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A Novel Chiral Sulfonium Ylide: Highly Enantioselective Synthesis of Vinylcyclopropanes

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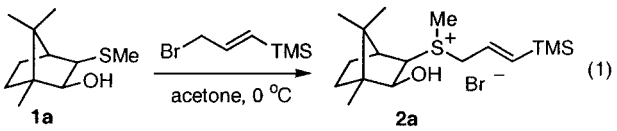
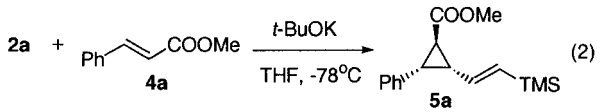
The occurrence of the vinylcyclopropane subunit in many natural and synthetic biologically active compounds,[1] as well as its utility as a synthetic intermediate,[2] has promoted many strategies for its construction.[3−6] No successful direct asymmetric synthesis of vinylcyclopropanes has been reported except for a few examples of those related to disubstituted or 1,1,2-trisubstituted compounds.[4] For the preparation of 1,2,3-trisubstituted cyclopropanes, Hanessian et al. reported a cycloaddition reaction of chiral chloroallylphosphonic amide to afford this type of compound with excellent diastereoselectivity.[5a] Very recently, Taylor found that these kind of compound also could be prepared from chiral homoallylic alcohol via several steps.[5b] In view of the difficulty associated with the regioselectivity and diastereoselectivity (cis/trans) and enantioselectivity, the highly selective synthesis of optically active 1,2,3-trisubstituted cyclopropanes in one step remains a challenging problem. In this paper, we wish to report our preliminary results on this subject.

In our previous publications, we found lithium ion played a crucial role on the stereoselective tuning of the cyclopropanation reaction of telluronium allylides with α,β-unsaturated esters or amides.[6] The mechanistic reason for this tuning in the presence of lithium ion has also been rationalized by the formation of a chelating six-membered-ring transition state, which is formed by coordination of lithium ion with carbonyl oxygen and ylidic carbanion simultaneously (A in Chart 1). On the basis of this mechanistic insight, we envisaged that it is possible to enhance the diastereoselectivity and enantionselectivity by formation of a rigid six-membered ring if a coordination group such as a hydroxyl, amino group is introduced into a chiral ylide molecule in the presence of metal ion (B in Chart 1). Thus, chiral sulfonium ylide **3a** was designed and its precursor **2a**[7] was found to be readily available from the corresponding sulfide **1a** that was easily prepared from D-camphor in two steps by a known procedure [8] (eq 1).



1a **2a** (1)

We are pleased to find that ylide **3a**, generated from the corresponding salt **2a** and KOBu^t (3.0 equiv) in situ, could react with methyl cinnamate in one pot to afford vinylcyclopropane **5a** with 97% ee in 85% yield (eq 2).



(2)

Chart 1

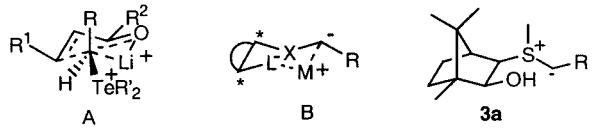
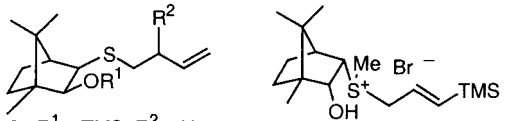


Chart 2



6a R^1 = TMS, R^2 = H
6b R^1 = H, R^2 = TMS

2b

The high yield and excellent enantioselectivity encouraged us to study the generality of this reaction by investigating a variety of α,β-unsaturated carbonyl compounds. As shown in Table 1, β-aryl-α,β-unsaturated esters, amides, ketones, and nitriles all worked well to give the desired products in good yields with excellent enantioselectivities (Table 1). For the esters, amides (entries 1−5), diastereoselectivities of this reaction were outstanding and only one diastereoisomer was obtained. When α,β-unsaturated ketones (entries 6 and 7) were applied, the chemoselectivities were excellent and no epoxides were detected. Both diastereoselectivities and enantioselectivities of their cyclopropanation reactions were excellent. Unlike simple sulfonium allylide that is hard to react with α,β-unsaturated nitrile,[9] to our surprise, ylide **3a** worked well. Moreover, their diasteroselectivities were outstanding and enantioselectivities were also excellent (entries 8 and 9). From the X-ray structure analysis of salt **2a**, the distance between the atom of sulfur and oxygen is only 2.78 Å[10] and the distortion angle of O−C_1−C_2−S is 0°. These results showed that there may exist a bonding interaction between the sulfur and the oxygen, which probably stabilizes the ylide and partially inhibits the [2,3]-σ rearrangement of ylide **3a**.

The diastereoselectivity of reaction with methyl acrylate was very high and a 95% ee was obtained (entry 10). The reaction with methyl crotonate afforded cyclopropanes **5k**/**5k′** with 84/16 diastereoselectivity and 92% ee in 20% yield (entry 11). The reaction with methyl *cis*-cinnamate only gave a trace of the desired product, probably due to its low activity (entry 12). In these two cases (entries 11 and 12) the ylide rearrangement products **6a** and **6b** (Chart 2) were obtained.

It is worth noting that the endo-isomer **2b** (Chart 2) could also react with methyl cinnamate to afford the corresponding cyclopropanation product with moderate, but opposite enantioselectivity (entry 13). Thus, either of the two enantiomers could be obtained at will just by the choice of *exo*- or *endo*-sulfonium salts, both of which were derived from cheap D-camphor.

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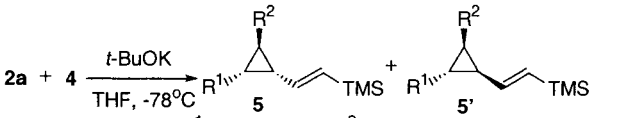
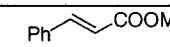
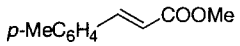
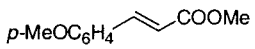
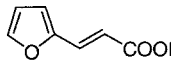
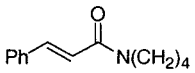
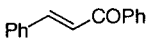
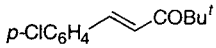
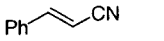
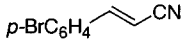
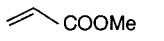
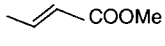
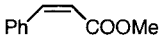
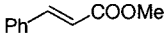
Table 1. Asymmetric Ylide Cyclopropanation of Sulfonium Salts **2a** or **2b** with Michael Acceptors



R^1 = H, CH_3, Ar; R^2 = COOR, $CONR_2$, COR, CN

Entry		4	5/5'[a]	Yield/%[b] (ee%[c])
1	**4a**		**5a** only	85 (97)
2	**4b**		**5b** only	80 (97)
3	**4c**		**5c** only	59 (96)
4	**4d**		**5d** only	57 (97)
5	**4e**		**5e** only	70 (97)
6	**4f**		90/10	81 (94[d])
7	**4g**		92/8	64 (95[d])
8	**4h**		**5h** only	61 (94)
9	**4i**		**5i** only	79 (99)
10	**4j**		**5j** only	83[e] (95)
11	**4k**		86/14	20[e,f] (92[d])
12	**4l**		ND[g]	trace[f]
13	**4a**		ent-**5a** only [h]	37 (74)

[a] Determined by ^{1}H NMR. [b] Isolated yield and sulfide **1a** was recovered in 50−70% yield. [c] Determined by chiral HPLC. [d] Enantiomeric excess of **5**. [e] 4 equiv of **4j** or **4k** was used. [f] The major products were sulfides **6a** and **6b** (Chart 2). [g] Not determined. [h] Sulfonium salt **2b** (Chart 2) was used and the enantiomer of **5a** was obtained.

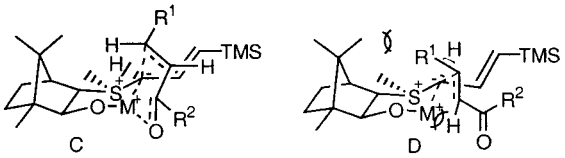
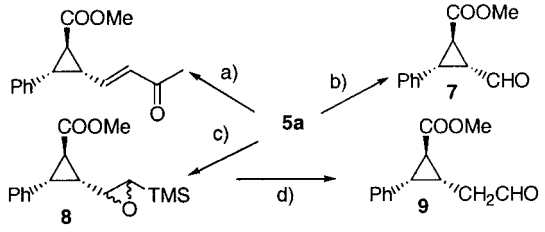


Figure 1. Proposed transition states.

The transition state model shown in Figure 1 supports all the experimental observations and is consistent with the X-ray crystal data for salt **2a**. The substrate could only approach the *re* face of the ylidic carbon due to both the effect of metal ion with the carbonyl group of the substrate and the steric effect of the *S*-methyl group. It appears that transition state C is favored over D for the effect of coordination factors. A clear mechanistic understanding waits for further investigation.

The silylvinylcyclopropane derivatives prepared by the current method should be synthetically useful. For example, compound **5a** was easily oxidized into aldehyde **7** without loss of ee, which is a key intermediate for the synthesis of biologically active compound PCCGs.[11] It could also be oxidized to afford the epoxide **8** that was treated with $HClO_4$ to form aldehyde **9** in quantitative yield (Scheme 1).

Scheme 1. Chemical Transformations of the Cyclopropane **5a**



[a] Conditions: (a) acetyl chloride, $AlCl_3$, DCM, room temperature, 72%, ref 6d; (b) $NaIO_4$, OsO_4 (cat.), Py, *t*-BuOH/H_2O, room temperature, 84%, 97% ee; (c) m-CPBA, CH_2Cl_2, room temperature, 89%; (d) $HClO_4$, THF/H_2O, room tmeperature, 100%.

In conclusion, we have developed an efficient method for one-step enantioselective synthesis of 1,3-disubstituted-2-silylvinylcyclopropanes. As a result, both diastereoselectivity (cis/trans) and enantioselectivity are excellent in most cases studied. Since the ylide is readily available from cheap D-camphor and the enantioselectivity is partially tunable, the current method has a high potential for practical use in organic synthesis. Asymmetrical ylide epoxidation is in progress in our laboratory.

Acknowledgment. We are grateful for financial support by the National Natural Sciences Foundation of China (No. 20172066). This paper is dedicated to professor Yao-Zeng Huang on the occasion of his 90th birthday.

Supporting Information Available: Synthesis and characterization of a key compound, chiral HPLC data of **5a**−**j**, *ent*-**5a**, and **7**, **and** determination of the absolute configurations of **5a**,**e**,**i**,**j** (PDF), and the X-ray structure of **2a** and **5i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Dimethylsulfonium 3′-(trimethylsilyl)allylide reacts with cinnamic nitrile under the same conditions to afford the cyclopropantion product in 4% yield with 1/1 diastereoselectivity.
(10) The van der Waals sum of S−O is 3.25 Å.
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