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Group-Selective Hydroalumination: A Novel Route to Stereogenic *tert*-Alcohol Centers

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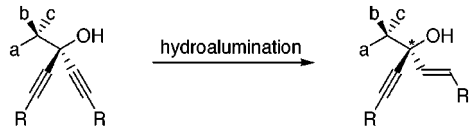
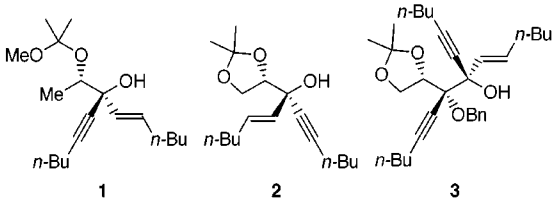
ABSTRACT



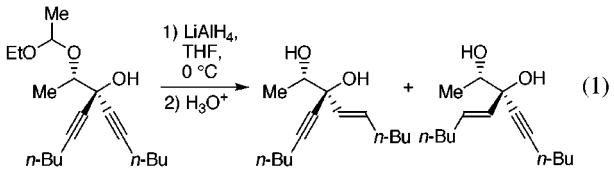
A new group-selective reaction is described, that is, the hydroalumination of bis-alkynyl alcohols armed with an adjacent stereogenic center, giving stereo-defined *tert*-alcohols of potential utility in natural product synthesis.

We report herein a new group-selective reaction[1] which provides us access to a class of stereo-defined *tert*-alcohols, e.g., **1**−**3**, with potential utility in natural product synthesis.



1 **2** **3**

Our interest in this topic traces back to a small, unexpected finding in our previous project shown in eq 1.[2] The reaction of bis-alkynyl alcohol **4**[3] with $LiAlH_4$ [4,5] stopped at the *mono*-hydroalumination stage, and amazingly, one of the two 1-hexynyl groups reacted predominantly, giving, after deprotection, the diol **5a** in favor of **5b**.[6]



4 **5a** **5b** (1)

80% (**5a**/**5b** = 88/12)

With no obvious rationale available, we undertook a systematic study on the structure-selectivity relationship,[7]

(1) For selected examples of group-selective reactions, see: (a) Curran, D. P.; Qi, H.; DeMello, N. C.; Lin, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8430−8431. (b) Curran, D. P.; Geib, S. J.; Lin, C.-H. *Tetrahedron: Asymmetry* **1994**, *5*, 199−202. (c) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477−5480. (d) Harada, T.; Wada, I.; Uchimura, J.; Inoue, A.; Tanaka, S.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1219−1222 (e) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529. (f) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303−5305. (g) Waldmann, H. *Organic Synthesis Highlights II*; VCH: New York; pp 203−222, and the references therein.

(2) Nagasawa, T.; Taya, K.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949−8950.

(3) Easily prepared from the corresponding ester derivative by treatment with 2.5 equiv of alkynyllithium.

(4) For the hydroalumination reaction of propargyl alcohols, see: (a) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094−1111. (b) Jorgenson, M. J. *Tetrahedron Lett.* **1962**, *13*, 559−562. (c) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. A. *J. Am. Chem. Soc.* **1967**, *89*, 4245−4247. (d) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618−5620. (e) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314−6319. (f) Semmelhack, M. F.; Wu, E. S. C. *J. Am. Chem. Soc.* **1976**, *98*, 3384−3386. (g) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114−4125. (h) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595−4597. For the mechanism of hydroalumination, see: (i) Franzus, B.; Snyder, E. I. *J. Am. Chem. Soc.* **1965**, *87*, 3423−3429. (j) Snyder, E. I. *J. Org. Chem.* **1967**, *32*, 3531−3534. (k) Borden, W. T. *J. Am. Chem. Soc.* **1970**, *92*, 4898−4901. (l) Grant, B.; Djerassi, C. *J. Org. Chem.* **1974**, *39*, 968−970. (m) Kakinuma, K.; Matsuzawa, T.; Eguchi, T. *Tetrahedron* **1991**, *47*, 6975−6982.

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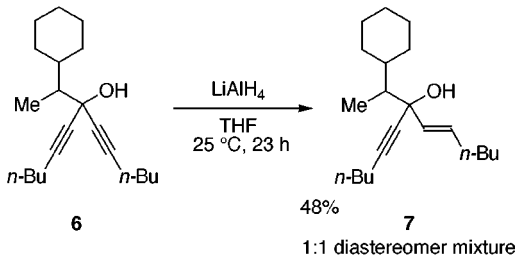
which has now allowed us to propose a working model for explaining and predicting the group selectivity.

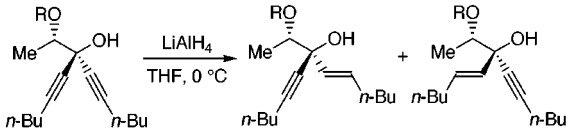
Three experimental results served as the basis for working out the model: (1) The presence of an α-alkoxy group is essential for the selectivity as well as the reactivity: the non-alkoxy substrate **6** underwent a very slow, nonselective reaction to give a poor yield of **7** as a 1/1 mixture of diastereomers (eq 2). (2) A bulky α-alkoxy group is



(2)

preferable. While a MOM group led to poor selectivity (Table 1, run 1; cf. run 2 = eq 1), a bulky protecting group such as

Table 1[7]

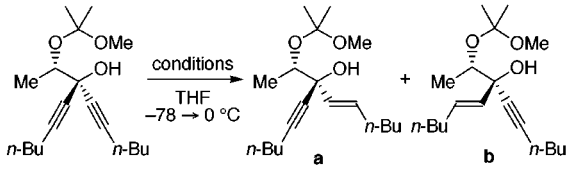


runs	R-	yield/%	a/b[a]
		a	b
1	MeO (MOM)	90	83/17
2 (= eq. 1)	Me EtO (EE)	80	88/12[b]
3	Me Me MeO (MME)	90	94/6
4	Me	87	59/41
5	*t*-Bu	87	>99/<1

[a] Determined by ^{1}H NMR. [b] After removal of the EE group, ratios of the diastereomers were assessed by ^{1}H NMR.

1-methyl-1-methoxyethyl (MME; run 3) led to high group selectivity. The same trend applied to the ether-type protection; *tert*-butyl ether gave a single product (run 5), which stands in contrast to a nonselective reaction with the methyl ether (run 4). (3) As the countercation, lithium is essential. The group selectivity decreased substantially when $NaAlH_4$ was used instead of $LiAlH_4$ (Table 2; cf. Table 1, run 3).

Table 2



conditions	yield/%	a/b[a]
$NaAlH_4$ (2.0 eq.)	90	73/27
$LiAlH_4$ (2.0 eq.), HMPA (10 eq.)	60[b]	76/24

[a] Determined by ^{1}H NMR. [b] The starting material was recovered (35%).

Also, a coordinating cosolvent, HMPA, reduced the selectivity, accompanied by a substantial decrease of the reaction rate.

On the basis of these data, we now propose a working model to explain this reaction as shown in Figure 1. Primarily

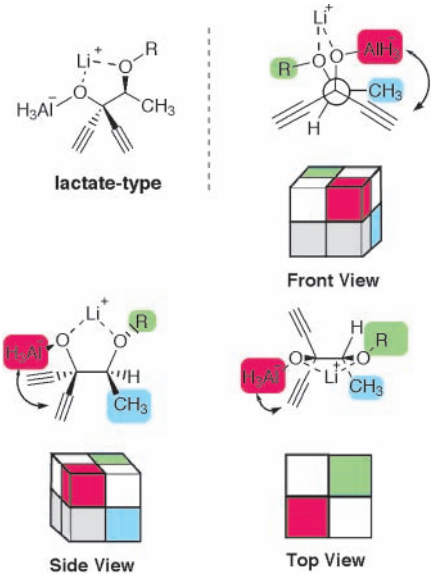


Figure 1.

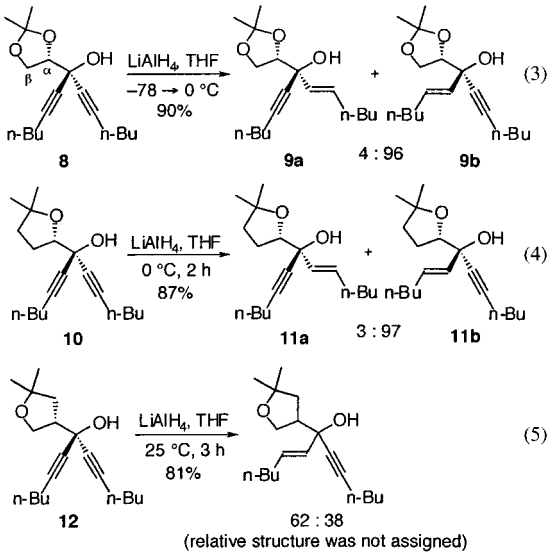
considered is a five-membered lithium chelate formed by the coordination of the Li-alkoxide to the α-alkoxy group. The group selection could be explained by the steric interaction of the substituents, which is nicely illustrated by a "space-filling model" with the views from three angles (front, side, and top). The alternate filling of the octant spaces

(5) For a review of the hydroalumination reaction, see: Zweifel, G; Miller, J. A. *Org. React.* **1984**, *32*, 375−517.

(6) **Experimental procedure for the hydroalumination of 4 with $LiAlH_4$:** To a solution of $LiAlH_4$ (35.0 mg, 0.922 mmol) in THF (2.0 mL) was slowly added a solution of **4** (212 mg, 0.688 mmol) in THF (2.0 mL) at 0 °C. After stirring at 25 °C for 1.3 h, the reaction was stopped by adding saturated aqueous Na_2SO_4 and the products were extracted with EtOAc (3×). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. To a solution of the crude product in MeOH (9.0 mL) was added a catalytic amount of PPTS. After stirring for 0.5 h, the reaction was stopped by adding saturated aqueous $NaHCO_3$, and the products were extracted with EtOAc (3×). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc = 80/20) to give **5** (131 mg, 80%, **5a**/**5b** = 88/12) as colorless oil.

by the methyl group (blue), the α-alkoxy protecting group (R, green), and the aluminate (red) as shown and the alkynyl group in the vicinity of the aluminate is selectively hydroaluminated (see arrows). The necessary steric bulkiness of the α-alkoxy protecting group (R) for attaining a high selectivity is consistent with this view.

While examining the validity of this model for various related substrates, a puzzling observation was made upon application to the glycerate-derived substrate **8** (eq 3).[3] Though the reaction proceeded also in high selectivity, *the sense of the group selection was opposite* to that of the lactate-derived cases (cf. the examples in Table 1). Note that the reacting alkynyl group is *anti* to the α-alkoxy group in **8** with the *zigzag* representation shown, while the *syn*-alkynyl group preferentially reacted in the former lactate-derived cases. The importance of the α-oxygen, rather than the *β*-oxygen, was proven by the comparison experiments by using two related substrates **10** and **12**, in which the *β*- and α-oxygen in **8** were replaced by a methylene, respectively. While a high group selectivity was attained for **10** (eq 4) with the same sense as in the case of **8** (see eq 3), a significant decrease of the selectivity was noted for the substrate **12** lacking the α-oxygen (eq 5).



With significance of the α-oxygen in mind, the apparent changeover of the sense of group selectivity could be explained again by the space-filling model shown in Figure 2. In the present Li-chelate for the glycerate derivative, the cyclic nature of the substituents (blue and green) demands both octant spaces be filled on one side, thereby locating the aluminate (red) to the opposite side (cf. Figure 1).

One important logical consequence of this working model was the assumption that, if we employed *the bulkier Al-ligands, we could expect a higher group selectivity, which proved indeed to be the case.*

(7) All new compounds were fully characterized by spectroscopic means and combustion analysis. The diastereomer ratios of the products were determined by NMR (400 MHz) analysis. Stereochemical assignments were based on extensive correlation studies.

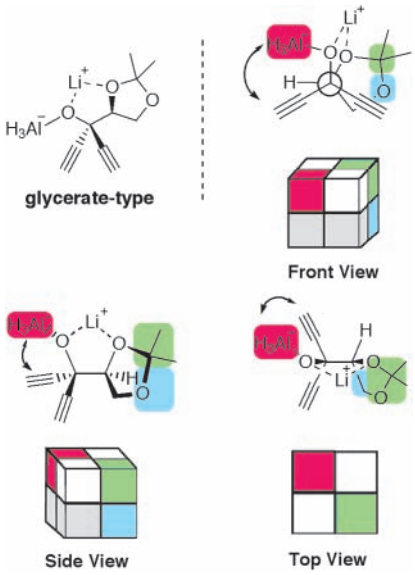
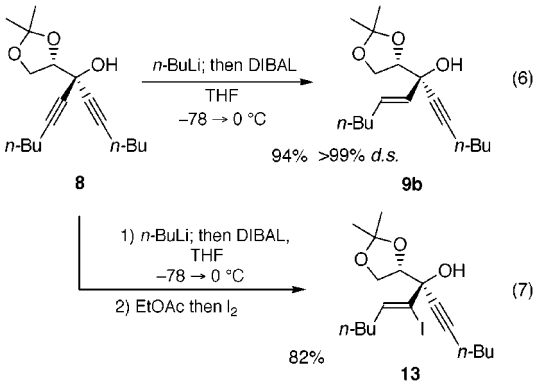


Figure 2.

Upon carrying out the reaction of **8** by first converting it to the corresponding lithium alkoxide followed by treatment with DIBAL (eq 6, Scheme 1), the product **9b** was obtained as the sole diastereomer within the limit of detection by high-field NMR (400 MHz).[8] Indeed, as shown in Figure 3, the increased steric bulkiness reinforced the group selectivity up to an almost perfect level.

Scheme 1



Furthermore, the alkenyl aluminate intermediate in this reaction could be used for the selective manipulation. For

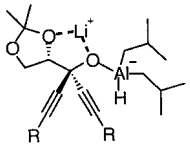
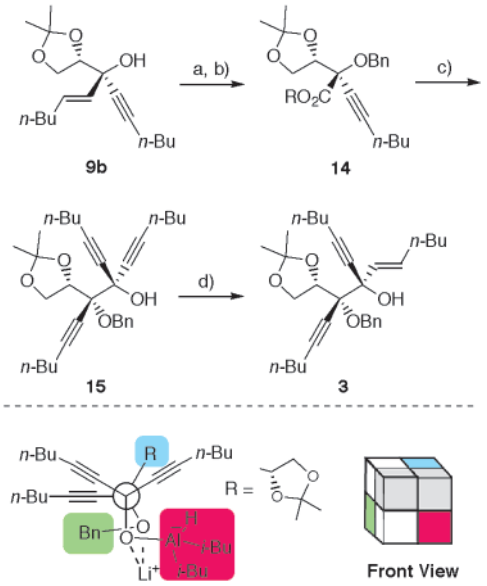


Figure 3.

Scheme 2[a]



[a] (a) BnBr, *n*-Bu_4NI, NaH, THF, 0 → 25 °C, 16 h (95%); (b) O_3, NaOH (8 equiv), MeOH, CH_2Cl_2, −78 °C, 2 h (77%); (c) 1-hexyne (3.0 equiv), *n*-BuLi (2.7 equiv), THF, −78 → 0 °C, 1 h (91%); (d) *n*-BuLi (1.2 equiv), DIBAL (1.3 equiv), THF, −78 → 0 °C, 2.5 h (89%, 99%, ds); DIBAL = diisobutylaluminum hydride.

example, upon quenching the hydroalumination reaction of **8** by ethyl acetate (to decompose excess hydride) followed by treatment with I_2,[4e−g] the vinyl iodide **13** was obtained as a sole product (eq 7, Scheme 1).

Furthermore, the hydroalumination reaction proved to be reiterative, thereby enabling the creation of two consecutive *tert*-alcohol centers as in **3** (Scheme 2). After the *tert*-hydroxyl group in **9b** was protected by a benzyl group, ozonolysis in methanol[9] gave the ester **14** (R = Me). After two 1-hexynyl groups were installed into **14** to give the alcohol **15**, the treatment with *n*-BuLi and DIBAL in THF gave the enynyl alcohol **3** again in an almost perfect group selectivity.

Such a compound as **3** with two consecutive *tert*-alcohol centers would be valuable in the total synthesis of natural products, e.g., zaragozic acids[10,11] and the cinatorins.[12] Further work is now in progress in our laboratories.

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(8) **Typical hydroalumination procedure with *n*-BuLi and DIBAL:** To a solution of **8** (1.00 g, 3.43 mmol) in THF (14.0 mL) was added *n*-BuLi (2.60 M hexane solution, 1.58 mL, 4.11 mmol) at −78 °C. After stirring for 30 min, to this solution was added DIBAL (2.83 M hexane solution, 1.52 mL, 4.30 mmol) at this temperature. The reaction mixture was gradually warmed to 0 °C, and the stirring was continued for 2.5 h. After quenching by addition of saturated aqueous potassium sodium tartrate and extracting with Et_2O (5×), the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc = 85/15) to afford **9b** (948 mg, 94%) as a colorless oil.

(9) Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, 643−645.

(10) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261−2266, and references therein.

(11) Recently, a report has appeared on the total synthesis of zaragozic acid A which employs a related hydroalumination reaction. However, different alkynyl groups were used, and the mechanism for the selection is different (personal communication from Dr. Tomooka): Tomooka, K; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P-.H.; Nakai, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4502−4505.

(12) Itazaki, H.; Nagashima, K.; Kawamura, Y.; Matsumoto, K.; Nakai, H.; Terui, Y. *J. Antibiot.* **1992**, *45*, 38−49.