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Remarkable Catalytic Activity of Me3Ga in the Alkylation of Hetero-Substituted Epoxides with Alkynyllithiums

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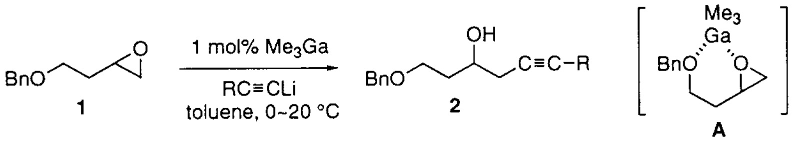
Abstract

Regio- and stereoselective ring-opening reaction of hetero-substituted epoxides with alkynyllithiums can be catalyzed by Me_3Ga with remarkable efficiency at 0~20 °C via pentacoordinate chelate-type complex.

Keywords: Alkylation, Epoxides, Gallium and Compounds, Lithium and Compounds

Recently, we disclosed the trimethylaluminum-catalyzed regio- and stereoselective ring opening of hetero-substituted epoxides with alkyllithiums, 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_3Ga 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_3Ga (10 mol%) at -78 °C and subsequent stirring at 0 °C for 5 h gave rise to the alkynylation product, 1-(benzyloxy)-6-phenylhex-5-yn-3-ol (**2**; R = Ph) in 90% yield (entry 1, Table I). Notably, reaction of a

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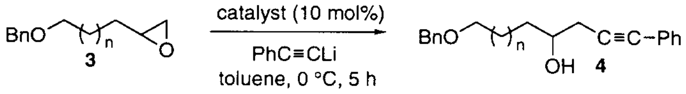
carbon analogue of **1**, 6-phenyl-1-hexene oxide with $PhC \equiv CLi$ under similar reaction conditions afforded only a trace amount of the alkynylation product, 1,8-diphenyl-1-octyn-4-ol (10% yield even after stirring at 20 °C for 5 h), indicating that the possible formation of chelate type complex **A** was responsible for obtaining sufficient reactivity. It should be emphasized that the catalytic amount of Me_3Ga can be reduced to 1 mol% without losing a synthetically satisfactory level of efficiency [4]. In the absence of Me_3Ga catalyst, the alkynylation of **1** proceeded quite reluctantly (3% with $PhC \equiv CLi$ at 0 °C for 5 h) [1]. Other selected examples are listed in Table I. The alkynylation also proceeded smoothly with $Me_3SiC \equiv CLi$ (entries 4 and 8) but, unfortunately, not with $C_4H_9C \equiv CLi$ (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 $PhC \equiv CLi$ and catalytic Me_3Ga (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 Me_3Al under otherwise similar reaction conditions (16%), indicating the advantage of Me_3Ga 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.

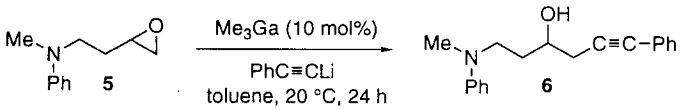
Scheme II



Me_3Ga : 71% (n = 1), 19% (n = 2)
Me_3Al : 16% (n = 1), 4% (n = 2)

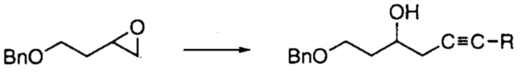
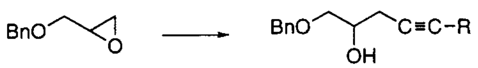
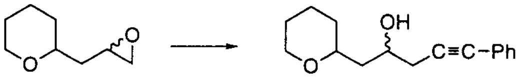
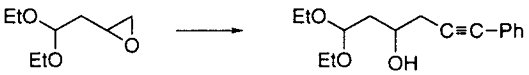
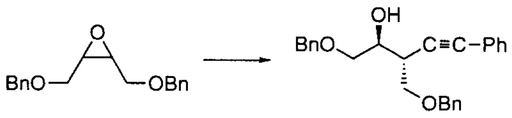
Another characteristic feature of the Me_3Ga-catalyzed alkynylation is its applicability to epoxy amines. For instance, treatment of epoxy amine **5** with $PhC \equiv CLi$ under the influence of Me_3Ga (10 mol%) in toluene at 20 °C for 24 h produced the alkynylation product **6** in 38% yield [5]. In contrast, however, the use of Me_3Al in place of Me_3Ga as a catalyst gave none of the desired amino alcohol **6** even after prolonged reaction time (Scheme III).

Scheme III



38% [~0% with Me_3Al]

Table I. Me_3Ga-Catalyzed Alkylation of Hetero-Substituted Epoxides with Alkynyllithiums [a]

entry	alkynyllithium ($RC \equiv CLi$)	condition (°C, h)	yield, % [b]
	 1 → 2		
1	R = Ph	-78, 0.1; 0, 5	90 [c]
2	R = Ph	-78, 0.1; 0, 5	47
3	R = Ph	-78, 0.1; 20, 5	71
4	R = Me_3Si	-78, 0.1; 20, 10	71
5	R = C_4H_9	-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_3Si	-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 [c]

[a] 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_3Ga. [b] Isolated yield. [c] Use of 10 mol% of Me_3Ga.

A typical experimental procedure follows (Table I, entry 3): To a solution of phenylacetylene (543 µL, 4.8 mmol) in freshly distilled toluene was added 1.56 M hexane solution of BuLi (2.82 mL, 4.4 mmol) at 0 °C under argon and the mixture was stirred for 30 min. After cooling to -78 °C, epoxy ether **1** (713 mg, 4 mmol) was added dropwise followed by the addition of 0.5 M hexane solution of Me_3Ga (80 µL, 0.04 mmol). The resulting mixture was then allowed to warm to 20 °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 Na_2SO_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 PhC ≡ CLi under the influence of Me_3Ga (1 mol%) in THF at 20 °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.