

## Remarkable Catalytic Activity of Me<sub>3</sub>Ga in the Alkylation of Hetero-Substituted Epoxides with Alkynyllithiums

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### Abstract

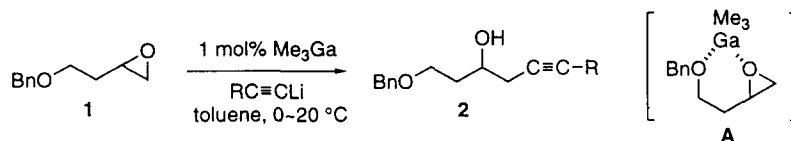
Regio- and stereoselective ring-opening reaction of hetero-substituted epoxides with alkynyllithiums can be catalyzed by Me<sub>3</sub>Ga with remarkable efficiency at 0–20 °C via pentacoordinate chelate-type complex.

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Recently, we disclosed the trimethylaluminum-catalyzed regio- and stereoselective ring opening of hetero-substituted epoxides with alkylolithiums, and demonstrated that the catalytic efficiency is ascribable to the intervention of unfamiliar pentacoordinate trialkylaluminum complexes [1]. Continuing of our interest in the reactivity and selectivity profile of pentacoordinate chelate-type complexes of other main group metals, trialkylgallium proved to be a greatly superior catalyst for this type of epoxide cleavage reaction, thereby further enhancing its synthetic potential [2]. We here wish to report that the reaction of alkynyllithiums with hetero-substituted epoxides can be effected by 1 mol% of Me<sub>3</sub>Ga catalyst in toluene at 0–20 °C via pentacoordinate chelate-type complex as a key intermediate (Scheme I) [3].

**Scheme I**

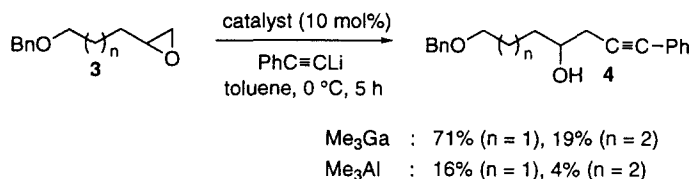


Initial treatment of epoxy ether, 1-(benzyloxy)-3-butene oxide (1) in freshly distilled toluene with PhC≡CLi in the presence of catalytic Me<sub>3</sub>Ga (10 mol%) at –78 °C and subsequent stirring at 0 °C for 5 h gave rise to the alkylation product, 1-(benzyloxy)-6-phenylhex-5-yn-3-ol (2; R = Ph) in 90% yield (entry 1, Table I). Notably, reaction of a

carbon analogue of **1**, 6-phenyl-1-hexene oxide with  $\text{PhC}\equiv\text{CLi}$  under similar reaction conditions afforded only a trace amount of the alkynylation product, 1,8-diphenyl-1-octyn-4-ol (10% yield even after stirring at 20 °C for 5 h), indicating that the possible formation of chelate type complex **A** was responsible for obtaining sufficient reactivity. It should be emphasized that the catalytic amount of  $\text{Me}_3\text{Ga}$  can be reduced to 1 mol% without losing a synthetically satisfactory level of efficiency [4]. In the absence of  $\text{Me}_3\text{Ga}$  catalyst, the alkynylation of **1** proceeded quite reluctantly (3% with  $\text{PhC}\equiv\text{CLi}$  at 0 °C for 5 h) [1]. Other selected examples are listed in Table I. The alkynylation also proceeded smoothly with  $\text{Me}_3\text{SiC}\equiv\text{CLi}$  (entries 4 and 8) but, unfortunately, not with  $\text{C}_4\text{H}_9\text{C}\equiv\text{CLi}$  (entry 5). The present catalytic method seemed to be applicable to the regio- and stereoselective cleavage of epoxy acetals and 1,2-disubstituted epoxy ethers (entries 11 and 12), though a certain decrease of the reactivity was observed.

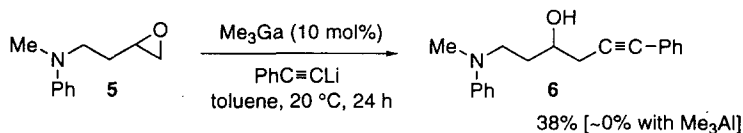
Interestingly, one carbon elongated epoxy ether, 1-(benzyloxy)-4-pentene oxide (**3**,  $n = 1$ ), also underwent smooth alkynylation with  $\text{PhC}\equiv\text{CLi}$  and catalytic  $\text{Me}_3\text{Ga}$  (10 mol%) at 0 °C giving the corresponding homopropargyl alcohol **4** ( $n = 1$ ) in 71% yield, whereas the yield was significantly lowered by use of  $\text{Me}_3\text{Al}$  under otherwise similar reaction conditions (16%), indicating the advantage of  $\text{Me}_3\text{Ga}$  in this type of epoxide cleavage assisted by chelate formation (Scheme II). In addition, subsequent examination of the alkynylation of **3** ( $n = 2$ ) revealed the limitation of our approach as also shown in Scheme II.

Scheme II



Another characteristic feature of the  $\text{Me}_3\text{Ga}$ -catalyzed alkynylation is its applicability to epoxy amines. For instance, treatment of epoxy amine **5** with  $\text{PhC}\equiv\text{CLi}$  under the influence of  $\text{Me}_3\text{Ga}$  (10 mol%) in toluene at 20 °C for 24 h produced the alkynylation product **6** in 38% yield [5]. In contrast, however, the use of  $\text{Me}_3\text{Al}$  in place of  $\text{Me}_3\text{Ga}$  as a catalyst gave none of the desired amino alcohol **6** even after prolonged reaction time (Scheme III).

Scheme III



**Table I.** Me<sub>3</sub>Ga-Catalyzed Alkylation of Hetero-Substituted Epoxides with Alkynyllithiums <sup>a</sup>

entry	alkynyllithium (RC $\equiv$ CLi)	condition (°C, h)	yield, % <sup>b</sup>
1	R = Ph	-78, 0.1; 0, 5	90 <sup>c</sup>
2	R = Ph	-78, 0.1; 0, 5	47
3	R = Ph	-78, 0.1; 20, 5	71
4	R = Me <sub>3</sub> Si	-78, 0.1; 20, 10	71
5	R = C <sub>4</sub> H <sub>9</sub>	-78, 0.1; 20, 13	21
6	R = Ph	-78, 0.1; 0, 5	69
7	R = Ph	-78, 0.1; 20, 3	80
8	R = Me <sub>3</sub> Si	-78, 0.1; 20, 10	80
9	R = Ph	-78, 0.1; 0, 5	66
10	R = Ph	-78, 0.1; 20, 5	77
11	R = Ph	-78, 0.1; 20, 5	47
12	R = Ph	-78, 0.1; 20, 5	46 <sup>c</sup>

<sup>a</sup> Unless otherwise specified, the reaction was carried out with 1.1 equiv of alkynyllithium in distilled toluene under the given reaction conditions in the presence of 1 mol% of Me<sub>3</sub>Ga. <sup>b</sup> Isolated yield. <sup>c</sup> Use of 10 mol% of Me<sub>3</sub>Ga.

A typical experimental procedure follows (Table I, entry 3): To a solution of phenylacetylene (543  $\mu\text{L}$ , 4.8 mmol) in freshly distilled toluene was added 1.56 M hexane solution of BuLi (2.82 mL, 4.4 mmol) at 0  $^{\circ}\text{C}$  under argon and the mixture was stirred for 30 min. After cooling to -78  $^{\circ}\text{C}$ , epoxy ether **1** (713 mg, 4 mmol) was added dropwise followed by the addition of 0.5 M hexane solution of  $\text{Me}_3\text{Ga}$  (80  $\mu\text{L}$ , 0.04 mmol). The resulting mixture was then allowed to warm to 20  $^{\circ}\text{C}$  and stirred there for 5 h. The solution was poured into 1 *N* HCl and extractive workup was performed with ether. The combined organic extracts were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (EtOAc/hexane = 1:4 as eluant) gave 1-(benzyloxy)-6-phenylhex-5-yn-3-ol (**2**, R = Ph; 796 mg, 2.84 mmol, 71% yield) as a colorless oil.

#### *Acknowledgments*

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#### *References and Notes*

- [1] Ooi T, Kagoshima N, Ichikawa H, Maruoka K. *J. Am. Chem. Soc.* 1999;121:3328. See also: Ooi T, Kagoshima N, Maruoka K. *J. Am. Chem. Soc.* 1997;119:5754.
- [2] For a review of epoxide chemistry including ring opening, see: Gorzynski SJ. *Synthesis* 1984:629.
- [3] Utimoto K, Lambert C, Fukuda Y, Shiragami H, Nozaki H. *Tetrahedron Lett.* 1984;25:5423.
- [4] Attempted reaction of **1** with  $\text{PhC}\equiv\text{CLi}$  under the influence of  $\text{Me}_3\text{Ga}$  (1 mol%) in THF at 20  $^{\circ}\text{C}$  for 5 h gave only a trace amount of **2**, probably because of interference with the crucial chelate formation by the coordination of THF solvent to the gallium center. This result could also exclude the possibility that the ate complex might be an active species for the present alkynylation. See ref. 3.
- [5] The reaction conditions were not optimized.