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Tandem Michael Addition/Ylide Epoxidation for the Synthesis of Highly Functionalized Cyclohexadiene Epoxide Derivatives

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Ylide reactions have been developed as one of the powerful approaches for the synthesis of small ring compounds.[1] Recently, much attention has been paid to the synthesis of fused bicyclic compounds via ylide routes.[2] During our study on ylide chemistry,[3] we developed a tandem reaction of allylic ylide with α,β-unsaturated ketones for the rapid construction of functionalized multisubstituted cyclohexadiene epoxides with multiple stereogenic centers. In particular, optically active cyclohexadiene epoxides could be easily prepared with high enantiomeric excesses in good yields by remote control of enantioselectivity via chiral sulfur ylides. In this communication, we will report our preliminary results.

The reactions of allylic sulfur ylides with chalcone were reported to give vinylcyclopropanes.[4] In the presence of K_2CO_3, unexpectedly, we found that the reaction of crotonate-derived sulfonium salt **1** with chalcone only gave the cyclohexadiene epoxides rather than cyclopropanes (Scheme 1). Further studies showed that both β-aryl- and β-alkyl-substituted α,β-unsaturated ketones are good substrates, affording the cyclohexadiene epoxide derivatives with excellent diastereoselectivities (>99/1) in good to high yields (60−93%). In all cases examined, cyclopropanes were not observed. As shown in Table 1, both electron-donating and electron-withdrawing substituents on the aryl ring proved to be well-tolerated but influenced slightly the yields (entries 1−4). Trifluoromethyl-substituted ketone **2e** gave cyclohexadiene epoxide **4e** in 86% yield (entry 5, Table 1). Propenylphenylketone **2f** furnished the desired product in 85% yield (entry 6). The reaction of ketone **2g** also proceeded well to afford product **4g** with high chemoselectivity (entry 7). (*E*)-Methyl-2-oxo-4-phenylbut-3-enoate and (*E*)-ethyl-2-oxopent-3-enoate also gave the desired epoxides in good yields (entries 9 and 10).

Encouraged by this tandem reaction, we also investigated its intramolecular version and found it proceeded very well (Table 2), giving the desired tricyclic cyclohexadiene epoxides with excellent diastereoselectivities (>99/1) in good to high yields (up to 85%). For example, allylic sulfonium salt **5a** was treated with K_2CO_3 to afford cyclohexadiene epoxide **6a** as a single product in 69% yield (entry 1, Table 2). Other sulfonium salts such as **5b**−**f**, which are readily available from crotonate, proved to be quite good for this cyclization (Table 2). This method provides a good way to prepare tricyclic compounds with a cyclohexadiene epoxide unit.

The present reaction makes it readily accessible to highly functionalized cyclohexadiene epoxide derivatives[6] with excellent diastereoselectivity and chemoselectivity, prompting us to develop its asymmetric version using chiral sulfur ylides. Using camphor-derived sulfonium salts **7** and **8**,[4b,c,8] fortunately, we found that both the intermolecular and the intramolecular

Scheme 1. An Unexpected Cyclization Reaction of **1**

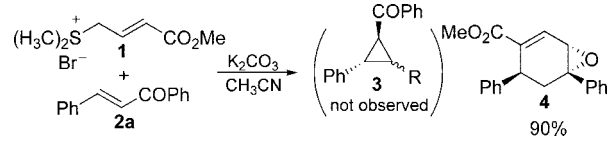
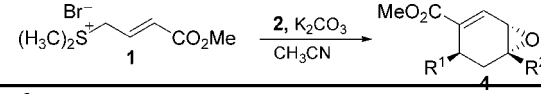


Table 1. Tandem Michael Addition/Ylide Epoxidation Reaction[5]



entry[a]	substrate **2**	T (°C)	yield (%)[b,c]
1	Ph, COPh (**2a**)	-20	90
2	p-BrC6H4, COPh (**2b**)	0	93
3	p-NO2C6H4, COPh (**2c**)	-20	80
4	p-MeOC6H4, COPh (**2d**)	0	77
5	p-MeOC6H4, COCF3 (**2e**)	-20	86
6	COPh (**2f**)	-15	85
7[d]	Ph, COPh (**2g**)	0	68
8	CO(p-Br-C6H4) (**2h**)	-20	60
9	Ph, COCO2Me (**2i**)	-20	81
10	COCO2Et (**2j**)	-20	67

[a] Conditions: sulfonium salt **1** (145 mg, 0.6 mmol), ketone (0.3 mmol), CH_3CN (3.0 mL), K_2CO_3 (166 mg, 1.2 mmol). [b] Cyclopropane derivative was not detected and dr >99/1 (by ^1H NMR). [c] Isolated yield. [d] Five equivalents of **1** was used.

reactions worked very well, furnishing the desired epoxides with higher than 91% ee in moderate to good yields (Scheme 2).[5] Thus, *the current reaction provides an excellent example for remote control of enantioselectivity*.[7]

The absolute configuration of epoxide **6d** was determined by X-ray ananlysis.[5] The stereochemical model, as shown in Figure 1, could explain the enantioselection,[4b] in which the first Michael addition attacked from the re face of the enone. A clear mechanism waits further investigation.

The functionalized epoxide derivatives[9] prepared by the current method are potentially useful. As shown in Scheme 3, for example, compound **4b** was found to react with sodium methoxide to give the corresponding ring opening product **9** with high regiospecificity. Interestingly, treatment of **4b** with $LiBEt_3H$ afforded bicyclic compound **10**[11] stereospecifically in 87% yield.

In summary, we have developed a tandem[10] Michael addition/ylide epoxidation for the rapid creation of highly functionalized cyclohexadiene epoxide skeletons with three stereocenters.

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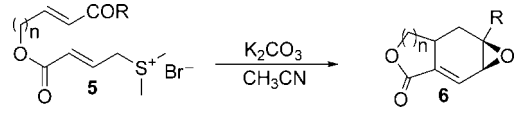
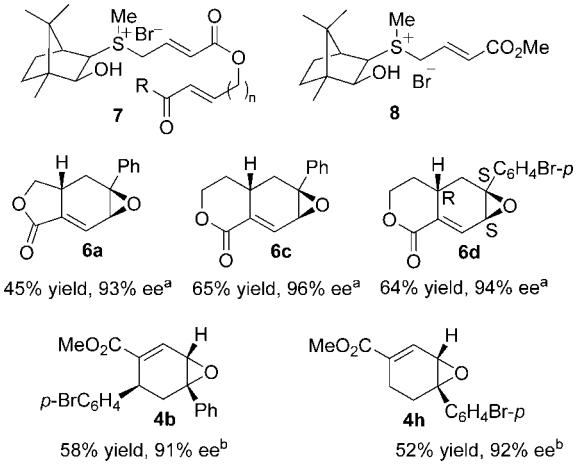
Table 2. Intramolecular Michael Addition/Ylide Epoxidation[5]



entry[a]	*n*	R	yield[b,c]
1	1	Ph (**5a**)	69
2	1	*p*-BrC_6H_4 (**5b**)	69
3	2	Ph (**5c**)	85
4	2	*p*-BrC_6H_4 (**5d**)	78
5	2	*p*-ClC_6H_4 (**5e**)	83
6	2	*p*-$OMeC_6H_4$ (**5f**)	78

[a] Conditions: **5** (0.2 mmol), CH_3CN (3.0 mL), K_2CO_3 (56 mg, 0.40 mmol), room temperature. [b] Cyclopropanes were not observed and dr >99/1 (by ^1H NMR). [c] Isolated yield.

Scheme 2. Asymmetric Michael Addition/Ylide Epoxidation[a]



[a] See ref 5. Reaction conditions: [a]**7** (0.2 mmol), K_2CO_3 (56 mg, 0.4 mmol), CH_3CN (3 mL), 0−50 °C and a trace amount of de-epoxidation product was observed; [b]**8** (dr >20/1, 171 mg, 0.45 mmol), Cs_2CO_3 (180 mg, 0.55 mmol), ketone (0.15 mmol), CH_3CN (4 mL), 0 °C.

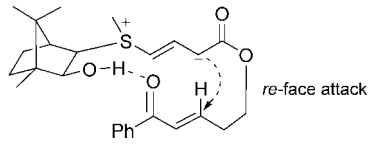
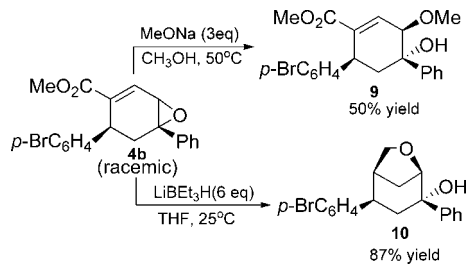


Figure 1. Stereochemical model.

Scheme 3. Product Elaboration



Although, its asymmetric version involving the remote control of selectivities, high enantioselectivity, and high diastereoselectivity could be obtained. The readily accessible starting material, mild reaction conditions, high selectivities, and recoverable chiral sulfide made the present reaction potentially useful in organic synthesis. Further studies on the mechanism are under investigation in our laboratory.

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Supporting Information Available: Detailed experimental procedures, characterization data for all new compounds (PDF), and cif files of single crystals **4a**, **6c**, **6d**, and **10** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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