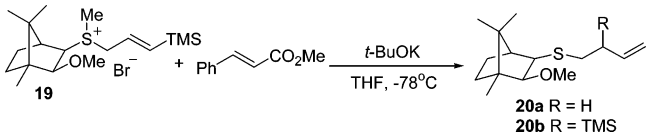


Figure 1. X-ray crystal structures of sulfonium salts **4a** and **19**.

Scheme 6



structure analysis of the salts, the distance between the sulfur and oxygen is only 2.78 Å, and the distortion angle O−C_1−C_2−S is 0° in salt **4a**; similarly, in salt **19**, they are 2.74 Å[21] and 4.2° respectively, indicating that both salts have similar structures with bonding interactions between sulfur and oxygen atoms. Therefore, the free hydroxyl group must play a crucial role in determining both the reactivity and stereoselectivity.

On the basis of these results, together with the absolute configuration of the product, stereochemical models were developed to explain the stereochemistry as shown in Scheme 7. When *exo*-salt **4a** was used, **4a** was deprotonated by ^{t}BuOK to afford the ylide, which attacked α,β-unsaturated carbonyl compounds to afford the desired cyclopropanes. The electron-deficient alkenes could only approach the *Re* face of the ylidic carbon, due to both effects of hydroxyl-directing and the steric hindrance of the S-methyl group. It appears that transition state A is favored over B and thus cyclopropanes **10** are obtained as the major products, which is consistent with the experimental results.

Theoretical Studies on Mechanism. Although a crude transition state model has been proposed (Scheme 7) to explain the high diastereo- and enantio-selectivities of the reaction of hydroxyl-assisted sulfur ylide with α,β-unsaturated substrates, the detailed reaction mechanism is waiting to be disclosed. Therefore, density functional theory has been employed for the study of the mechanism and stereochemistry of the aforementioned cyclopropanation reactions. First, the reactions of *exo*-sulfur ylide 1**a** with methyl acrylate **9m** and *endo*-sulfur ylide with methyl cinnamate **9a** were chosen as models (Scheme 8).

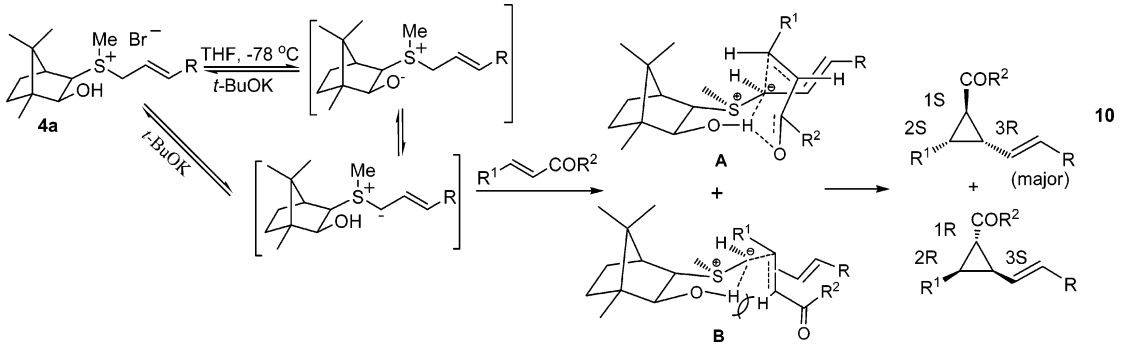
Computational Methodology

All calculations were performed with the Gaussian 03 program.[22] Geometries were fully optimized with the density functional theory of B3LYP method.[23,24] For the part of *exo*-ylide calculation, the 6-31+G*

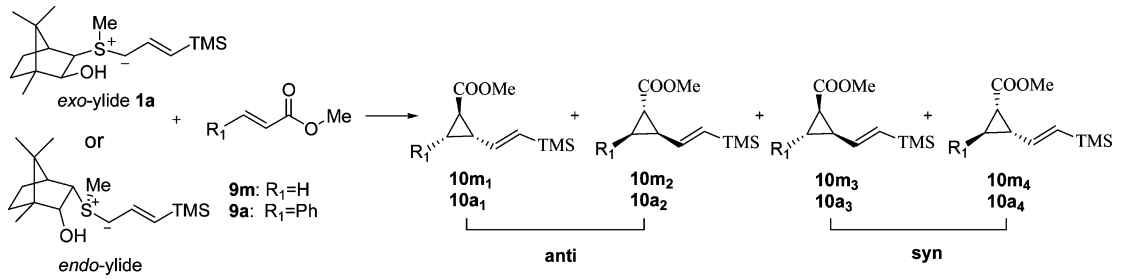
(21) The van der Waals sum of S−O is about 3.25 Å.

(22) *Gaussian 03, Revision B.03*, Frisch, M. J. et al. Gaussian, Inc., Pittsburgh, PA. **2003**.

Scheme 7



Scheme 8



basis set was used for carbon, hydrogen, and oxygen atoms and LANL2DZ basis set[25] with effective core potential (ECP) for silicon and sulfur atoms; while for the part of *endo*-ylide calculation, the standard 6-31G* basis set[26] was used for carbon, hydrogen, and oxygen atoms and ECP (LANL2DZ) basis set[25] for silicon and sulfur atoms. Harmonic vibration frequency calculations were carried out for all the stationary points to confirm each structure being either a minimum (no imaginary frequency) or a transition structure (one imaginary frequency). Solvent effect has been considered by using the IEFPCM[27] (UAHF atomic radii) model in THF ($\epsilon = 7.58$) based on the gas-phase structures. The relative Gibbs free energies given in this paper are at 298 K.

Computation Results and Discussion

We proposed that the reaction might go through a hydrogen bond model, as shown in Figure 2. Since the ylide has two conformations, with the vinyl group either syn (e.g., in **TS 21** and **TS 24**) or anti (e.g., in **TS 22** and **TS 23**) to the sulfur lone-pair. Therefore, four transition structures are possible with the hydrogen bond model for each ylide as shown in Figure 2. Such hydrogen bond model should be favorable for reducing the activation energy. We also calculated several transition structures without a hydrogen bond and indeed they have higher activation energies, and they are not discussed here.

The stereoviews of the four calculated transition structures for the reaction of exo-ylide **1a** are shown in Figure 3. In the 10-membered-ring transition structures, the H−O−C−C−S−C moiety is in a boatlike conformation. The methyl acrylate moiety is in an S-cis conformation, with the C═C−C═O dihedral angle varying from −6° to 3°. The OH- - -O═C hydrogen bonds are formed in the carbonyl planes. These hydrogen bonds are quite strong, judging from the short H- - -O distances of 1.691−1.772 Å and the nearly linear O−H- - -O angles. Three of the transition structures, **TS 21**, **TS 23**, and **TS 24**, are considerably eclipsed about the forming C- - -C bond, whereas **TS 22** is more close to a staggered conformation. Calculations indicate that in **TS 21** and **TS 23**, the methyl acrylate approaches the ylide from the front side, so that it has no steric interaction with H_8 and

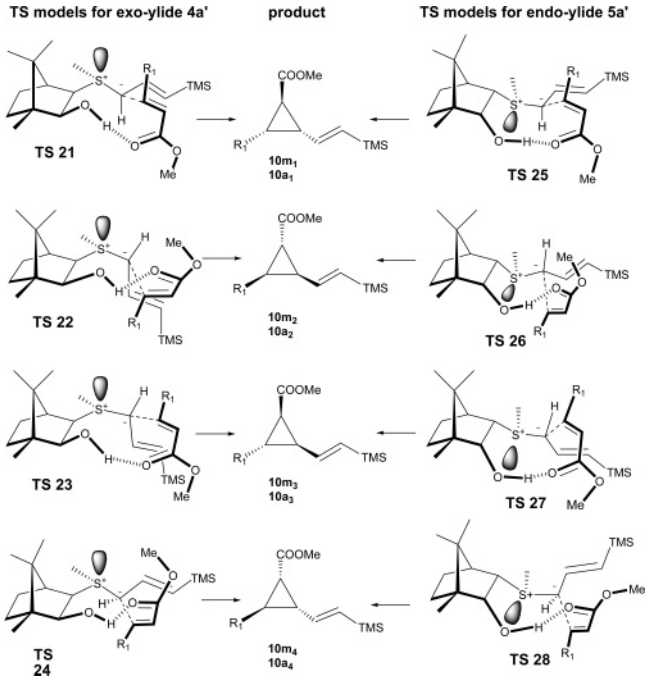


Figure 2. Analysis of hydrogen-bonded transition structure models for the reactions of *exo*-ylide **1a** with methyl acrylate **9m** and *endo*-ylide with methyl cinnamate **9a**.

(23) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785.
(24) For reviews of density-functional methods, see: (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651. (c) *Density Functional Methods in Chemistry*; Labanowski, J., Andzelm, J., Eds.; Springer: Berlin, 1991.
(25) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284.
(26) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (b) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081.
(27) (a) Cances, M. T.; Mennucci, V.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (b) Cossi, M.; Barone, V.; Tomasi, J. *Phys. Lett.* **1998**, *286*, 253.

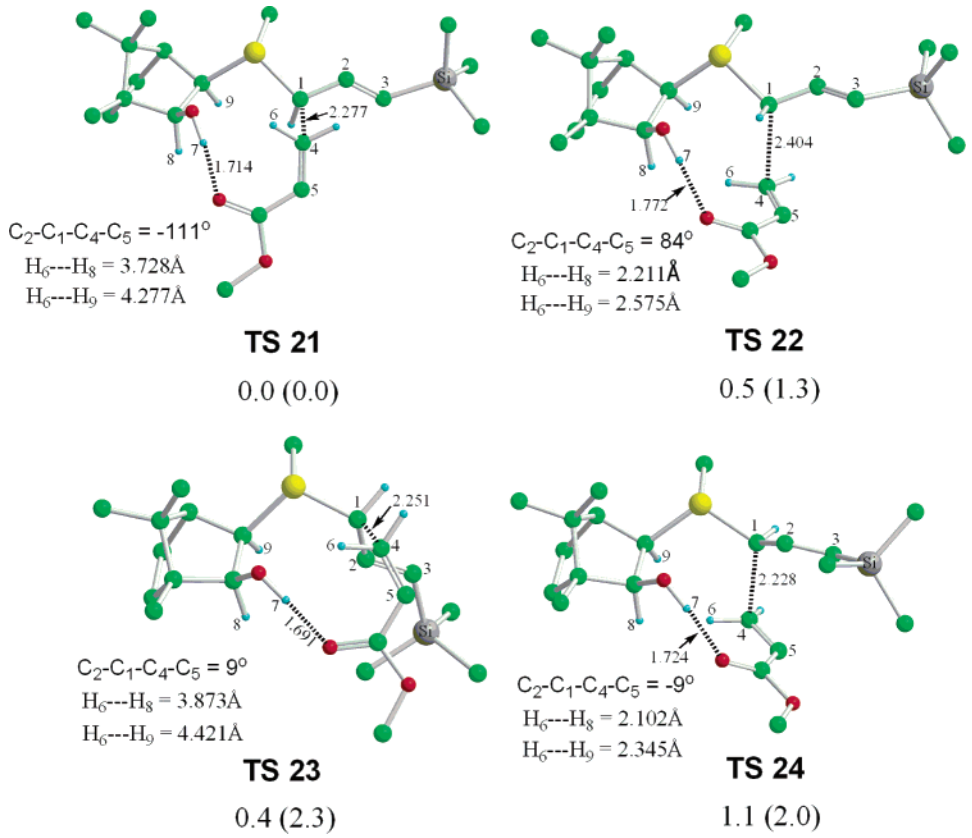


Figure 3. Stereoviews of the addition transition structures for the reaction of *exo*-sulfur ylide **1a** with methyl acrylate. Most of the H atoms in these structures are omitted for clarity. Bond distances are in angstrom. The calculated relative free energies in the gas phase and in THF solution (in parentheses) with respect to **TS 21** are in kcal/mol.

H_9 of the norbornyl moiety. On the other hand, in **TS 22** and **TS 24**, to maintain a good hydrogen-bonding, the methyl acrylate and the ylide have to rotate by about 90°. As a result, the acrylate suffers from steric interactions with the H_8 and H_9, as indicated by short H_6- - -H_8 and H_6- - -H_9 distances (Figure 3). Therefore, they are found to be less stable than **TS 21** and **TS 23**, respectively. In addition, solvent also has an effect on the stability of the transition structures. Although calculated solvent effect should be treated with care, the calculation results can be qualitatively understood. **TS 21**, which has the largest surface, benefits the most from the solvent effect. On the other hand, **TS 23** has the least surface area and benefits least from solvation. We failed to locate an intermediate for the reaction. In contrast to epoxidation and aziridination where sulfur ylide reactions with the appropriate electrophiles occur via betaine intermediates,[29] these addition transition structures lead directly to the formation of cyclopropane product and ring closure must occur without barrier. So the stereochemistry of the reaction is determined by the relative stabilities of these transition structures. As shown in Figure 3 and Table 6, the calculated results are qualitatively similar in the gas phase and in solution. That is, **TS 21** is most stable and its stability over the other transition structures is increased in solution. The calculations indicate a high selectivity for the anti product over syn product and a high enantioselectivity, both agree with the experimental observations well.

Table 6. Stereo-Selective Reactions of *Exo*-Sulfur Ylide with Methyl Acrylate and *Endo*-Sulfur Ylide with Methyl Cinnamate[28]

entry	TS	ΔH[a] (kcal/mol)	ΔS[b] (cal/mol-K)	ΔG_{gas}[c] (kcal/mol)	ΔG_{sol}[d] (kcal/mol)	PR[e]	syn:anti	ee (%)
exo-ylide	**21**	0.0	0.0	0.0	0.0	**10m$_1$**	1/99	93
	22	0.56	0.38	0.45	1.28	**10m$_2$**	(calcd)[f]	(calcd)[f]
	23	−0.12	−1.80	0.41	2.27	**10m$_3$**	<1/99	95
	24	−0.06	−3.79	1.07	2.02	**10m$_4$**	(excpt)	(expt)
endo-ylide	**25**	−0.06	−1.44	0.37	0.93	**10a$_1$**	2:98	83
	26	0.0	0.0	0.0	0.0	**10a$_2$**	(calcd)[f]	(calcd)[f]
	27	−0.67	−6.23	1.19	2.03	**10a$_3$**	<1/99	74
	28	−0.61	−4.51	0.74	1.46	**10a$_4$**	(expt)	(expt)

[a] Relative enthalpy in gas phase. [b] Relative entropy in gas phase. [c] Relative Gibbs free energy in gas phase. [d] Relative Gibbs free energy in solution (THF). [e] The corresponding cyclopropane products of each transition state (Scheme 9). [f] Calculated based on the relative Gibbs free energies in solution.

Figure 4 shows the stereoviews of the four addition transition structures for the reaction of *endo*-ylide. These transition structures have similar geometrical features with the transition structures for the reaction of the *exo*-ylide. That is, the H−O−C−C−S−C moiety is in boatlike conformation and the C═C−C═O is in an S-cis conformation. The forming C- - -C bond is in a staggered conformation in **TS 25** (−77°) and **TS 26** (83°) and it is more close to an eclipsed conformation in **TS 27** (16°) and **TS 28** (−16°).

(28) Calculations have also been carried out for the reaction of endo-sulfur ylide with methyl acrylate. The results, which are given in the Supporting Information (Table S2 on page S37−38), reproduce the experimental observation very well (Table 2, entry 20).
(29) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747.

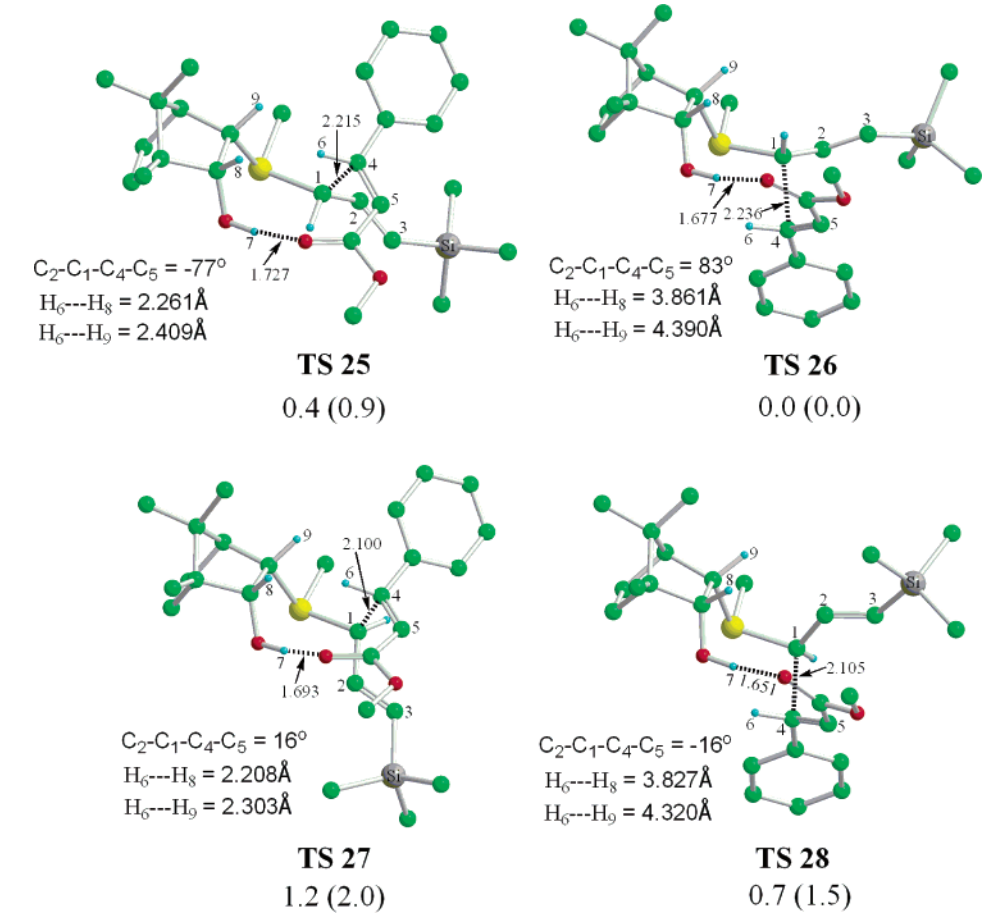


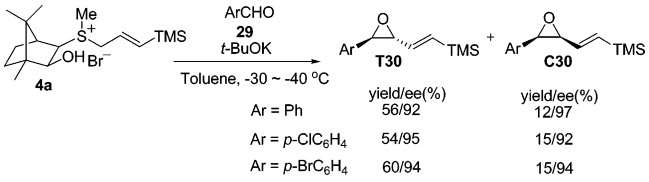
Figure 4. Stereoviews of the addition transition structures for the reaction of *endo*-sulfur ylide with methyl cinnamate. Most of the H atoms in these structures are omitted for clarity. Bond distances are in Å. Dihedral angles are in degrees. The calculated relative free energies in gas phase and in THF solution (in parentheses) with respect to **TS 26** are in kcal/mol.

Because of the constraint of the 10-membered-ring hydrogen-bonding, the methyl cinnamate in **TS 26** and **TS 28** can approach the ylide from the front side without geometrical distortion, but a rotation of the methyl cinnamate and the ylide is needed in **TS 25** and **TS 27**. Thus, the cinnamate moiety in **TS 26** and **TS 28** does not have steric interaction with the H_8 and H_9 of the norbornyl group but **TS 25** and **TS 27** suffer steric interactions, as indicated by the calculated H_6- - -H_8 and H_6- - -H_9 distances shown in Figure 4. As a result, **TS 26** and **TS 28** are more stable than **TS 25** and **TS 27**, respectively. When solvent of THF is included, **TS 26** becomes about 0.9, 2.0, and 1.5 kcal/mol more stable than **TS 25**, **TS 27**, and **TS 28**, respectively. This gives roughly a 2/98 (syn/anti) diastereoselectivity and an 83% ee enantioselectivity for the anti product, in quite good agreement with the experimental observations, as shown in Table 6.

In summary, the ten-membered-ring hydrogen-bonding model gave an excellent explanation for the opposite enantioselectivities of *exo*- and *endo*-sulfur ylide cyclopropanation reactions. Because of the ring constraint, **TS 22**, **TS 24**, **TS 25**, and **TS 27** are forced to distort so that they suffer from steric interaction with the H_8 and H_9 of the norbornyl group. In addition, solvent also seems to play an important role in enhancing both diastereoselectivity and enantioselectivity.

Highly Enantioselective Synthesis of Vinylepoxides. [30] The high selectivity in the cyclopropanation of α,β-unsaturated carbonyl compounds with sulfonium salt **4a** encouraged us to extend **4a** to the epoxidation of aldehydes (Scheme 9).

Scheme 9



Under the optimal conditions, as shown in Scheme 9, the enantioselectivities were excellent although the diastereoselectivities of the reaction of **4a** with aromatic aldehydes were only moderate (ranged from 78/22 to 82/18). For aliphatic aldehydes, epoxides were not observed.

Product Elaboration. The usefulness of the present work was exemplified in a short formal synthesis of PCCG-4, a potential and selective group II mGluRs antagonist.[31] Cyclopropylaldehyde **31** is regarded as a key intermediate for the synthesis of PCCG-4 and was reported to be synthesized from a diazoacetate in five steps.[31a] It was found that this compound could be readily prepared in high yield (total yield in two

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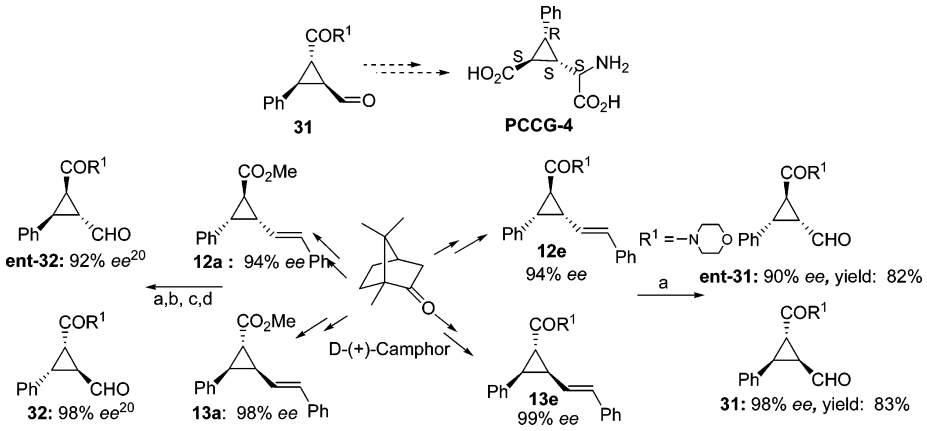
(31) (a) Marinozzi, M.; Natalini, B.; Costantino, G.; Tijskens, P.; Thomsen, C.; Pellicciari, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2243. (b) Pellicciari, R.; Marinozzi, M. M.; Natalini, B.; Costantino, G.; Luneia, R.; Giorgi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1996**, *39*, 2259.

Scheme 10 [a]



[a] Reaction conditions: (a) O_3/Ph_3P, 93%; (b) $NaClO_2 + NaH_2PO_4$, $(CH_3)_2C{=}CHCH_3$; (c) NCS + Ph_3P/morphine, 80%; (d) (i) $NaBH_4$ + LiCl, THF/EtOH, (ii) Dess−Martin oxidation, 65%.

steps: 83%) with 98% ee using the present process by ylide cyclopropanation of amide **11e**, followed by oxidation (Scheme 10). One of the advantages is that both enantiomers of **31** could be prepared with excellent enantioselectivities and in high yields. Thus, this new process allowed us to access both optically pure cyclopropylaldehyde **31** easily.

The other two stereoisomers **32** and **ent-32** of cyclopropylaldehyde **31** could also be synthesized from the vinylcyclopropane **13a** and **12a**, respectively (Scheme 10). And thus, four optically active trisubstituted cyclopropylaldehydes could be prepared easily using D-(+)-Camphor as the chiral source.

Conclusion

The newly designed chiral sulfonium ylide **1** by a sidearm approach has proven to be a highly efficient reagent for asymmetric cyclopropanation. Using the present method, both enantiomers of various functionalized vinylcyclopropanes with high enantioselectivities can be prepared conveniently from the cheap chiral source D-(+)-Camphor. A catalytic asymmetric ylide cyclopropanation using chiral sulfonium salts and phenyl allylic bromide has also been developed. The extension of this ylide to the epoxidation of aromatic aldehydes provides an easy access to vinylepoxides in excellent enantioselectivity. The role of the sidearm free hydroxyl group has been investigated and proven to be crucial in controlling the enantioselectivity. The origin of the enantioselectivity and diastereoselectivity in the current asymmetric cyclopropanation has been studied by both experiments and density functional theory calculations, revealing the importance of the hydrogen-bonding between the sidearm hydroxyl group and the substrate. The readily available ylides from cheap D-camphor, the controllable enantioselectivity, together with the easy chemical transformation make the current method highly potential for practical use in organic synthesis.

Acknowledgment. We are grateful for the financial support from the Natural Sciences Foundation of China, The Science and Technology Commission of Shanghai Municipality, and the Croucher Foundation (Hong Kong) for a studentship.

Supporting Information Available: Experimental section containing characterization of key compounds, chiral HPLC data of **10**, **12**, **13**, **16**, **30**, **31**, and **32** (**PDF**) and X-ray crystallographic files (CIF), calculated total energies and coordinates of the transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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