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Highly Selective Ylide-Initiated Michael Addition/Cyclization Reaction for Synthesis of Cyclohexadiene Epoxide and Vinylcyclopropane Derivatives

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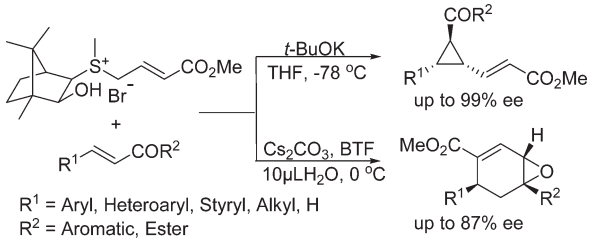

On the basis of the reactions of camphor-derived sulfur ylide with α,β-unsaturated ketone, highly efficient and selective synthesis of optically active cyclohexadiene epoxides and vinylcyclopropanes with excellent diastereoselectivities, moderate to high enantioselectivities, and yields has been achieved.

The control of reaction pathways for selective synthesis of different products from the same starting materials has attracted much attention recently[1] because such research not only maximizes the diverse utility of reactants but also benefits the understanding of reaction mechanism. During our previous research on this subject,[2] we documented that HMPA could switch the stereochemistry of the cyclopropanation reaction between telluronium allylides with α,β-unsaturated esters and amides, providing a facile synthesis of two geometrical isomers of vinylcyclopropane derivatives.[2b,c] We also observed solvent-reversed enantioselectivity in the Friedel−Crafts reaction of indole with arylidene malonates catalyzed by trisoxazoline (TOX)-derived copper complex[2f] and temperature-controlled diastereoselection in the 1,3-dipolar cycloaddition of nitrones with arylidene malonates.[2d] In addition, we reported that 2*H*-chromenes and 4*H*-chromenes could be synthesized controllably from the same starting material just by the choice of base via tetrahydrothiophene-catalyzed ylide annulation reaction.[2g]

Optically active cyclohexadiene epoxide and vinylcyclopropane derivatives are important subunits in a number of biologically active compounds[3] and also valuable synthetic intermediates.[4] Very recently, we developed a tandem reaction of crotonate-derived sulfur ylide with α,β-unsaturated ketone for the rapid construction of functionalized cyclohexadiene epoxide derivatives.[5] Further study revealed the reaction profile between sulfonium salt **1** with α,β-unsaturated ketone **2** could be switched to give rise to enantioenriched vinylcyclopropane.[6] As part of our research in ylide chemistry[7] and tunable reaction, we wish to describe the details about the aforementioned process.

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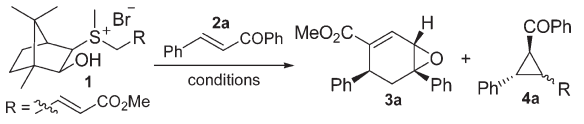
TABLE 1. Effects of Reaction Conditions on the Tandem Michael Addition/Ylide Epoxidation Reaction[a]



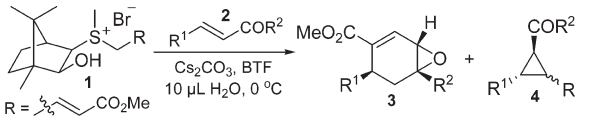
					3a	
entry	solvent	base/additive	temp (°C)	3a/4a[b]	yield[c] (%)	ee[d] (%)
1[e]	MeCN	Cs_2CO_3	0	100/0	20	88
2	MeCN	K_2CO_3	0	12.0/1	60	57
3	MeCN	$CsOH \cdot H_2O$	0	4.7/1	47	57
4	MeCN	Cs_2CO_3	0	9.8/1	49	62
5	MeCN	*t*-BuOK	0		disordered	
6	DCE	Cs_2CO_3	0	4.9/1	54	63
7	THF	Cs_2CO_3	0	3.4/1	54	57
8	AcOEt	Cs_2CO_3	0	2.9/1	55	54
9	DMF	Cs_2CO_3	0	6.5/1	52	51
10	DM SO	Cs_2CO_3	0	4.3/1	26	61
11	BTF	Cs_2CO_3	0	1.3/1	52	67
12[f]	BTF	Cs_2CO_3	0	5.2/1	67	83
13[f]	BTF	K_2CO_3	0	5.4/1	65	75
14[f,g]	BTF	Cs_2CO_3/H_2O	0	9.2/1	83	80
15[f,g]	BTF	Cs_2CO_3/H_2O	rt	7.8/1	78	79
16[f,h]	BTF	Cs_2CO_3/ n-Pr_4NI	0	5.0/1	65	77

[a]**2a** (1.0 equiv, $c = 0.07$ M) and **1** (1.5 equiv, dr = 5/1) were mixed in solvent, and then base (2.0 equiv) was added. [b]Determined by isolated yield. [c]Isolated yield. [d]Determined by chiral HPLC. [e]Ketone was added after sulfonium salt **1** and Cs_2CO_3 were mixed in CH_3CN for 1 h. [f]dr (at sulfur atom) of **1** > 25/1. [g]10 μL of H_2O was added [h]2.0 equiv of *n*-Pr_4NI was added.

Initially, we used chalcone as a substrate instead of (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one to extend the scope of our previously reported reaction.[5] Unfortunately, under the same stepwise reaction conditions (adding **2a** 1 h after mixing **1** with Cs_2CO_3),[5] only 20% yield was obtained after purification by preparative HPLC, although an excellent ratio of **3a**/**4a** and a good ee of **3a** could be delivered (entry 1). Further efforts to improve the yield failed.[8] Then, we tested a one-pot reaction. As summarized in Table 1, the solvent, base, temperature, additive, and diastereomeric purity of sulfonium salt **1** all strongly influenced the ratio of **3a** to **4a** and ee of product **3a**. When the reaction was run in MeCN with K_2CO_3 as a base, **3a** could be isolated in 60% yield and 57% ee with 12/1 ratio of **3a**/**4a** (entry 2). A slightly better ee was obtained when Cs_2CO_3 was used as a base (entries 2 vs 4). However, in the case of strong base *t*-BuOK, we observed a disordered system (entry 5). Of all solvents screened, trifluoromethylbenzene (BTF) was found to be the best in terms of the ee of compound **3a** (entry 11).

Further study demonstrated the dr of sulfonium salt **1** had profound effect on the ratio of **3a**/**4a** and ee of **3a**.[7e,9] For example, salt **1** with dr 5/1 resulted in compound **3a** with only 67% ee and a 1.3/1 ratio of **3a**/**4a** (entry 11). When a nearly diastereomeric pure salt **1** (dr > 25/1) was employed, 83% ee of **3a** could be achieved, and the ratio of **3a**/**4a** was raised to 5.2/1 (entry 12). Additives like H_2O and *n*-Pr_4NI, which would possibly benefit the formation of sulfur ylide by improving the solubility of Cs_2CO_3 and/or sulfonium salt **1**, have also been tested in order to further improve those results (entries 14−16). To our delight, the addition of H_2O could give **3a** in 83% yield and better ratio of **3a**/**4a**, albeit at cost of slightly decreased ee of **3a** (entries 12 vs 14). In all cases, no other diastereoisomer of the cyclohexadiene epoxide **3a** was observed.

TABLE 2. Stereoselective Synthesis of Cyclohexadiene Epoxides via Camphor-Derived Sulfur Ylide[a]



				3	
entry	R^1	R^2	3/4[b]	yield[c] (%)	ee[d] (%)
1	Ph	Ph (**2a**)	9.2/1	83	80
2	*p*−Cl-C_6H_4	Ph (**2b**)	13.0/1	91	85
3	*p*−Br-C_6H_4	Ph (**2c**)	7.9/1	87	87
4	*p*-NO_2−C_6H_4	Ph (**2d**)	18.8/1	75	88
5	*p*-Me-C_6H_4	Ph (**2e**)	12.7/1	76	79
6	*p*-MeO-C_6H_4	Ph (**2f**)	5.0/1	65	74
7	(*E*)-PhCH=CH	Ph(**2g**)	9.5/1	57	78
8	Me	Ph(**2h**)	8.2/1	82	67
9	H	*p*−Br-C_6H_4 (**2i**)	6.5/1	52	85
10	Ph	*p*-Me-C_6H_4(**2j**)	5.0/1	80	82
11	Ph	*p*−Cl-C_6H_4 (**2k**)	3.8/1	72	71
12	Ph	CO_2Me (**2l**)	22.5/1	45	54

[a]**2** (0.2 mmol) and **1** (113.8 mg, 0.3 mmol, dr > 25/1) were mixed in BTF (3.0 mL) at 0 °C, 15 min, Cs_2CO_3 (130.4 mg, 0.4 mmol) was added, then 10 μL H_2O was added. [b]Determined by isolated yield. [c]Isolated yield. [d]Determined by chiral HPLC.

We then decided to investigate the scope and limitation of the enantioselective tandem ylide-initiated Michael addition/epoxidation process by employing a variety of α,β-unsaturated ketones bearing different R^1 and R^2 substituents. As shown in Table 2, aryl- and alkyl-substituted as well as unsubstituted α,β-unsaturated ketones all proved to be suitable substrates to afford cyclohexadiene epoxide derivatives over the competing cyclopropanes; however, a significant substituent effect was identified. Introducing an electron-withdrawing group on the aryl substituent at the R^1 position led to increased ee (entries 1−4), which was opposite to the effect of the electron-donating group (entries 5 and 6). A vinyl-type group was also tolerable, although the yield decreased to 57% (entry 7). β-Methyl α,β-unsaturated ketone **2h** furnished the desired product in 82% yield and 67% ee (entry 8). Switching R^2 to an electron-deficient group deteriorated both the yield and ee (entries 1 vs 11 and 12). Substrate **2j**, containing a *p*-methylphenyl group at the R^2 position, participated in this tandem reaction and afforded **3j** as a major product in 80% yield with 82% ee (entry 10). To our surprise, the ee of the cyclohexadiene epoxide formed from **2i** could be up to 85% (entry 9). Noticeably, cyclohexadiene epoxide derivatives all were formed as a single diastereoisomer as depicted in Table 2.

During the study of this tandem intermolecular ylide-initiated Michael addition/epoxidation reaction, it was noticed that the distribution between **3** and **4** was variable (Table 1), which prompted us to consider the possibility that optically active vinylcyclopropanes are

(8) We also tried other different combinations of base and solvent using this addition sequence, but all gave complex systems and a low yield was obtained.

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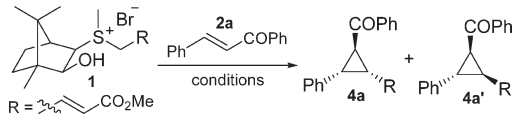
TABLE 3. Effects of Reaction Conditions on the Cyclopropanation of Sulfonium Salt 1 with Chalcone[a]



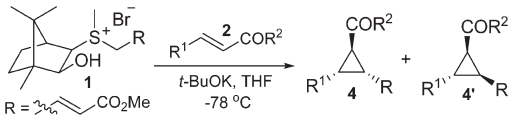
					4a	
entry	solvent	base/additive	temp (°C)	4a/4a'[b]	yield[c] (%)	ee[d] (%)
1	DME	*t*-BuOK	−50	25/1	61	98
2	EtOAc	*t*-BuOK	−78	25/1	24	98
3	CH_2Cl_2	*t*-BuOK	−78	25/1	28	97
4	EtOH	*t*-BuOK	−78		0	
5	DMF	*t*-BuOK	−40		trace	
6	MeCN	*t*-BuOK	−40		trace	
7	THF	*t*-BuOK	−78	25/1	66	97
8[e]	THF	*t*-BuOK	−78	10/1	24	98
9[f]	THF	*t*-BuOK	−78	5.0/1	50	96
10	THF	LiHMDS	−78		trace	
11	THF	NaHMDS	−78	25/1	25	96
12	THF	KHMDS	−78	3.5/1	44	98
13	THF	*t*-BuONa	−78	11/1	76	99
14[g]	THF	*t*-BuOK	−78	>99/1	65	99
15[g,h]	THF	*t*-BuOK	−78	>99/1	77	99
16[g,i]	THF	*t*-BuOK/HMPA	−78	>99/1	61	99
17[g,j]	THF	*t*-BuOK/18-crown-6	−78		trace	

[a]**2a** (62.4 mg, 0.3 mmol c = 0.05 M) and **1** (137.0 mg, 0.36 mmol, dr = 5/1) were mixed in solvent, 15 min, then base (0.72 mmol) was added in one portion. [b]Determined by ^{1}H NMR. [c]Isolated yield. [d]Determined by chiral HPLC. [e]Base (0.36 mmol). [f]Base (1.08 mmol). [g]dr (at sulfur atom) of **1** is 10/1. [h]Base was added by trisection. [i]*t*-BuOK/HMPA = 1/3. [j]*t*-BuOK/18-crown-6 = 1/3.

formed predominantly.[10] Fortunately, we found that cyclopropane **4a** was obtained in 66% yield and 97% ee in the presence of strong base *t*-BuOK using THF as solvent, and the corresponding cyclohexadiene epoxide **3a** was not observed (entry 7, Table 3). As shown in Table 3, after detailed investigation on the effects of reaction conditions, the best result was achieved when *t*-BuOK (2.4 equiv) was added in three portions to the mixture of chalcone **2a** (1.0 equiv) and sulfonium salt **1** (1.2 equiv, dr = 10/1) at −78 °C in THF. In this case, the reaction could deliver cyclopropane **4a** in 77% yield with excellent diastereo- and enantioselectivities (entry 15).

With the optimal conditions for the selective synthesis of optically active cyclopropane derivatives in hand, we set out to examine the effects of substituents at the R^1 and R^2 positions on α,β-unsaturated ketones. As exhibited in Table 4, cyclohexadiene epoxide derivatives were not observed in all cases examined. Variation of the electronic property of aryl substituents at the R^1 and R^2 positions did not influence the diastereo- and enantioselectivities too much. In this case, both excellent dr (> 25/1) and ee (99%) were consistently obtained (entries 1−7). However, introducing an electron-withdrawing group on the phenyl substituent at either the R^1 or R^2 position diminished the yield of cyclopropane (entries 1 vs 2, 3, and 7), probably because the ring-closing reaction of intermediates formed by Michael addition between ylide and unsaturated ketones is slowed in these cases. In addition, the heteroaromatic group 2-furyl could be tolerated, affording the corresponding cyclopropane in 67% yield with 97% ee and good diastereoselectivity (entry 8).

TABLE 4. Asymmetric Cyclopropanation of Sulfonium Salts 1 with Michael Acceptor[a]



entry	R^1	R^2	4/4'[b]	yield[c] (%)	ee[d] (%)
1	Ph	Ph (**2a**)	>99/1	77	99
2	*p*−Cl-C_6H_4	Ph(**2b**)	>99/1	57	99
3	*p*−Br-C_6H_4	Ph (**2c**)	>25/1	61	99
4	*p*-Me-C_6H_4	Ph (**2e**)	>99/1	87	99
5	*p*-MeO-C_6H_4	Ph (**2f**)	>99/1	78	99
6	Ph	*p*-Me-C_6H_4(**2j**)	>25/1	75	99
7	Ph	*p*−Cl-C_6H_4 (**2k**)	>25/1	56	99
8	2-furyl	Ph(**2m**)	90/10	61	97

[a]**2** (0.3 mmol, c = 0.05 M) and **1** (137.0 mg, 0.36 mmol, dr >10/1) were mixed in THF (6.0 mL) for 15 min, then *t*-BuOK (81.0 mg, 0.72 mmol) was added in three portions. [b]Determined by ^{1}H NMR. [c]Isolated yield. [d]Determined by chiral HPLC.

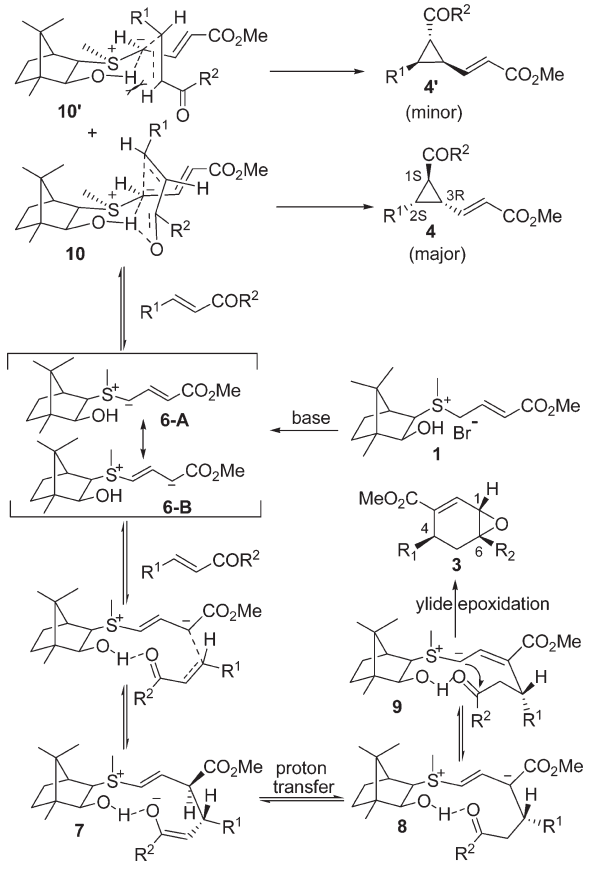


FIGURE 1. Proposed mechanism for controllable synthesis of cyclohexadiene epoxides and vinylcyclopropanes.

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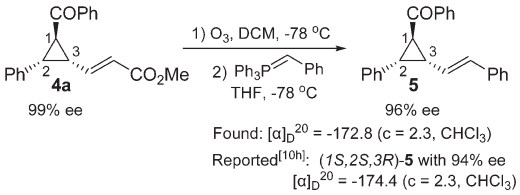
SCHEME 1. Determination of Absolute Configuration of Cyclopropane 4a



The relative configuration of cyclohexadiene epoxide and cyclopropane derivates were determined by ^{1}H NMR spectra. The absolute structures of cyclohexadiene epoxide **3c** and cyclopropane **4a** were further elucidated by X-ray analysis[11] and chemical transformation (Scheme 1)[10h] as (1*S*,4*S*,6*S*)-**3c** and (1*S*,2*S*,3*R*)-**4a**, respectively.

A mechanism is proposed to account for the observed results of the asymmetric tunable ylide-initiated reaction, although the detailed mechanistic pathway is not clear. As depicted in Figure 1, the sulfur ylide has two major contributing resonances **6-A** and **6-B**, and the latter one undergoes Michael addition with unsaturated ketone to form intermediate **7**. In the presence of a weak base such as Cs_2CO_3, the base cannot remove the proton smoothly on the α-position of ester group in intermediate **7**, and thus, the proton transfers to enolate to form **8**, allowing the intramolecular ylide epoxidation to afford the product **3** as a major product. In the presence of strong base and under low temperature condition, the intermediate **7** disfavors a proton-transfer process to form ketone **8**, and as a consequence, a normal ylide cyclopropanation between ylide **6-A** and unsaturated ketone is preferred to afford enantiomer **4** as a major product.[10h]

In summary, the camphor-derived sulfonium salt has proven to be a highly efficient reagent for asymmetric tandem intermolecular ylide-initiated Michael addition/cyclization reaction, furnishing either highly functionalized cyclohexadiene epoxide or vinylcyclopropane derivatives selectively by employing appropriate conditions as indicated above. We are now working on the understanding of the detailed mechanism, especially by theoretical chemistry.

Experimental Section

General Procedure for Asymmetric Tandem Michael Addition/Ylide Epoxidation Reaction between Sulfonium Salt 1 and α,β-Unsaturated Ketone 2c. To a stirred solution of sulfonium salt **1** (113.8 mg, 0.3 mmol) and ketone **2c** (57.4 mg, 0.2 mmol) in trifluoromethylbenzene (3 mL) was added Cs_2CO_3 (130.4 mg, 0.4 mmol) in one portion at 0 °C, followed by 10 μL of H_2O. The resulting mixture was stirred at 0 °C until the reaction was complete (monitored by TLC). The reaction mixture was passed through a short pad of silica gel and eluted with ethyl acetate. The filtrate was concentrated, and the residue was purified by flash column chromatography (petroleum ether/EtOAc = 50:1) to afford cyclohexadiene epoxide **3c**: white solid; yield 87%; **3c**/**4c** = 7.9/1; $[\alpha]^{20}_D = -172.5$ (c = 1.00, $CHCl_3$), 87% ee (determined by HPLC, Chiralcel AD, 10/90 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm, t_R (minor) = 18.95 min, t_R (major) = 23.28 min); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) 7.45 (d, J = 2.7 Hz, 2H), 7.42−7.24 (m, 5H), 7.15−7.07 (m, 1H), 7.04 (d, J = 2.4 Hz, 2H), 3.90 (ddd, J = 9.6, 7.2, 2.4 Hz, 1H), 3.52 (s, 3H), 3.40 (d, J = 3.9 Hz, 1H), 2.68 (dd, J = 15.0, 7.5 Hz, 1H), 2.42 (dd, J = 14.7, 9.9 Hz, 1H).

General Procedure for Asymmetric Cyclopropanation Reaction between Sulfonium Salt 1 and α,β-Unsaturated Ketone 2c. To a stirred solution of sulfonium salt **1** (137.0 mg, 0.36 mmol) and ketone **2c** (86.0 mg, 0.3 mmol) in THF (6 mL) was added t-BuOK (81.0 mg, 0.72 mmol) by trisection at −78 °C. The resulting mixture was stirred at −78 °C until the reaction was complete (monitored by TLC). The reaction mixture was passed through a short pad of silica gel and eluted with ethyl acetate. The filtrate was concentrated, and the residue was purified by flash column chromatography (petroleum ether/EtOAc = 20:1) to afford vinylcyclopropane **4c**: white solid; yield 61%; **4c**/**4c**′ > 25/1; mp 109−111 °C; $[\alpha]^{20}_D = -65.8$ (c = 0.75, $CHCl_3$), 99% ee (determined by HPLC, Chiralcel AD-H, 10/90 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm, t_R (major) = 14.89 min, t_R (minor) = 22.46 min); IR (thin film) ν/cm^{-1} 3066, 2945, 1709, 1659, 1450, 1260, 1143, 1022, 753; MS (EI, m/z, rel. intensity) 384 (M^+, 0.17), 105(100); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) 8.04 (d, J = 7.5 Hz, 2H), 7.65−7.45 (m, 5H), 7.16 (d, J = 8.1 Hz, 2H), 6.39 (dd, J = 15.3, 10.5 Hz, 1H), 6.06 (d, J = 15.6 Hz, 1H), 3.68 (s, 3H), 3.38−3.27 (m, 2H), 2.74 (td, J = 10.2, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 196.6, 166.2, 144.8, 137.1, 134.3, 133.5, 131.8, 130.6, 128.8, 128.1, 122.7, 121.3, 51.5, 34.6, 33.9, 32.2. Anal. Calcd for $C_{20}H_{17}BrO_3$: C, 62.35; H, 4.45. Found: C, 62.49; H, 4.44.

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Supporting Information Available: Full experimental details, CIF file for **3c**, and chiral HPLC spectra of **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) See the Supporting Information. CCDC 764421(**3c**) contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.