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# *Anti*-Hydroalumination of Homo- and Bishomopropargyl Alcohols

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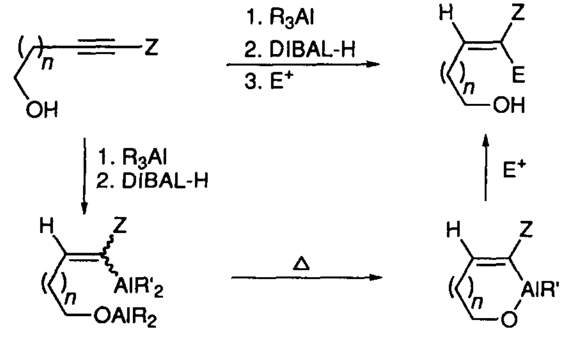
*Abstract:* The reaction of ω-$Me_3Si$- or ω-$Me_3Ge$-substituted 3-butyn-1-ol, 4-pentyn-1-ol, and their derivatives with DIBAL-H and a small trialkylalane, *e.g.*, $Me_3Al$ or $Et_3Al$, at 23 °C gives, after iodinolysis, the corresponding (*Z*)-4-iodo-3-buten-1-ols and (*Z*)-5-iodo-4-penten-1-ols in a highly stereo- and regioselective manner, most probably via endo-dig mode cyclic *anti*-hydroalumination, while treatment of ω-carbosubstituted 3-butyn-1-ols with Red-Al or $LiAlH_4$ at high temperatures followed by iodinolysis can give the corresponding (*Z*)-4-iodo-3-buten-1-ols also in a highly regio- and stereoselective manner.

We recently reported some prototypical examples of *anti*-carboalumination of homopropargyl alcohols and their higher homologues.[1] Although *anti*-hydroalumination of propargylic alcohols, which appears to be chelation-assisted, is a well-established synthetic method,[2,3] relatively little is known about *anti*-hydroalumination or any other synthetically useful *anti*-hydrometallation of hompropargyl alcohols and higher homologues. A high temperature *anti*-hydroalumination of homopropargyl alcohols and higher homologues with $LiAlH_4$ and related reagents to give the corresponding (*E*)-alkenols has been reported,[4] but neither deuterolysis nor iodinolysis of the addition products was performed. So, the product structure and the synthetic utility of the reaction were not adequately explored.

Herein, we report a novel *anti*-hydroalumination of ω-trimethylsilyl- or ω-trimethylgermyl-substituted homopropargyl and bishomopropargyl alcohols by their sequential treatment with $Me_3Al$ (or $Et_3Al$) and DIBAL-H (Scheme 1). As supported by the results discussed later, the reaction probably is not fully chelation-controlled in the initial nonstereoselective addition step, and a subsequent chelation-controlled stereoisomerization step is necessary to attain the observed high *E*/*Z* ratios. It is worth mentioning here that, despite some favorable results reported on the *anti*-hydroalumination of silylated alkynes and related compounds with DIBAL-H,[5] its scope is limited to those cases where the alkyne moiety is substituted with either a tertiary alkyl, *e.g.*, *t*-Bu, or an unsaturated, *e.g.*, Ph or vinyl, group. With common alkyl groups, *e.g.*, Me, the reaction fails to give the desired addition products in more than trace amounts.[5] We have confirmed this with *n*-HexC≡$CSiMe_3$.

**Scheme 1**



Z = Alkyl, phenyl, $SiMe_3$ or $GeMe_3$.
R = Me or Et.
R' = Bu-*i*, Me or Et.
E = H or I.
*n* = 1 or 2.

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In view of the favorable results observed in the *anti*-carboalumination of ω-trimethylsilyl- and ω-trimethylgermyl-substituted homopropargyl alcohols and their higher homologues, we sought similar *anti*-hydroalumination reactions and treated 4-trimethylsilyl-3-butyn-1-ol with 2.4 equivalents of DIBAL-H in hexanes. After 16 h at 23 °C, treatment of the reaction mixture with aqueous $NH_4Cl$ led to the formation of an essentially 1:1 mixture of the *E* and *Z* isomers of 4-trimethylsilyl-3-buten-1-ol. In sharp contrast, the reaction of the same alkynol, *i.e.*, $Me_3SiC{\equiv}C(CH_2)_2OH$, first with 1 equivalent of $Me_3Al$ in $CH_2Cl_2$ to convert it to its dimethylalumino derivative and then with DIBAL-H (2.1 equiv) for 16 h at 23 °C gave, after quenching with aqueous $NH_4Cl$, a 56% isolated yield of ≥98% stereoisomerically pure (*E*)-4-trimethylsilyl-3-buten-1-ol. In a 1:1 mixture of $Et_2O$-hexane, known *syn*-hydroalumination[5b] is observed under reflux for 24 h with no indication of stereoisomerization. To explore the scope of this promising reaction as well as to delineate the effects of some reaction parameters, the reactions of 5-trimethylsilyl-4-pentyn-1-ol with various aluminum hydride reagent systems were carried out. The experimental results are summarized in Table 1.

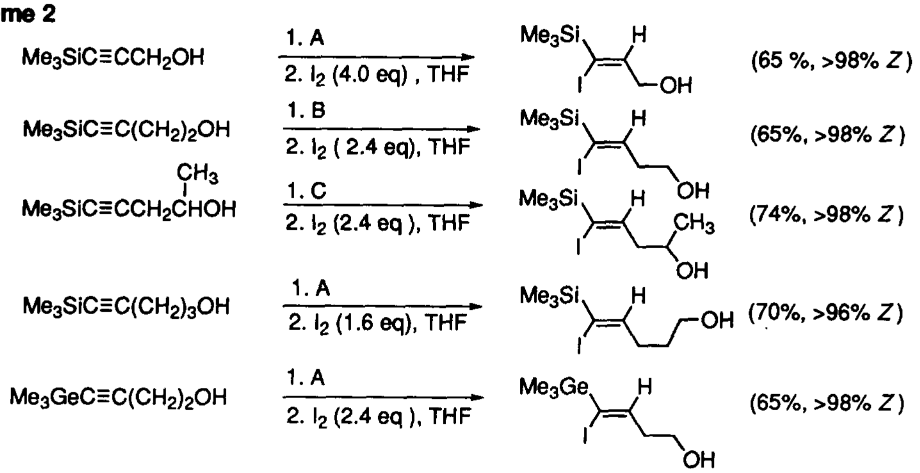
**Table 1.** Hydroalumination of 5-Trimethylsilyl-4-pentyn-1-ol with DIBAL-H or Red-Al

| Entry | Aluminum hydride[a] | Metalating agent[b] | Solvent | Reaction time, h | Product yield,[c] % | *E*/*Z* |
|---|---|---|---|---|---|---|
| 1 | DIBAL-H | $Me_3Al$ | $CH_2Cl_2$ | 17 | 77 | >96/4 |
| 2 | DIBAL-H | $Me_3Al$ | hexanes | 23 | 77 | 89/11 |
| 3 | DIBAL-H | $Et_3Al$ | $CH_2Cl_2$ | 27 | 64 | >96/4 |
| 4 | DIBAL-H | *i*-$Bu_3Al$ | $CH_2Cl_2$ | 21 | 57 | 36/64 |
| 5 | DIBAL-H[d] | DIBAL-H[d] | $CH_2Cl_2$ | 24 | 52 | 61/39 |
| 6 | DIBAL-H[e] | DIBAL-H[e] | $CH_2Cl_2$ | 72[f] | 53 | >96/4 |
| 7 | Red-Al[g] | Red-Al[g] | $CH_2Cl_2$ | 24 | NR[h] | – |
| 8 | Red-Al[g] | Red-Al[g] | ether | 24 | NR[h] | – |

[a] 1.1 equiv of the reagent was used, unless otherwise mentioned. [b] For metalation of the OH group. [c] The NMR yield of $Me_3CH{=}CH(CH_2)_3$-OH obtained after protonolysis with aqueous $NH_4Cl$. [d] 2.4 equiv of DIBAL-H was used for both metalation and hydroalumination. [e] 2.0 equiv of DIBAL-H was used for both metalation and hydroalumination. [f] Reflux . [g] 1.6 molar equiv of Red-Al was used for both metalation and hydroalumination. [h] The starting alkynol was recovered to the extent of >90%.

The results shown in Table 1 indicate the following: The most favorable *anti*-hydroalumination can be achieved by the use of relatively small $Me_3Al$ or $Et_3Al$ as an agent for metalating OH and DIBAL-H as a hydroaluminating agent in $CH_2Cl_2$ (Entries 1 and 3). The highest *E*/*Z* ratio observed in hexanes has been limited to 89/11 (Entry 2), due presumably to a slower *Z*-to-*E* isomerization. Neither DIBAL-H alone nor *i*-$Bu_3Al$—DIBAL-H led to a satisfactory *E*/*Z* ratio under comparable conditions (Entries 4 and 5), strongly suggesting that the *Z*-to-*E* isomerization process must be chelation-assisted and subject to steric hindrance. However, after refluxing the reaction mixture for 3 days, a 53% NMR yield of ≥96% isomerically pure (*E*)-5-trimethylsilyl-4-penten-1-ol was obtained (Entry 6). The NMR yields reported in this paper were determined using $CH_2Br_2$ as an internal standard. Finally, a coordinatively saturated nucleophilic reagent Red-Al is totally ineffective in inducing hydroalumination of 5-trimethylsilyl-4-pentyn-1-ol (Entries 7 and 8). The reagent combination of $Me_3Al$ (1.1-1.2 equiv) and DIBAL-H (1.1 equiv) in $CH_2Cl_2$ is also satisfactory for converting 3-trimethylsilyl-2-propyn-1-ol into >98% stereoisomerically pure (*E*)-3-trimethylsilyl-2-propen-1-ol in 50% yield. On the other hand, the benefit of putative chelation-assisted isomerization does not extend to the reaction of 6-trimethylsilyl-5-hexyn-1-ol. Thus, under the same conditions, 6-trimethylsilyl-5-hexen-1-ol obtained in 60% yield is a 61:39 mixture of the *E* and *Z* isomers. The synthetic utility of the procedure reported herein may be further demonstrated by the stereoselective synthesis of various iodoalkenols shown in Scheme 2.[6,7] The regioselective attachment of Al to the alkenyl carbon atom distal to the OH group is also observed in the conversion of 5-trimethylsilyl-4-pentyn-1-ol into ≥96% stereoisomerically pure (*Z*)-5-iodo-5-trimethylsilyl-4-penten-1-ol in 70% yield with ≥98% regioselectivity under the optimized conditions mentioned above.

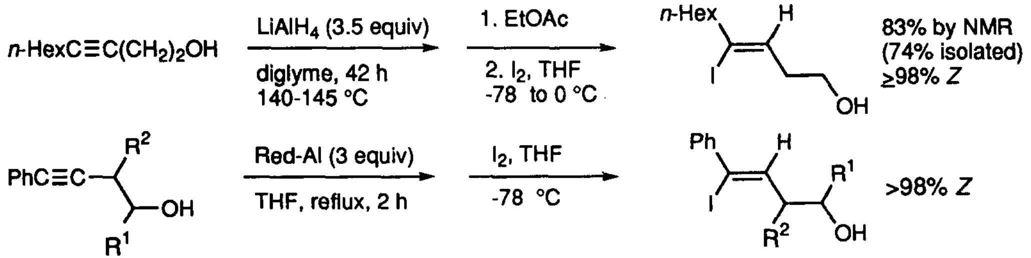
**Scheme 2**



A: i) $Me_3Al$ (1.1 equiv), $CH_2Cl_2$, 23 °C ii) DIBAL-H (1.05 equiv), 23 °C, 18-24 h. B: $Et_3Al$ (1.1 equiv) was used in place of $Me_3Al$. C: Same as A except that the DIBAL-H reaction was run for 48 h.

As indicated by the last entry in Scheme 2, a trialkylgermyl group is a satisfactory substituent in alkynols. On the other hand, a trialkylstannyl substituent is replaced by an aluminum-containing group under the reaction conditions and is hence unsatisfactory. More disappointing is the inability of either the terminally unsubstituted alkynols, *e.g.*, 3-butyn-1-ol, or their alkyl-substituted derivatives, *e.g.*, 3-pentyn-1-ol, to participate in the *anti*-hydroalumination reaction with DIBAL-H and a trialkylalane. Although these substrates are consumed under the same conditions, the desired products have not been detected in more than trace quantities. We therefore examined the feasibility of applying the reaction of nucleophilic aluminum hydrides[4] to the synthesis of iodoalkenols. As reported previously,[4] the reaction of 3-decyn-1-ol with 3.5 equivalents of $LiAlH_4$ in diglyme at 140-145 °C for 42 h produced, after protonolysis, ≥98% isomerically pure (*E*)-3-decen-1-ol in >80% yield. Although previously unknown, treatment of the *anti*-hydroalumination product first with EtOAc (11 equiv) and then with $I_2$ (1.5 equiv) in THF at -78 to 0 °C cleanly produced ≥98% isomerically pure (*Z*)-4-iodo-3-decen-1-ol in 83% NMR yield (74% isolated) (Scheme 3). In the absence of the OH group, unsymmetrical internal alkynes would produce a mixture of regioisomers. So, the observed high regioselectivity must be a consequence of a chelation-assisted hydroalumination. In contrast with a known 5-exo-dig carbotitanation of 4-pentyn-1-ols,[8] the 6-endo-dig mode must be strongly favored over the 5-exo-dig mode in this reaction. A similar reaction of 4-phenyl-3-butyn-1-ol with $LiAlH_4$ (3.5 molar equiv) proceeded to completion under milder conditions (75 °C, 24 h). For as yet unclear reasons, however, iodinolysis under the same conditions as above led to the incorporation of iodine only to the extent of 5%, the major products being (*E*)-4-phenyl-3-buten-1-ol (67%). On the other hand, the corresponding reaction of Red-Al (3 molar equiv) in refluxing THF for 2 h followed by iodinolysis afforded ≥98% isomerically pure (*Z*)-4-iodo-4-phenyl-3-buten-1-ol in 90% NMR yield along with a trace of (*E*)-4-phenyl-3-buten-1-ol (Scheme 3). Although the reaction conditions are quite vigorous, nucleophilic aluminum hydrides, *e.g.*, $LiAlH_4$ and Red-Al, can satisfactorily convert ω-carbo-substituted 3-butyn-1-ols into (*Z*)-4-iodo-3-alken-1-ols, thereby nicely complementing the DIBAL-H reaction described earlier.

**Scheme 3**



| $R^1$ | $R^2$ | isolated yield (%) |
|---|---|---|
| H | H | 62 |
| H | Me | 50 |
| Me | H | 82 |

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(6) **(*Z*)-4-Iodo-4-trimethylsilyl-3-buten-1-ol. Representative Procedure.** A solution of 4-trimethylsilyl-2-butyn-1-ol (72 mg, 0.50 mmol) in $CH_2Cl_2$ (2 mL) was successively treated with $AlMe_3$ (59 μL, 0.62 mmol) (25 °C, 30 min) and DIBAL-H (95 μL, 0.53 mmol) (25 °C, 18 h). The reaction mixture was successively quenched with $I_2$ (20 mg, 1.18 mmol) (-78 °C), aqueous $Na_2S_2O_3$, and aqueous $NH_4Cl$ (0 °C). After the usual workup, chromatography on silica gel (10:1 hexanes-EtOAc) afforded 77 mg (56%) of the title compound with ≥98% stereoisomeric purity: $^1H$ NMR ($CDCl_3$, $Me_4Si$) $\delta$ 0.28 (s, 9 H), 1.65 (s, 1 H), 2.52 (q, $J = 7.4$ Hz, 2 H), 3.75 (t, $J = 7.4$ Hz, 2 H), 6.22 (5, $J = 7.4$ Hz, 1 H) ppm; $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) $\delta$ -1.47, 42.17, 60.82, 116.27, 143.55 ppm; IR (neat) 3332, 1610 $cm^{-1}$; HRMS calcd for $C_7H_{15}IOSi$ ($M^+$) 269.9937, found 269.9931.

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