Anti-Carbometalation of Homopropargyl Alcohols and Their Higher Homologues via Non-Chelation-Controlled *Syn*-Carbometalation and Chelation-Controlled Isomerization†

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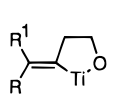
Highly stereoselective *anti*-carbometalation reactions of alkynes are rare,[1] the great majority of the synthetically useful carbometalation reactions of alkynes, such as Zr-catalyzed carboalumination[2] and carbocupration,[3] being *syn*-addition processes. One notable example of stereoselective *anti*-carbometalation is the Cu-catalyzed carbomagnesiation reaction of propargylic alcohols.[4] Unfortunately, the scope of this reaction does not generally extend to homopropargyl alcohols and higher homologues.

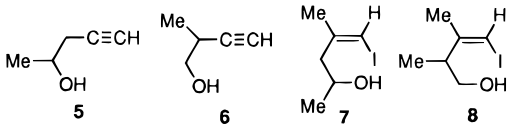
We report herein a novel strategy for achieving net *anti*-carbometalation of homopropargyl alcohols and even some higher homologues. This strategy critically hinges on our finding that the *syn*- and stereorandom-carboalumination products obtained from *ω*-hydroxyalkynes represented by HORC≡CZ, where Z = H, Si, or Ge, can be thermally isomerized to give nearly exclusively or predominantly alkenylalanes that correspond to *anti*-carboalumination of alkynes (Scheme 1). The reactions shown in Scheme 1 are fundamentally different from the carbotitanation reaction of homopropargyl alcohols and longer alkynols,[5] which displays the opposite regioselectivity of carbometalation, producing **1**, and must therefore be chelation-controlled in the addition step itself. The reactions presented here are also critically different from the Cu-catalyzed carbomagnesiation[4] of propargylic alcohols producing **2** in that these two classes of reactions display essentially nonoverlapping and hence complementary scopes.



1

2

Specifically, treatment of 3-butyn-1-ol with Me_3Al (3 equiv) and 25 mol % of Cp_2ZrCl_2 in $(CH_2Cl)_2$ at 23 °C produced the expected *syn*-methylalumination product **3** (>98% *E*) as previously reported by us.[6] Upon refluxing the reaction mixture for 72 h, however, a complete reversal of the stereochemistry from >98% *E* to >98% *Z* took place to produce, after iodinolysis, a 60% yield of **4a** (E = I). Similarly, 1- and 2-methyl-substituted homopropargyl alcohols **5** and **6** were converted to **7** and **8**, both of which were >98% *Z*, in 61 and 50% yields, respectively.[7] These products appear to represent a class of compounds not readily accessible by any of the previously known reactions.[8]



5 **6** **7** **8**

It is important to note that, in the absence of the homopropargylic hydroxy group, the *E*-to-*Z* isomerization does not occur. Thus, the corresponding reaction of 1-decyne merely gave (*E*)-1-iodo-2-methyl-1-decene (>98 *E*) in about 80% yield, and neither the stereochemistry nor the yield detectably changed even after 72 h at the refluxing temperature of 1,2-dichloroethane. In fact, no detectable isomerization was observed even with 4-pentyn-1-ol. The observed isomerization of **3** must therefore be chelation-controlled. We tentatively propose a Lewis acid-induced chelation-controlled mechanism producing **9** as the product as shown in Scheme 2. Although we have thus far been unsuccessful in obtaining definitive structural data on **9**, the corresponding reaction of the terminally Me_3Ge-substituted derivative **10** was faster (36−48 h, 25 °C, CD_2Cl_2) and cleaner, producing a >80% NMR yield of **11**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ −0.58 (bs, 3 H), 0.22 (s, 9 H), 1.84 (s, 3 H), 2.0−2.5 (m, 2 H), 3.9−4.25 (m, 2 H); ^{13}C NMR (50 MHz, CD_2Cl_2) δ −6.50, 1.15, 28.29, 41.02, 64.63, 110.31, 110.62. Hydrolysis with aqueous Na_2CO_3 and iodinolysis gave **12a** (E = H, >98% *E*) and **12b** (*E* = I, >95% *Z*) in 77 and 73% isolated yields, respectively. Furthermore, treatment of **11** with ClCOOMe gave **13**, albeit 12% yield.

Substitution of the terminal alkynyl hydrogen atom with a metal-containing group, such as Si and Ge, not only accelerates stereoisomerization[9] but also expands the scope of reaction. As summarized in Table 1, the reaction of a series of *ω*-(trimethylsilyl)alkynols with Me_3Al (3 equiv) and Cp_2ZrCl_2 (1 equiv) at the refluxing temperature of CH_2Cl_2 gave stereoselectively the *anti*-methylalumination products. The *anti*/*syn* ratios were >98/<2 for 3-butyn-1-ol derivatives, ≥97/≤3 for 4-pentyn-1-ols, and 88/12 for 5-hexyn-1-ols. However, those for the 6-heptyn-1-ol and 10-undecyn-1-ol derivatives were roughly in the 40/60−60/40 range and were very similar to that observed with 1-(trimethylsilyl)-1-octyne.[10] These latter results reinforce our view that the high *anti*/*syn* ratios observed with the C_4 and C_5 *ω*-alkynols must be chelation-controlled, involving the formation of six- and seven-membered aluminacycles, respectively. The *anti*/*syn* ratio of 88/12 observed with 6-(trimethylsilyl)-5-hexyn-1-ol is very intriguing. It suggests that the reaction may be largely chelation-controlled. If so, it

† We wish to dedicate this paper to Professor D. Seebach of ETH, Zürich, on the occasion of his 60th birthday.

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(7) Conversion of **6** to **8** was performed by Ms. F. Liu in our laboratories.

(8) See, however: Kocienski, P.; Wadman, S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363.

(9) Facile stereoisomerization of Si-substituted alkenylalanes and alkenyllithiums has been previously reported and discussed. (a) Miller, J. A.; Negishi, E. *Israel J. Chem.* **1984**, *24*, 76. (b) Negishi, E.; Takahashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 3402.

(10) Snider, B. B.; Karras, M. *J. Organomet. Chem.* **1979**, *179*, C37.

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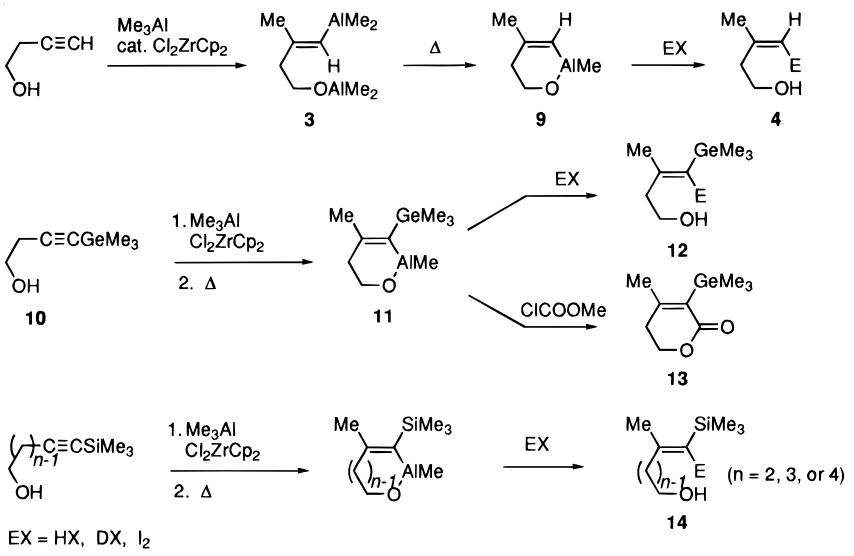
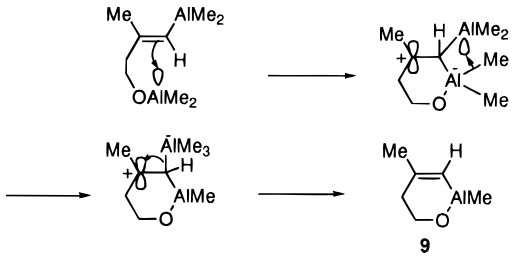
Scheme 1



Scheme 2



Scheme 3

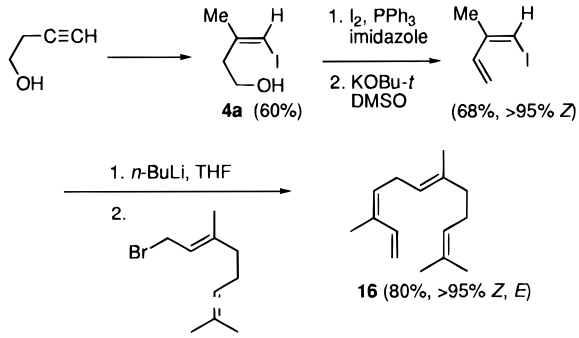
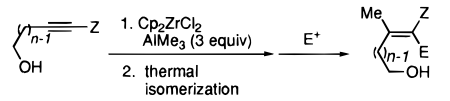


Table 1. *Anti*-Carboalumination of Homopropargyl Alcohols and Their Higher Homologues[a]



entry	alkynol n	Z	cond for isomerization temp, °C	time, d	product E	yield,[b] %	*anti/syn*[c]
1[d]	2	H	reflux	3	I (**4a**)	60	>98:2
2[d]	**5**[e]		reflux	5	I (**7**)	61	>98:2
3[d]	**6**[f]		reflux	5	I (**8**)	50	>98:2
4	2	$SiMe_3$	25	3	I (**14a**)	73 (77)	>98:2
5[d]	2	$SiMe_3$	50	3	I (**14a**)	52 (52)	>98:2
6	2	$SiMe_3$	25	3	H (**14b**)	64 (70)	>98:2
7	**19**[g]		45	4	I (**14c**)	60 (60)	>98:2
8	3	$SiMe_3$	25	3.5	I (**14d**)	59 (66)	>97:3
9	4	$SiMe_3$	45	0.7	I (**14e**)	60 (65)	88:12
10	4	$SiMe_3$	25	3.5	H (**14f**)	80 (82)	86:14
11	5	$SiMe_3$	45	0.5	I (**14g**)	54 (64)	60:40
12	9	$SiMe_3$	25	3	I (**14h**)	*h* (62)	47:53
13	2	$GeMe_3$	25	1.5	I (**12b**)	73 (84)	>95:5
14	2	$GeMe_3$	25	1.5	H (**12a**)	77 (84)	>98:2

[a] Unless otherwise stated, the reaction was carried out in CH_2Cl_2 by using 1 equiv of Cp_2ZrCl_2. [b] Isolated yield with the NMR yield in parentheses. [c] The thermally equilibrated ratio of the anti-carboalumination to syn-carboalumination products. [d] The reaction was carried out in $(CH_2Cl)_2$ using 25% of Cp_2ZrCl_2. [e] **5** = 4-pentyn-2-ol. [f] **6** = 2-methyl-3-butyn-1-ol. [g] **19** = 5-(trimethylsilyl)-4-pentyn-2-ol. [h] Not determined.

must involve the preferential formation of an eight-membered aluminacycle. The differences in the ease and scope between stereoisomerization of terminally unsubstituted ω-alkynols and that of ω-silyl-substituted analogues are striking. One plausible explanation for the observed differences might be that isomerization of unsubstituted ω-alkynols must be not only thermodynamically driven by chelation but also kinetically chelation-initiated and that the latter benefit must be practically limited only to the cases of 3-butyn-1-ols. On the other hand, isomerization of the Si-substituted derivatives must kinetically rely on their intrinsic configurational instability,[10] and chelation is significant only in a thermodynamic sense. Regardless of their mechanism, these favorable isomerization reactions observed even with 4-pentyn-1-ol and 5-hexyn-1-ol derivatives were quite unexpected but of considerable synthetic potential. For example, treatment of **14e** (*Z*/*E* = 88/12) with NaOMe in MeOH at 65 °C for 12 h gave an 85% yield of the desilylated product, *i.e.*, 6-iodo-5-methyl-5-hexen-1-ol (**15**), which was also 88% *Z*.

The conversion of **4a** into (3*Z*)-α-farnesene[11] (**16**) as summarized in Scheme 3 provides an example of natural products synthesis employing the newly developed strategy.

Acknowledgment. We thank the National Science Foundation (CHE-9402288) for support of this research. We also thank Ms. F. Liu for providing some experimental data.

Supporting Information Available: Experimental details for the preparation of **4a**, **13**, **14a**, **14b**, **14e**, and **16** as well as spectral data of **7**, **8**, **12a**, **12b**, **13**, **14d**, **14f**, **14g**, **14h**, and **15** (7 pages).

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(11) For a recent synthesis of (3*Z*,6*E*)-α-farnesene, which was 80% stereoselective, see: Ramaiah, P.; Pegram, J. J.; Millar, J. G. *J. Org. Chem.* **1995**, *60*, 6211.