

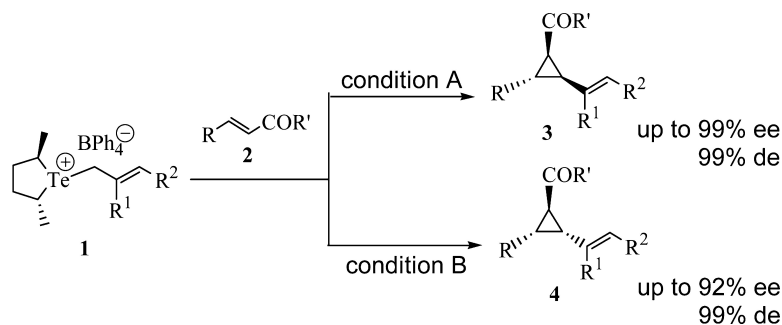
Communication

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## Controllable Diastereoselective Cyclopropanation. Enantioselective Synthesis of Vinylcyclopropanes via Chiral Telluronium Ylides

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Compounds containing vinylcyclopropane fragments have received considerable attention because of their frequent occurrence in biologically active compounds,<sup>1</sup> as well as their utility as valuable synthetic intermediates.<sup>2</sup> Although many synthetic methods have been developed,<sup>3</sup> asymmetric synthesis of multisubstituted vinylcyclopropanes with high diastereoselectivities and enantioselectivities remains a challenging problem. One of the most common methods is the transition metal-catalyzed cyclopropanation<sup>4</sup> of  $\alpha$ -diazo carbonyl compounds with electron-rich alkenes. Suzuki<sup>5a</sup> and Taylor<sup>5b</sup> found that these kinds of compounds could be prepared from optically pure homoallylic alcohol via several steps. The addition of allylic ylides  $L_nM^+CH^-CH=CHX$  to Michael acceptors is also a convenient and attractive method because ylides are readily available and  $L_nM$  is easily recovered and reused. However, practical methods for the highly enantioselective synthesis of multisubstituted vinylcyclopropanes via an ylide remain undeveloped probably due to the difficulties associated with both enantioselectivity and diastereoselectivity. Hanessian et al.<sup>6</sup> described an efficient protocol for the preparation of these kinds of compounds with excellent diastereoselectivity using a phosphonic amide as a chiral auxiliary. Recently, Aggarwal et al.<sup>7</sup> reported the reaction of a chiral silylated allylic sulfur ylide with  $\alpha$ -aminoacrylate to afford the desired vinylcyclopropane with 71% de and 75% ee. Very recently, our laboratory discovered an efficient method for the one-step enantioselective synthesis of 1,3-disubstituted-2-silylvinylcyclopropanes with high diastereoselectivity via a sulfur ylide.<sup>8</sup> However, this method is limited to the cyclopropanation of  $\beta$ -aryl- $\alpha,\beta$ -unsaturated esters, amides, ketones, and nitriles. For  $\beta$ -alkyl- $\alpha,\beta$ -unsaturated esters such as methyl crotonate, low yields are obtained due to the rearrangement of the sulfur ylide although the enantioselectivity is high. In addition, there is still lack of access to other optical isomers with different relative configurations. Despite their importance, few reports have appeared from the literature on catalytic asymmetric synthesis of 1,2,3-trisubstituted cyclopropanes with high enantioselectivity and diastereoselectivity via ylide routes. In this communication, we report an enantioselective synthesis of trisubstituted cyclopropanes with controllable diastereoselectivity and its catalytic version.

Metzner found that a  $C_2$ -symmetric sulfur ylide is a good reagent for the preparation of diarylepoxydes with high enantioselectivities.<sup>9a</sup> Very recently, they reported that the sulfur ylide could react with aldehydes enantioselectively to afford vinyl epoxides and the enantiomeric excess ranged from 37 to 90%.<sup>9b</sup> Considering that allylic telluronium ylides<sup>10</sup> are more reactive<sup>11</sup> than the corresponding sulfur ylides, we designed new telluronium salts **1** to start our study. These salts were readily prepared from (2*S*,5*S*)-(+)-2,5-hexanediolethanesulfonate.<sup>9a,12</sup> Gratifyingly, it was found that the salt **1a**, after deprotonation by LiTMP/HMPA in situ, could react with methyl cinnamate to afford vinylcyclopropane **3a** with high diastereoselectivity (96/4, **3/4**) and 96% ee in 95% yield (entry

**Table 1.** Enantioselective Cyclopropanation via Telluronium Ylides<sup>13</sup>

1a: R<sup>1</sup> = H; R<sup>2</sup> = TMS; 1b: R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = H; 1c: R<sup>1</sup> = H; R<sup>2</sup> = H;

| Entry           | Substrate | <b>1</b>  | <b>3/4</b> <sup>a</sup> | Yield(%) <sup>b</sup> | Ee (%) <sup>c</sup> |
|-----------------|-----------|-----------|-------------------------|-----------------------|---------------------|
| 1               |           | <b>1a</b> | 96/4                    | 95                    | 96                  |
| 2               |           | <b>1a</b> | 98/2                    | 97                    | 97                  |
| 3               |           | <b>1a</b> | 97/3                    | 63                    | 94                  |
| 4               |           | <b>1a</b> | 98/2                    | 88                    | 97                  |
| 5               |           | <b>1a</b> | 88/12                   | 99                    | 96                  |
| 6               |           | <b>1a</b> | 97/3                    | 97                    | 96 <sup>d</sup>     |
| 7               |           | <b>1a</b> | 94/6                    | 81                    | 97                  |
| 8               |           | <b>1a</b> | 92/8                    | 57                    | 94 <sup>e</sup>     |
| 9               |           | <b>1a</b> | 98/2                    | 95                    | 95                  |
| 10              |           | <b>1a</b> | 99/1                    | 94                    | 99 <sup>d</sup>     |
| 11              |           | <b>1a</b> | 99/1                    | 99                    | 96                  |
| 12              |           | <b>1a</b> | 98/2 <sup>f</sup>       | 78                    | 99                  |
| 13              |           | <b>1a</b> | 96/4 <sup>f</sup>       | 49                    | 98                  |
| 14              |           | <b>1a</b> | 99/1                    | 83(23 <sup>g</sup> )  | 93                  |
| 15              |           | <b>1b</b> | 97/3 <sup>f</sup>       | 81                    | 96                  |
| 16              |           | <b>1c</b> | 93/7                    | 42                    | 95                  |
| 17 <sup>h</sup> |           | <b>1a</b> | -                       | <1                    | -                   |

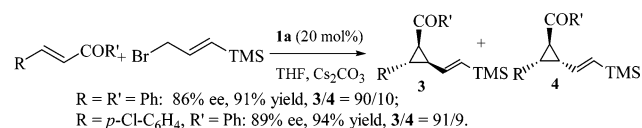
<sup>a</sup> Determined by GC and/or <sup>1</sup>H NMR except noted. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC using chiral stationary phases and for **3**. <sup>d</sup> The absolute configurations were determined by X-ray diffraction. <sup>e</sup> Determined by GC using chiral stationary phases. <sup>f</sup> Determined by GC-MS. <sup>g</sup> Conversion. <sup>h</sup> The ester recovered in 98% yield.

1, Table 1). Encouraged by the high diastereoselectivity and excellent enantioselectivity, we evaluated a variety of  $\alpha,\beta$ -unsaturated carbonyl compounds as substrates. As shown in Table 1,  $\alpha,\beta$ -unsaturated esters, amides, ketones were suitable substrates for the reaction. The reactions afforded high diastereoselectivity and enantioselectivity for  $\beta$ -aryl- and  $\beta$ -heteroaryl unsaturated esters in high yields. This ylide also proved to be efficient for methyl crotonate, which gave 94% ee in moderate yield (entry 8). Noticeably,  $\alpha,\beta$ -unsaturated ketones gave cyclopropanes in high regioselectivity (entries 9–13). No epoxides were detected in this reaction. Additionally, whatever  $\beta$ -aryl- or  $\beta$ -alkyl substituted ketones were employed, excellent ee (up to 99%) and high diastereoselectivities were obtained.  $\alpha,\beta$ -Unsaturated amides are less effective substrates in this reaction. Although both the yield and enantioselectivity were high, the conversion of cinnamylamide was low for reasons that remain unclear (entry 14). Unlike the sulfur

**Table 2.** Controlled Reversal of Diastereoselectivities<sup>13</sup>

| Entry | Substrate   | 1  | 3/4 <sup>a</sup> | Yield(%) <sup>b</sup> | Ee (%) <sup>c</sup> |
|-------|---|----|------------------|-----------------------|---------------------|
| 1     | Ph-CH=CH-CO <sub>2</sub> Me   | 1a | 4/96             | 98                    | 81 <sup>d</sup>     |
| 2     | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> -CH=CH-CO <sub>2</sub> Me              | 1a | 2/98             | 87                    | 80                  |
| 3     | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> -CH=CH-CO <sub>2</sub> Me               | 1a | 3/97             | 98                    | 83                  |
| 4     | <i>p</i> -F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub> -CH=CH-CO <sub>2</sub> Me | 1a | 7/93             | 98                    | 68                  |
| 5     | CH <sub>2</sub> =CH-CO <sub>2</sub> Me  | 1a | 18/82            | 70                    | 43 <sup>e</sup>     |
| 6     | Ph-CH=CH-C(=O)N(CH <sub>2</sub> ) <sub>5</sub>                                    | 1a | 0/100            | 83                    | 92                  |
| 7     | Ph-CH=CH-CO <sub>2</sub> Me   | 1c | 7/93             | 58                    | 61                  |

<sup>a</sup> Determined by GC and/or <sup>1</sup>H NMR except noted. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC using chiral stationary phases and for **4**. <sup>d</sup> The absolute configuration was determined by comparing the optical rotation with that of the known compounds.<sup>8</sup> <sup>e</sup> Determined by GC using chiral stationary phases.

**Scheme 1**

ylide in our previous report,<sup>8</sup>  $\alpha$ -methyl allylic and simple allylic telluronium salts **1b** and **1c** also worked well (entries 15 and 16).

In our previous study on ylide chemistry, we found that the diastereoselectivity in the cyclopropanation of  $\alpha,\beta$ -unsaturated esters and amides with telluronium allylide could be tuned by reaction conditions.<sup>14</sup> On the basis of this mechanistic insight, it is possible to tune the diastereoselectivity of this reaction, and thus, it provides a facile method for the synthesis of two optically pure isomers of trisubstituted cyclopropanes with high selectivity using the same chiral telluronium ylide, just by changing reaction conditions. As expected, by optimizing the reaction conditions, it was found that telluronium salt **1** could also react with  $\alpha,\beta$ -unsaturated esters and amides in the presence of LDA/LiBr to afford the desired products, with different diastereoselectivities compared with using LiTMP/HMPA. In most cases,  $\beta$ -aryl esters and amides gave good to high diastereoselectivities and enantioselectivities. The reaction with methyl crotonate was less enantioselective, and only 43% ee was obtained. Optical purity of the product (up to 99% ee) could be enhanced by recrystallization in some cases.<sup>13</sup> Thus, *either one of the two diastereomers could be enantioselectively synthesized at will just by the choice of LiTMP/HMPA or LDA/LiBr*. Considering that the telluride will be regenerated during the cyclopropanation, we tried a catalytic process of this reaction. It was found that, in the presence of 20 mol % of salt **1** in THF, chalcones gave the desired cyclopropane with high diastereoselectivity in high yield with up to 89% ee (Scheme 1).

To summarize, we have developed an efficient method and the first example of catalytic ylide reaction for the enantioselective synthesis of 1,3-disubstituted 2-vinylcyclopropanes with high diastereoselectivity. Noticeably, two diastereomers could be obtained at will with high enantioselectivity in some cases. Compared with our previous report, both the yields and enantioselectivities

are improved. The facile synthesis of telluride, controllable diastereoselectivity, and high enantioselectivity give this methodology high potential for practical use in organic synthesis.

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**Supporting Information Available:** Synthesis and characterization of key compounds, GC and HPLC data of **3** and **4**, mechanistic model for diastereoselectivity (PDF). X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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