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trans-Hydroalumination/Alkylation: One-Pot Synthesis of Trisubstituted Allylic Alcohols

Neil F. Langille and Timothy F. Jamison*

Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

tfj@mit.edu

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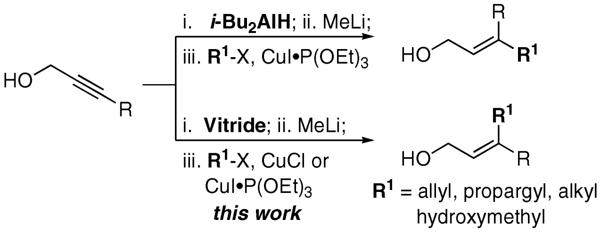
ABSTRACT



Described herein is a method of stereoselective synthesis of trisubstituted allylic alcohols by alkylation of alkenyl alanates, formed in situ through treatment of propargyl alcohols with Vitride (Red-Al). This technique represents the first of its kind to feature a *trans*-hydrometalation, and is particularly effective for the formation of 1,4-dienes. Applications involving primary, secondary, and tertiary alcohols are discussed, as well as limitations regarding both alkyne and electrophile components.

Alkyne hydrometalation reactions are among the most vital and reliable methods of stereoselective alkene synthesis.[1] Among these methods, those that utilize the transient alkenylmetal species directly for carbon−carbon bond formation are particularly powerful, resulting in highly substituted alkene products that may otherwise be accessible only through tedious multistep synthetic transformations. Indeed, a number of protocols have been developed to meet this challenge, including some involving alkylation of activated vinyl alanates.[2,3] However, each of these hydroalumination/alkylation methods incorporates the emerging carbon−carbon bond cis to the hydrogen.[4]

As part of ongoing research in our laboratories exploring the synthetic utility of skipped polyenes,[5] we required trisubstituted alkenes bearing the hydrogen atom positioned trans to a newly formed carbon−carbon bond. *trans*-Selective hydroalumination reactions of alkynols are well-understood transformations that have been frequently utilized since Corey's pioneering syntheses of farnesol[6] and the C_{18} *Cecropia* juvenile hormone.[7] However, previous studies involved quenching the intermediate vinyl alanes exclusively with H_2O, D_2O, or iodine. A logical extension of existing methods would be the direct alkylation of a vinyl alane or alanate derived from a *trans*-hydroalumination of an alkynol. Such a sequence would provide the requisite alkene structures

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[1] Review: (a) Hudrlik, P. F.; Hudrlik, A. M. *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; John Wiley and Sons: New York, 1978; Part 1, Chapter 7, pp 199−273. See also: (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

[2] With *i*-Bu$_2$AlH: (a) Lynd, R. A.; Zweifel, G. *Synthesis* **1974**, 658−659. (b) Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.* **1976**, *41*, 2214−2215. (c) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215−2217. (d) Baba, S.; Van Horn, D. E.; Negishi, E. *Tetrahedron Lett.* **1976**, *17*, 1927−1930. (e) Ziegler, F. E.; Mikami, K. *Tetrahedron Lett.* **1984**, *25*, 131−134.

[3] With LiAlH$_4$: Sato, F.; Kodama, H.; Sato, M. *J. Organomet. Chem.* **1978**, *157*, C30−C32.

[4] For a similar *carbometalation* example with Me$_3$Al, see: Hu, T.; Schaus, J. V.; Lam, K.; Palfreyman, M. G.; Wuonola, M.; Gustafson, G.; Panek, J. S. *J. Org. Chem.* **1998**, *63*, 2401−2406.

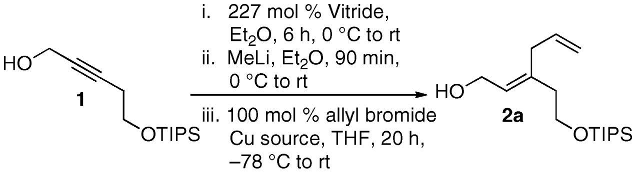
[5] (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339−2442. (b) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056−1057.

[6] Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245−4247.

[7] Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618−5620.

10.1021/ol0613721 CCC: $33.50

Table 1. Optimization of *trans*-Hydrometalation/Alkylation



entry	MeLi (mol %)	Cu source (mol %)	**2a**:^{1}H quench[a]
1	none	CuI·P(OEt)$_3$ (100)	0.5:1
2	250	CuI·P(OEt)$_3$ (100)	2:1
3	125	CuI·P(OEt)$_3$ (100)	8:1
4	125	CuI·P(OEt)$_3$ (50)	1.3:1
5[b]	125	CuI·P(OEt)$_3$ (100)	>20:1
6[b]	125	CuCl (100)	>20:1

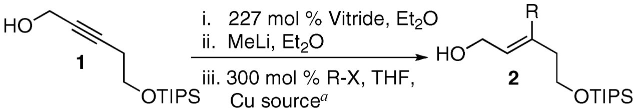
[a] Determined by ^{1}H NMR analysis of crude reaction mixture after aqueous workup. [b] 300 mol % allyl bromide used.

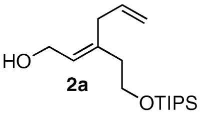
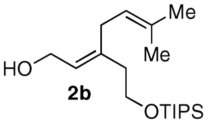
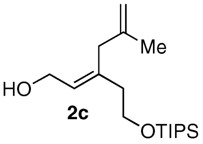
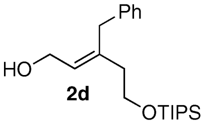
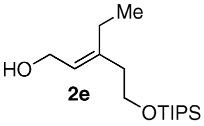
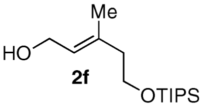
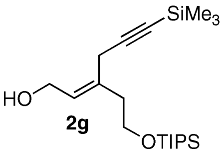
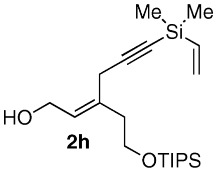
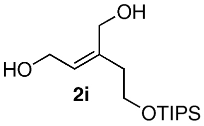
directly from readily available alkyne starting materials, and would complement existing *i*-Bu$_2$AlH and LiAlH$_4$-based strategies which involve *cis*-hydroalumination.

To test the viability of this concept, propargyl alcohol **1** was subjected to hydrometalation, with Vitride[8] as the metal hydride source. Representative examples are shown in Table 1. Subsequent experiments identified Ziegler's CuI·P(OEt)$_3$ salt[2e,9] as ideal for this transformation, providing excellent conversion to the desired diene **2a** with only 100 mol % allyl bromide used as the electrophilic component.

The stereochemical configuration of diene **2a** was readily determined to be *E* by nOe experiments, indicating that the geometry of the *trans*-hydrometalated alkene was maintained through the alkylation step. In accord with related precedent,[1b] we observed exclusive metal incorporation onto the carbon distal to the hydroxymethyl substituent. It should be noted that substoichiometric amounts of the copper salt (entry 4) proved less effective, although the actual conversion suggests a catalytic role for the copper species. Further, CuCl displayed efficacy similar to CuI·P(OEt)$_3$, indicating potential application to substrates impeded by difficult chromatographic separation from trialkyl phosphite residue. Inferior additives included CuCN·2LiCl, Fe(acac)$_3$, and InCl$_3$. Importantly, full conversion was readily achieved when excess allyl bromide was utilized (entries 5 and 6).

Table 2. *trans*-Hydrometalation/Alkylation: Electrophile Scope



entry	R-X	product	yield[b] (CuI•P(OEt)$_3$)	yield[b] (CuCl)
1	R-Br	 **2a**	86%	97%
2	R-Br	 **2b**	81%	82%
3	R-Br	 **2c**	84%	94%
4	R-Br	 **2d**	62%	60%
5	R-I	 **2e**	(1 : 2)[c]	(1 : 3)[c]
6	R-I	 **2f**	(1 : 1)[c]	(1 : 1.5)[c]
7	R-I	 **2g**	37%	22%
8	R-I	 **2h**	62%	47%
9	–[d]	 **2i**	55%	71%

[a] Standard conditions: (i) Vitride, Et$_2$O (0.5 M), 0 °C to room temperature, 6 h; (ii) MeLi, Et$_2$O, 0 °C to room temperature, 1.5 h; (iii) R−X, Cu source, THF (0.2 M), −78 °C to room temperature, 20 h. [b] Isolated yield after purification (SiO$_2$ chromatography). [c] Reflects ratio of product:^{1}H quench (measured by ^{1}H NMR analysis of crude reaction mixture). [d] *para*-Formaldehyde used as the electrophile.

With successful reaction conditions in hand, we sought to define the electrophile scope of this transformation (Table 2). A number of allyl halides proved effective in this sequence, resulting in good yields of the desired 1,4-diene structures (entries 1−4). Importantly, substitution on the proximal or distal carbon of the electrophile was well tolerated. Similarly, unactivated alkyl halides also participated in this reaction (entries 5 and 6), although full conversion to trisubstituted alkene products remained elusive. Additionally, although allene products dominated when 1-bromo-2-butyne was utilized (not shown), propargyl halides bearing silyl substituents on the alkyne resulted in the formation of 1,4-enynes in moderate yield (entries 7 and 8). Finally, *para*-formaldehyde proved competent in this protocol, resulting in installation of a hydroxymethyl sub-

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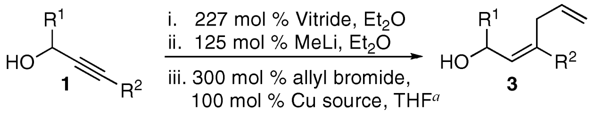
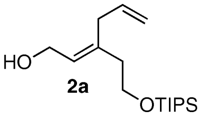
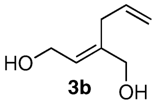
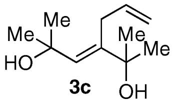
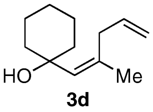
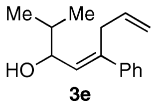
(8) Vitride is the common name for sodium bis(2-methoxyethoxy)-aluminum hydride, also known as SMEAH or Red-Al.

Table 3. *trans*-Hydrometalation/Alkylation: Alkynol Scope



entry	product	yield[b] ($CuI•P(OEt)_3$)	yield[b] (CuCl)
1	 **2a**	86%	97%
2	 **3b**	82%	89%
3	 **3c**	82%	91%
4	 **3d**	96%	95%
5	 **3e**	81%	89%

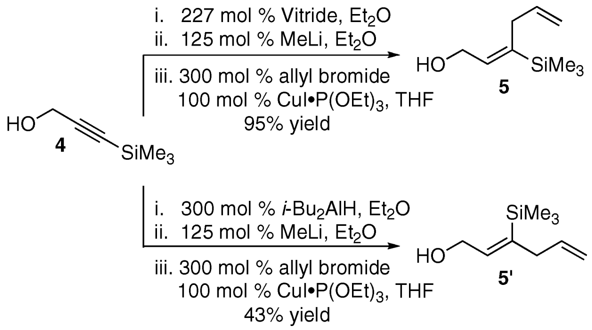
[a] Standard conditions: (i) Vitride, Et_2O (0.5 M), 0 °C to room temperature, 6 h; (ii) MeLi, Et_2O, 0 °C to room temperature, 1.5 h; (iii) allyl bromide, Cu source, THF (0.2 M), −78 °C to room temperature, 20 h. [b] Isolated yield after purification (SiO_2 chromatography).

stituent on alkene **2i**. In all cases, the alkene was generated as a single regio- and stereoisomer.

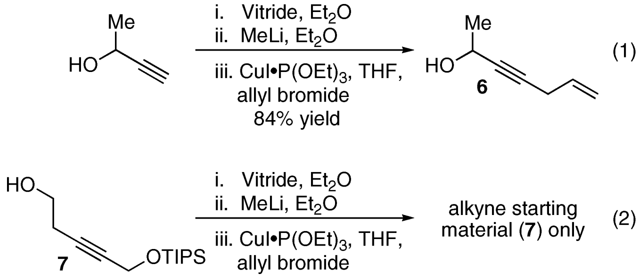
A broad range of propargyl alcohols were also exposed to this optimized reaction protocol (Table 3). Importantly, complete regioselectivity was observed with a number of primary, secondary, and tertiary alcohols, as well as two diols, yielding products **3b** and **3c** (entries 2 and 3). Interestingly, Me_3Si-substituted propargyl alcohol **4**[10] allowed the demonstration of divergent reaction pathways, where employment of Vitride or *i*-Bu_2AlH resulted in formation of the complementary products **5** and **5′** (Scheme 1).

Two important limitations to this method deserve comment. First, terminal alkynes were converted cleanly to the corresponding 1,4-enynes (**6**) by this procedure, where simple deprotonation/alkylation precluded reduction of the alkyne function (Scheme 2, eq 1). Even forcing conditions (reflux, 18 h) did not result in appreciable hydrometalation of these substrates. A second limitation was observed in the attempted hydrometalation of homopropargylic alcohols (eq 2), where only minimal conversion was observed even after prolonged reaction time. Indeed, Vitride-mediated hydrometalations of a number of homopropargylic and bishomopropargylic alcohols were ineffective. Despite these cases, this procedure is well suited for a number of propargylic alcohol/electrophile combinations.

Scheme 1. *trans*- and *cis*-Hydrometalation/Alkylation Sequences



Scheme 2. Limitations to *trans*-Hydrometalation/Alkylation



Having demonstrated this *trans*-hydroalumination/alkylation method on simple diene substrates, we applied this protocol to the preparation of a more complex skipped 1,4,7-dienyne structure. Accordingly, we synthesized allylic iodide **9** in two steps from the known compound 2,5-heptadiyn-1-ol[11] (**8**), via reduction with $LiAlH_4$ in refluxing ether[12] and iodination under standard conditions (Scheme 3). Copper-mediated reaction of **9** with the alkenyl alanate derived from **1**, however, produced a mixture of products **10** and **10′**, the latter indicating that the alkylation reaction proceeded through a S_N2' pathway. In this example, steric factors conferred a minor effect on product distribution (51% isolated yield of **10**, 46% isolated yield of isomer **10′**). This result was not entirely unexpected, as S_N2' alkylation reactions of organocopper reagents are well precedented.[13] Despite this mixture of products, the *trans*-hydrometalation/alkylation sequence allowed the convergent synthesis of the target dienyne **10** in four linear steps from commercially available material.[14]

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(9) Nishizawa, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 1170−1178.

(10) For synthesis and *trans*-hydrometalation of alkynol **4**, see: Jones, T. K.; Denmark, S. E. *Org. Synth.* **1986**, *64*, 182−188.

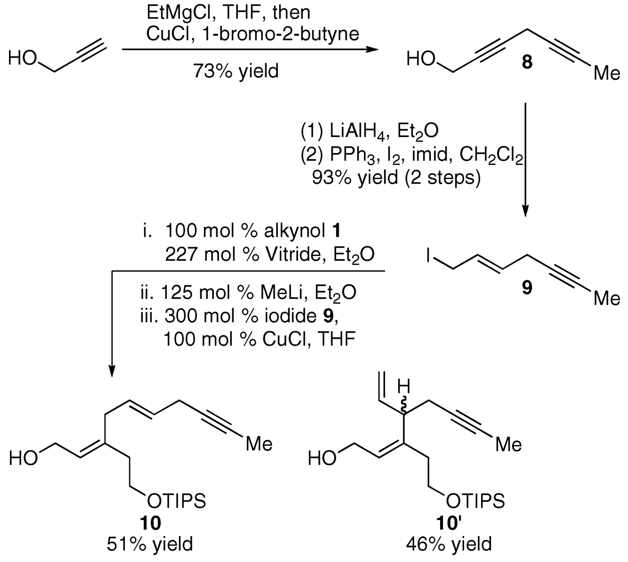
(11) Bushby, R. J.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 563−569.

(12) Aebi, J. D.; Deyo, D. T.; Sun, C. Q.; Guillaume, D.; Dunlap, B.; Rich, D. H. *J. Med. Chem.* **1990**, *33*, 999−1009.

(13) Reviews: (a) Magid, R. *Tetrahedron* **1980**, *36*, 1901−1930. (b) Krause, N.; Gerold. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186−284.

(14) Alkynol **1** was synthesized in three steps from 3-butyn-1-ol. See the Supporting Information for details.

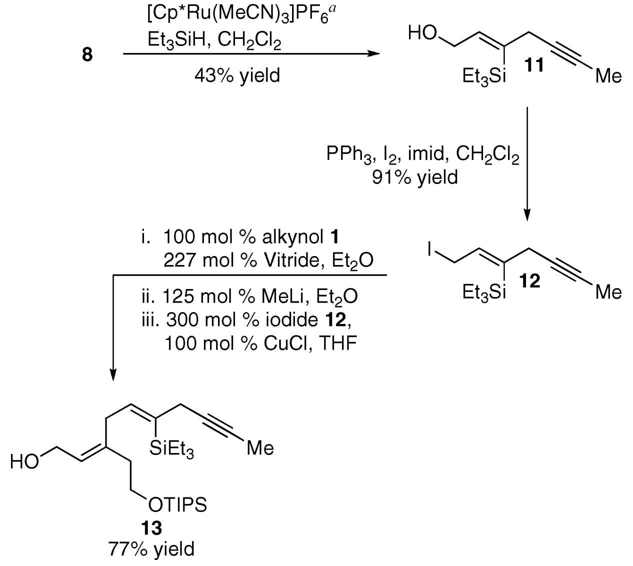
Scheme 3. Synthesis and Alkylation Reaction of Iodide **9**



We hypothesized that a second substituent on the distal alkene carbon of the allylic iodide would promote exclusive alkylation on the α-carbon, yielding a single dienyne isomer. Therefore, to suppress S_N2' displacement, we initiated the synthetic route illustrated in Scheme 4. Trost's Ru-catalyzed *trans*-hydrosilylation[15] and iodination afforded allylic iodide **12**, representing a C3-silyl substituted congener of iodide **9**. Gratifyingly, iodide **12** proved well-suited for the *trans*-hydrometalation/alkylation protocol, producing compound **13** in 77% yield as a single 1,4,7-dienyne isomer. Products of S_N2' displacement were not observed in this experiment.

In summary, we have developed a one-pot *trans*-hydroalumination/alkylation sequence that affords trisubstituted allylic alcohols as single geometric isomers in a highly controlled fashion. Although best suited for simple activated electrophiles, this new technique represents the first carbon−carbon bond forming method of its kind to incorporate a *trans*-hydrometalation and has proven quite effective for the stereoselective formation of skipped polyene-containing compounds. Investigations into the usefulness of these products are currently underway, and the results of these studies will be reported in due course.

Scheme 4. Synthesis of Alkenyl Silane Analogue **13**[a]



[a] Cp* = pentamethylcyclopentadienyl.

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Supporting Information Available: Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644−17655. (b) Chung, L. W.; Wu, Y.-D.; Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 11578−11582.