Effect of Crown Ethers on the Regioselectivity of Allylation of Benzaldehyde with Allylic Barium Reagents

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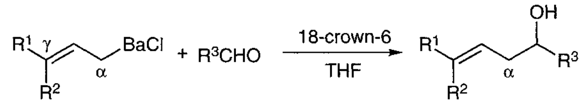
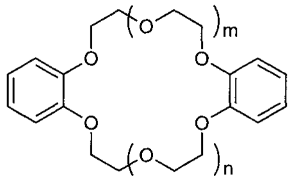
Abstract: An increase of α-regioselectivity was observed in the reaction of allylic barium reagents with aldehydes employing crown ether as an additive. For example, an α/γ regioselectivity was improved to 98/2 from 92/8, when an equimolar amount of 18-crown-6 was added to geranylbarium reagent in THF at -78 °C prior to the reaction with benzaldehyde.

An allylic barium reagent is an unprecedented allylating agent which reacts highly selectively at the least substituted allylic terminus (α-carbon) and the double-bond geometry of the barium reagent is completely retained throughout the reactions at low temperature.[1] A variety of electrophiles can be allylated in high yield with the new allylic organometallics, however, there exists a problem with the regioselectivity. In general, allylic barium reagents possessing small alkyl substituents at the γ-position such as prenyl- or crotylbarium and (*Z*)-2-alkenylbarium reagents show relatively lower α-regioselectivity in the allylation reactions. Reported herein is a solution to this problem. The α-regioselectivity was improved using crown ether as an additive for the reaction of allylic barium reagents with aldehydes (eq 1).



$$R^1R^2C{=}CH\text{-}CH_2BaCl + R^3CHO \xrightarrow[\text{THF}]{\text{18-crown-6}} R^1R^2C{=}CH\text{-}CH_2CH(OH)R^3 \quad (1)$$

THF is usually the most effective solvent for preparation of an allylic barium reagent from the corresponding allylic chloride and reactive Rieke barium,[1,2] and for the subsequent allylation reaction. Use of other solvent results in low yield of the product or no generation of the Rieke barium. We anticipated that if a stable complex of an allylic barium reagent with an appropriate ligand was formed and had enough reactivity toward electrophiles, a higher α-regioselectivity might be obtained. Thus, we examined various polyethers as additives for the reaction of allylic barium reagents with aldehydes. An equimolar amount of polyether was added to geranylbarium chloride in dry THF at -78 °C followed by treatment with benzaldehyde to afford a mixture of α- and γ-products. When dioxane, DME, or diglyme was used as an additive, no definite difference in regioselectivity from the control experiment (α/γ = 92/8) was observed. However, employment of longer acyclic polyethers, triglyme and tetraglyme provided lower α/γ selectivities, 90/10 and 82/18, respectively. In contrast, addition of crown ether to the allylic barium reagent produced good results (Table 1). Among the crown ethers tested, 18-crown-6 indicated the highest α-selectivity (α/γ = 98/2, entry 4).[3] Further improvement of the α/γ ratio was not observed with more than one equivalent of 18-crown-6 (entries 5 and 6). Smaller or larger ring size of crown ethers decreased the α-regioselectivity (entries 2, 3, and 7-9). Asymmetric allylation is a challenging subject[4] and as far as we know, an enantioselective α-allylation using allylic metal reagents has not yet been realized. We applied an optically active crown ether, (2*R*,3*R*)-2,3-dimethyl-18-crown-6 (**4**)[5] to this reaction system, however, the enantioselectivity of the α-product was low (6% ee, entry 10).



1 (m = 1; n = 2)
2 (m = 2; n = 2)
3 (m = 3; n = 3)

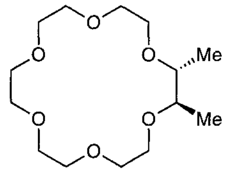


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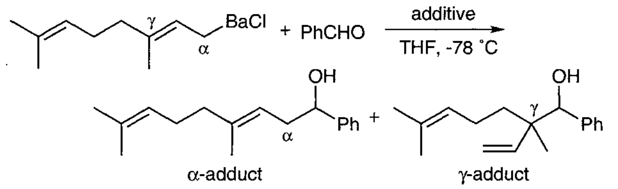
Table 1. Additive effect of crown ether on the regioselectivity of allylation of benzaldehyde with geranylbarium reagent[a]



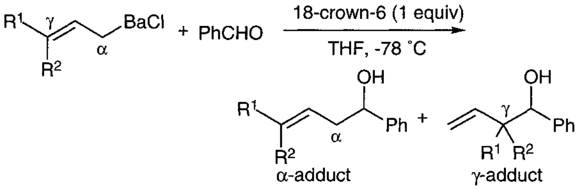
Entry	Additive	Yield (%)[b]	α/γ[c]
1	—	99	92/8
2	12-crown-4	10	62/38
3	15-crown-5	59	82/18
4	18-crown-6	99	98/2
5	18-crown-6 (2 equiv)	99	98/2
6	18-crown-6 (3 equiv)	62	96/4
7	Dibenzo-21-crown-7 (**1**)	97	58/42
8	Dibenzo-24-crown-8 (**2**)	67	53/47
9	Dibenzo-30-crown-10 (**3**)	99	74/26
10	(2*R*,3*R*)-2,3-Dimethyl-18-crown-6 (**4**)	65	98/2 (6% ee)[d]

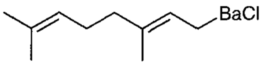
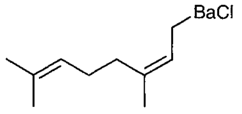
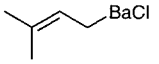
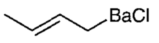
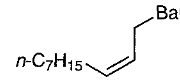
[a] Unless otherwise specified, the reaction was carried out using geranylbarium reagent (1 equiv), crown ether (1 equiv), and benzaldehyde (0.5 equiv) in THF at -78 °C for 30 min. [b] Isolated yield. [c] Determined by GLC analysis. The *E*/*Z* ratios of the α-products were 98/2 ~ 96/4. [d] The enantiomeric excess corresponds to the *E*-isomer of the α-product. The value was determined by HPLC analysis (Chiralcel AD, Daicel Chemical Industries, Ltd.) of the acetate ester of the product.

Next, we investigated the reaction of various allylic barium reagents with benzaldehyde in the presence of 1 equiv of 18-crown-6. Some of the results are summarized in Table 2. In addition to geranylbarium reagent, its Z-isomer, nerylbarium reagent also gave an α/γ ratio of 98/2 (entry 2). Similar additive effect was observed with prenyl-, (*E*)-crotyl-, and (*Z*)-2-decenylbarium reagents and the α-selectivities were improved by 11 ~ 6% (entries 3-5).

It is unknown why an allylic barium reagent reacts selectively at the α-carbon with an electrophile, however, a four-membered cyclic transition-state structure involving C–Ba and C=O bonds is a probable model for the α-selective allylation since the long C–Ba bond (2.76 ~ 2.88 Å)[6] might interrupt the formation of an ordinary six-membered cyclic structure leading to a γ-product. Complexation of the allylic barium reagent with 18-crown-6 will cause the C–Ba bond to elongate and thus enlarge the difference in stability between the two transition-state structures to supply a higher α-selectivity (Figure 1).

Table 2. Allylation of benzaldehyde with various allylic barium reagents in the presence of 18-crown-6[a]



Entry	Allylic barium reagent[b]	Yield (%)[c]	α/γ[d]
1		99	98/2[e] (92/8)
2		56	98/2[f] (96/4)
3		99	81/19 (75/25)
4[g]		48	75/25 (66/34)
5		73	81/19[h] (70/30)

[a] The reaction was carried out using an allylic barium reagent (1 equiv), 18-crown-6 (1 equiv), and benzaldehyde (0.5 equiv) in THF at -78 °C for 30 min. [b] Unless otherwise noted, the allylic barium reagent was prepared from the corresponding stereochemically pure (>99%) allylic chloride. [c] Isolated yield. [d] Determined by GLC analysis. The α/γ ratios of the reaction in the absence of 18-crown-6 are indicated in parentheses. [e] The E/Z ratio of the α-product was 97/3. [f] The E/Z ratio of the α-product was <1/99. [g] A 87:13 mixture of (E)- and (Z)-crotyl chloride was used for preparation of the crotylbarium reagent. [h] The E/Z ratio of the α-product was <1/99.

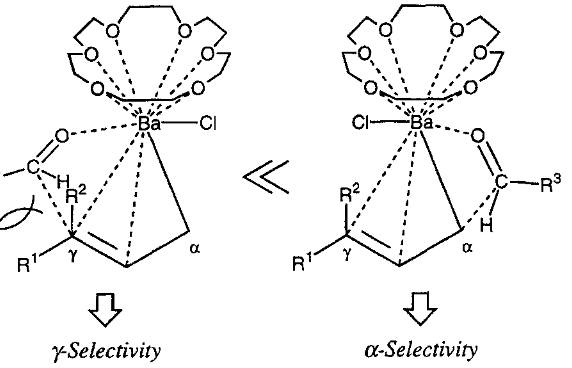


Figure 1. Plausible transition-state structures of the α-selective reaction of allylic barium reagents with aldehydes in the presence of 18-crown-6

A representative experimental procedure is given by the reaction of benzaldehyde with geranylbarium chloride in the presence of 1 equiv of 18-crown-6 (entry 4 in Table 1 and entry 1 in Table 2): An oven-dried, 20 mL Schlenk tube equipped with a Teflon®-coated magnetic stirring bar was flushed with argon. Freshly cut lithium (14 mg, 2.0 mmol) and biphenyl (320 mg, 2.1 mmol) were put into the apparatus and covered with dry THF (5 mL), and the mixture was stirred for 2 h at 20-25 °C (lithium was completely consumed). Anhydrous BaI_2[7] (400 mg, 1.0 mmol) was placed in a separate oven-dried, 50 mL Schlenk tube also equipped with a Teflon®-coated magnetic stirring bar under argon atmosphere; this was covered with dry THF (7 mL), and stirred for 5 min at room temperature. To the solution of BaI_2 in THF was added at room temperature a solution of the lithium biphenylide in THF through a stainless steel cannula under an argon stream. The reaction mixture was stirred for 1 h at room temperature. A solution of geranyl chloride (168 mg, 1.0 mmol) in THF (2 mL) was added over a period of 20 min with a syringe pump to the resulting dark brown suspension of reactive Rieke barium (1.0 mmol) in THF (12 mL) at -78 °C. After being stirred for 20 min, the mixture was treated with 18-crown-6 (260 mg, 1.0 mmol) in THF (5 mL) at -78 °C and again stirred for 10 min at this temperature. Then, a solution of benzaldehyde (52 mg, 0.49 mmol) in THF (1 mL) was added at -78 °C and the reaction mixture was stirred for 30 min. To the mixture was added a saturated NH_4Cl aqueous solution (10 mL) at -78 °C and the aqueous layer was extracted with ether (10 mL). The combined organic extracts were washed with 1 N sodium thiosulfate solution (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration. The crude product was purified by flush column chromatography on silica gel (1:20 ether/hexane and then 1:10 ethyl acetate/hexane as the eluants) to afford a mixture of 4,8-dimethyl-1-phenyl-3,7-nonadien-1-ol (α-adduct) and 2,6-dimethyl-1-phenyl-2-vinyl-5-hepten-1-ol (γ-adduct) in 99% combined yield (119 mg) as a colorless oil; the α/γ and E/Z ratios were determined to be 98/2 and 97/3, respectively by GLC analysis.[8]

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References and Notes

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(6) Kaupp, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1992**, *114*, 491.

(7) Anhydrous BaI_2 was prepared by drying $BaI_2 \cdot 2H_2O$ (extra pure reagent, Nacalai Tesque) at 150 °C for 2 h under reduced pressure (<10 Torr).

(8) 4,8-Dimethyl-1-phenyl-3,7-nonadien-1-ol (α-adduct): TLC R_f 0.33 (1:5 ethyl acetate/hexane); IR (neat) 3630-3120, 2967, 2917, 2857, 1670, 1603, 1495, 1453, 1377, 1049, 911 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 6 H, 2 CH_3), 1.69 (s, 3 H, CH_3), 1.98-2.15 (m, 5 H, 2 CH_2 and OH), 2.39-2.56 (m, 2 H, CH_2), 4.69 (dd, 1 H, *J* = 5.6, 7.5 Hz, CH), 5.07 (m, 1 H, vinyl), 5.17 (t, 1 H, *J* = 7.8 Hz, vinyl), 7.25-7.41 (m, 5 H, aromatic). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.55; H, 10.10.