



# An efficient catalytic ylide route to vinyl epoxides

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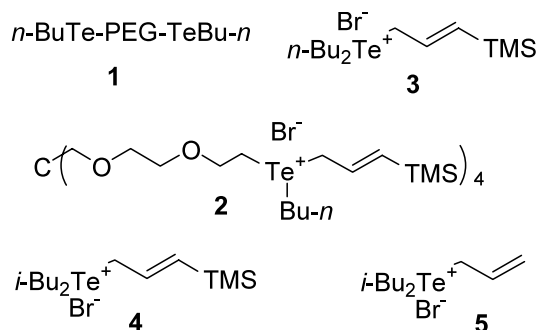
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**Abstract**—The ylide epoxidation catalyzed by telluronium salts provides a simple and extremely efficient route to vinyl epoxides in excellent yields. Both aromatic and aliphatic aldehydes work well. The best results were obtained by using 2 mol% of telluronium salts with  $\text{Cs}_2\text{CO}_3$  in *t*-BuOH. © 2003 Elsevier Science Ltd. All rights reserved.

Vinyl epoxides have proven utility as building blocks for the preparation of pharmaceutical targets<sup>1</sup> and natural products.<sup>2</sup> Of the methods available for their synthesis,<sup>3</sup> ylide epoxidation<sup>4</sup> is especially attractive as it involves the regioselective construction of the vinyl epoxide unit with concomitant formation of a carbon–carbon bond. However, in contrast to the reactions of benzylide<sup>5</sup> with aldehydes in which considerable progress has been made, the addition<sup>6</sup> of allylides to aldehydes to form vinyl epoxides is still less developed. This is probably due to the difficulties associated with [2,3]-Wittig rearrangement<sup>7</sup> and stereoselectivity.<sup>6a,8</sup> Reports from both the Osuka and Huang groups demonstrated that allylic telluronium ylides<sup>6a–c</sup> could react with aldehydes to afford desired compounds. Dai described that the stereoselectivity of ylide epoxidation could be tuned in some cases by changing both the reaction conditions and the ligands of the sulfur ylides.<sup>9</sup> To the best of our knowledge, only one catalytic version was documented, in which Huang et al. found that aldehydes could react with allyl bromide in the presence of diisobutyl telluride to give vinyl epoxides.<sup>8</sup> However, the amount of diisobutyl telluride used was 20 mol% and reduction of catalyst loading resulted in low yields even if the reaction times were prolonged. In addition, this reaction could not be extended to  $\beta$ -substituted allylic bromides, such as  $\beta$ -trimethylsilylallyl bromide. In this case, no product was formed even when a stoichiometric amount of diisobutyl telluride was used.<sup>10</sup> In our studies of ylide chemistry,<sup>11</sup> we focused on the catalytic efficiency of ylide reactions and found that PEG-telluride **1** (Scheme

1)<sup>12</sup> is a good catalyst for Wittig-type reactions, in which the catalyst loading could be reduced to 2 mol%. In this communication, we wish to report a highly efficient catalytic ylide reaction of aldehydes with  $\beta$ -silylated allyl bromide and allyl bromide to form vinyl epoxides, in which the catalyst loading was as low as 2 mol%.

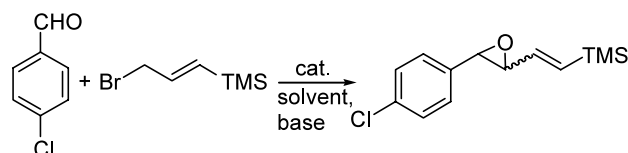
The initial attempt to employ PEG-telluride **1** as the catalyst to conduct the epoxidation under Huang's reaction conditions failed (entry 1 in Table 1). Considering that salts of PEG-telluride are more efficient than PEG-telluride itself in catalytic Wittig-type olefination, we tried 20 mol% of telluronium salt **2**, an analogue of PEG-telluronium salt, as the catalyst. We were pleased to find that the desired epoxide was isolated in 66% yield (entry 2). This suggested that the scope of catalytic ylide reaction to prepare vinyl epoxides could be extended by employing a suitable catalyst and this result encouraged us to optimize the reaction conditions to improve both the yield and catalytic efficiency. As shown in Table 1, although  $\text{K}_2\text{CO}_3$  was good as the



Scheme 1. Catalysts.

**Keywords:** catalytic ylide epoxidation; solvent effect.

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**Table 1.** Effects of reaction conditions on the catalytic ylide epoxidation<sup>a</sup>

Entry	Catalyst	Loading <sup>b</sup>	Solvent	Base <sup>c</sup>	<i>cis/trans</i>	Yield <sup>d</sup> (%)
1	<b>1</b>	20	THF	Cs <sub>2</sub> CO <sub>3</sub>	/	0
2	<b>2</b>	20	THF	Cs <sub>2</sub> CO <sub>3</sub>	47:53	66
3	<b>2</b>	20	THF–H <sub>2</sub> O	Cs <sub>2</sub> CO <sub>3</sub>	42:58	12
4	<b>2</b>	20	THF	K <sub>2</sub> CO <sub>3</sub>	44:56	62
5	<b>2</b>	20	THF	Na <sub>2</sub> CO <sub>3</sub>	/	0
6	<b>2</b>	20	THF	NaOH	/	0
7	<b>2</b>	20	THF	KOH	/	0
8	<b>2</b>	20	Toluene	Cs <sub>2</sub> CO <sub>3</sub>	/	0
9	<b>2</b>	20	DME	Cs <sub>2</sub> CO <sub>3</sub>	42:58	60
10	<b>2</b>	20	CH <sub>3</sub> CN	Cs <sub>2</sub> CO <sub>3</sub>	/	0
11	<b>2</b>	20	Dioxane	Cs <sub>2</sub> CO <sub>3</sub>	49:51	49
12	<b>2</b>	20	DMF	Cs <sub>2</sub> CO <sub>3</sub>	37:63	32
13	<b>2</b>	20	EtOH	Cs <sub>2</sub> CO <sub>3</sub>	49:51	55 <sup>g</sup>
14	<b>2</b>	20	<i>i</i> -PrOH	Cs <sub>2</sub> CO <sub>3</sub>	48:52	89 <sup>g</sup>
15	<b>2</b>	20	<i>t</i> -BuOH	Cs <sub>2</sub> CO <sub>3</sub>	48:52	84
16	<b>2</b>	10	<i>i</i> -PrOH	Cs <sub>2</sub> CO <sub>3</sub> <sup>e</sup>	49:51	69 <sup>g</sup>
17	<b>1</b>	10	<i>i</i> -PrOH	Cs <sub>2</sub> CO <sub>3</sub> <sup>e</sup>	/	0
18	<b>3</b>	10	<i>i</i> -PrOH	Cs <sub>2</sub> CO <sub>3</sub> <sup>e</sup>	49:51	77 <sup>g</sup>
19	<b>3</b>	10	<i>i</i> -PrOH	Cs <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	49:51	83 <sup>g</sup>
20	<b>3</b>	10	<i>t</i> -BuOH	Cs <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	49:51	92
21	<b>3</b>	2	<i>t</i> -BuOH	Cs <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	49:51	82
22	<b>4</b>	2	<i>t</i> -BuOH	Cs <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	49:51	86

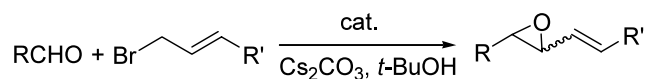
<sup>a</sup> All reactions were carried out under reflux for 10 h.<sup>b</sup> Mol% according to telluronium salt.<sup>c</sup> 2 equiv. of base used.<sup>d</sup> Isolated yield.<sup>e</sup> 1.5 equiv. of base used.<sup>f</sup> 1.1 equiv. of base used.<sup>g</sup> Etherification of alcohol with the allylic bromide was observed and this side reaction lowered the yield.

base, Cs<sub>2</sub>CO<sub>3</sub> was better. In the presence of a trace of water, the yield decreased greatly (entry 3). This reaction was found to be solvent-dependant. In toluene, no epoxide was detected at all. In ethereal solvents, this reaction gave the desired product in only moderate yields (entries 2, 9 and 11 in Table 1). Alcoholic solvents proved to be better than THF (entries 14–16 and 18–21), probably due to the formation of hydrogen bonds between the solvent and aldehydes, which activated the aldehydes.<sup>13</sup> The best solvent of those screened was *t*-BuOH (entries 20, 21). The amount of base also influenced the yield of this reaction. The best results were achieved when 1.1 equiv. of Cs<sub>2</sub>CO<sub>3</sub> was used (entry 20). Increasing the amount of base led to lower yield. Finally, we found that both dibutyl telluronium salt **3** and diiso-butyl telluronium salt **4** were better than salt **2**. The catalyst loading could be lowered from 20 to 2 mol% (entries 21, 22 in Table 1) when compound **3** or **4** was used as a catalyst. Noticeably, although the stereoselectivity was not good, the isomers could be separated easily by flash-chromatography.

Using the optimized conditions, we studied the generality of this reaction by investigating a variety of struc-

turally different aldehydes. The results are summarized in Table 2. As shown in Table 2, both electron-rich and electron-deficient aromatic aldehydes gave vinyl-type epoxides in excellent yields (entries 1–8). Compared with aromatic aldehydes, aliphatic aldehydes such as cyclohexanecarboxaldehyde and nonyl aldehyde are usually less active in catalytic ylide reactions, but they worked well (entries 9, 10) in our conditions in the presence of 20 mol% of salt **4**. It is worth noting that allyl bromide also participated in this reaction to give the desired epoxide in excellent yield (entry 11).

In the past decades, highly efficient catalysis has become one of the most important frontiers in exploratory organic synthesis research.<sup>14</sup> Compared with diisobutyl telluride and dibutyl telluride, we have found that the corresponding salts **3**, **4** and **5** are much better in catalytic ylide epoxidation reactions. The mild reaction conditions, in particular the high catalytic efficiency, provides a possibility for the regioselective synthesis of vinyl-type epoxides. Improvement of the stereoselectivity in this epoxidation is currently being studied in our laboratory.

**Table 2.** Reactions of different aldehydes with allylic bromides<sup>15</sup>

Entry	Catalyst	Loading <sup>a</sup>	R	R <sup>1</sup>	cis/trans	Yield <sup>b</sup> (%)
1	<b>3</b>	2	4-ClC <sub>6</sub> H <sub>4</sub>	TMS	49:51	82
2	<b>4</b>	2	4-ClC <sub>6</sub> H <sub>4</sub>	TMS	49:51	86
3	<b>3</b>	2	C <sub>6</sub> H <sub>5</sub>	TMS	51:49	88
4	<b>3</b>	2	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	TMS	50:50	83
5	<b>4</b>	2	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	TMS	49:51	88
6	<b>3</b>	2	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	TMS	51:49	78
7	<b>3</b>	2	2-ClC <sub>6</sub> H <sub>4</sub>	TMS	45:55	82
8	<b>3</b>	2	2-Naphthyl	TMS	52:48	92
9	<b>4</b>	20	<i>n</i> -C <sub>9</sub> H <sub>19</sub>	TMS	54:46	83
10	<b>4</b>	20	Cyclohexyl	TMS	58:42	73
11	<b>5</b>	2	4-ClC <sub>6</sub> H <sub>4</sub>	H	55:45	92

<sup>a</sup> Mol% according to telluronium salt.<sup>b</sup> Isolated yield.

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15. **Typical procedure.** To a Schlenk tube was added materials under nitrogen in the following sequence: *p*-chlorobenzyl aldehyde (350 mg, 2.5 mmol), catalyst **4**

(22 mg, 0.05 mmol), (3-trimethylsilyl)allyl bromide (723 mg, 3.75 mmol), dry  $\text{Cs}_2\text{CO}_3$  (907 mg, 2.7 mmol), and dry *tert*-butyl alcohol (5 ml). The resulting mixture was refluxed for 4 h. After the reaction was complete (monitored by GC), the reaction mixture was filtered through a silica gel pad. The filtrate was concentrated under vacuum. The residue was purified by flash-chromatographic (hexane/ethyl acetate, 200:1) to afford the product: Yield: 86%, 270 mg (*trans*-product, white solid,) and 269 mg (*cis*-product, colorless oil).