Diastereoselective and Enantioselective Synthesis of Homopropargyl and Allenylcarbinols from Nonracemic Propargyl Mesylates via the Derived Allenyl and Propargyl Trichlorosilanes

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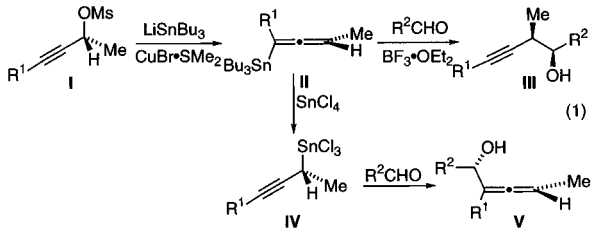
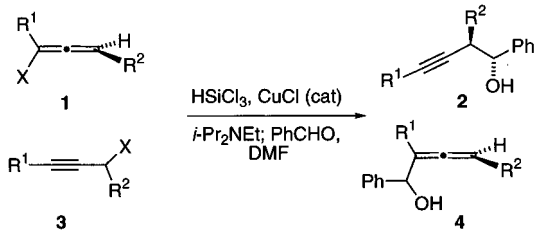
In connection with projects involving the total synthesis of bioactive polypropionate and polyether natural products, we have been exploring S_E2' additions of chiral allenyl and propargyl organometallic reagents to aldehydes leading to homopropargylic and allenylcarbinols, respectively. Initial efforts in these investigations showed that chiral allenylstannanes **II**, obtained by S_N2' displacements of enantioenriched propargylic mesylates **I**, afford either the homopropargylic alcohols **III** or allenylcarbinols **V** of high enantiomeric purity under appropriate reaction conditions (eq 1).[1,2] The former represent possible intermediates for polypropionate synthesis,[3] and the latter serve as precursors of tetrahydrofuran subunits of polyethers.[1]



Recent findings by Kobayashi and co-workers on additions of allylic and propargylic trichlorosilanes to aldehydes led us to consider an alternative, and possibly more direct, approach to adducts related to **III** and **V**.[4,5] The appropriate extension of this methodology would involve the use of substituted chiral allenyl or propargyl halides **1** or **3** as precursors to propargyl or allenyl trichlorosilane intermediates that would add to aldehydes to afford the homopropargyl or allenyl adducts **2** or **4** (Table 1). To test the feasibility of the silylation protocol and the regio- and diastereoselectivity of the ensuing additions, we conducted preliminary experiments on the racemic allenyl and propargylic halides **1** and **3** with benzaldehyde. The results of these experiments are summarized in Table 1.

It was found that the ratio of homopropargylic to allenic adduct (**2**:**4**) is dependent upon the R^1 and R^2 substituents in the starting halide. Both the allenyl and the propargyl TMS bromides **1c** and **3a** led to the exclusive formation of the allenylcarbinol adduct **4c**, suggestive of a common propargylsilane precursor. The stereochemistry of the allenyl adduct **4c** was not determined, but the ^{1}H and ^{13}C NMR spectra are consistent with a single diastereomer. The homopropargylic adducts **2** were shown to be mainly *anti* by comparison of the ^{1}H NMR spectra with those of the authentic *syn* isomers.[1]

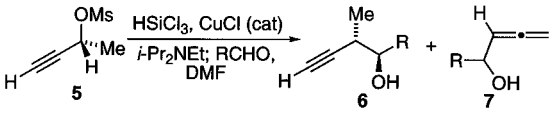
Table 1. Additions of Racemic Propargyl/Allenyl Trichlorosilanes to Benzaldehyde



halide	X	R^1	R^2	yield, %	**2**:**4**[a,b]
1a	Br	H	C_5H_{11}	86	94:6 (**a**)[c]
1b	I	H	Me	77	86:14 (**b**)[d]
1c	Br	TMS	Me	73	0:100 (**c**)
3a	Br	TMS	Me	60	0:100 (**c**)
3b	Br	C_7H_{15}	Me	76	40:60 (**d**)[e]

[a] Racemic. [b] The relative stereochemistry of **4** was not determined. [c] ~85:15 *anti*:*syn*. [d] ~80:20 *anti*:*sin*. [e] ~70:30 *anti*:*syn*.

Table 2. Adducts from Chlorosilylation of Mesylate 5 and *in Situ* Addition to Aldehydes



R	yield, %	**6**:**7**	*anti*:*syn* (**6**)	ee, %
c-C_6H_{11} (**a**)	72	96:4	982 (**a**)	*a*
C_6H_{13} (**b**)	79	95:5	89:11 (**b**)	96[b]
(*E*)-BuCH=CH (**c**)	80	>99:1	70:30 (**c**)	94[b]
$DPSOCH_2CH_2$ (**d**)	92	86:14	92:8 (**d**)	*a*

[a] Not determined. [b] Determined by GC analysis and corrected for the ee of the starting material.

A second series of experiments was conducted with nonracemic propargyl and allenyl reagents. As we were concerned that the preparation of highly enantioenriched propargylic halides would be problematic,[6] we explored the use of mesylate **5**, derived from (*R*)-(+)-3-butyn-2-ol,[7] as the precursor of the chlorosilane intermediate. Reaction with $HSiCl_3$ and catalytic CuCl in the presence of Hunig's base, followed by addition of representative aldehydes in DMF, afforded mainly the *anti* adducts **6a**−**d** with high regio- and diastereoselectivity (Table 2). The ee of adducts **6b** and **6c** was determined by GC analysis. The carbinyl stereochemistry was assigned on the basis of the ^{1}H NMR spectra of the *O*-methylmandelates.[8] The stereochemistry of adducts **6a** and **6d** is assigned by analogy.

The TMS propargylic mesylate **8** afforded the allenylcarbinols **9a**−**d** as the major products (Table 3). The configuration of the carbinyl center was surmised from the ^{1}H NMR spectrum of the *O*-methylmandelates.[8]

(1) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550.
(2) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.
(3) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230.
(4) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. Kobayashi, S.; Yasuda, M.; Nishio, K. *Synlett* **1996**, 153.
(5) Kobayashi, S.; Nisho, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392.
(6) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3055. In fact, when nonracemic bromide **3** (R^1 = TMS, R^2 = Me, X = Br; $[\alpha]_D$ = +5.1), prepared from the alcohol precursor of mesylate **8** (CuBr, LiBr, THF; 81% yield), was treated with $HSiCl_3$, CuCl (cat.), *i*-PrNEt, and then *c*-$C_6H_{11}CHO$, adduct **9b** was secured (74% yield) in racemic form.
(7) Available from DSM Fine Chemicals, Inc., Saddlebrook, NJ, in ~97% ee.
(8) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

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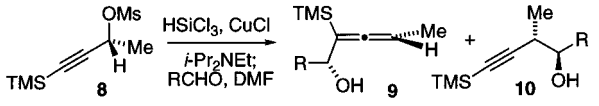
Table 3. Adducts from Chlorosilylation of Mesylate 8 and *in Situ* Addition to Aldehydes

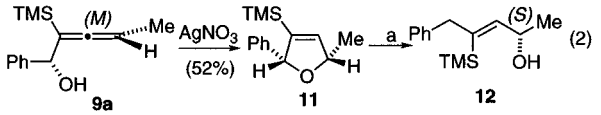


R	yield, %	ee, % (**9**)	**9**:**10**	$[\alpha]_D$
C_6H_5 (**a**)	92	*a*	89:11 (**a**)	−108
c-C_6H_{11} (**b**)	55	99[b]	98:2 (**b**)	−42
C_6H_{13} (**c**)	67	95[b]	95:5 (**c**)	−18
$PhCH_2CH_2$ (**d**)	67	*a*	98:2 (**d**)	−12

[a] Not determined. [b] From analysis of the ^{1}H NMR spectrum of the *O*-methylmandelates.

The allene configuration of **9a**−**d** can be tentatively assigned by consideration of the Lowe−Brewster rules.[9] All show a negative rotation in accord with the *M* configuration.

Additional evidence for the configuration of **9a** was accomplished through $AgNO_3$-catalyzed cyclization to the 2,5-dihydrofuran **11**[1] and subsequent hydrogenolysis of the benzylic ether with Na/NH_3 (eq 2). The resulting allylic alcohol **12** was found to have the (*S*) configuration (98% ee) through ^{1}H NMR analysis of the *O*-methylmandelates.[8]



A possible reaction pathway for these transformations is depicted in Figure 1. Accordingly, the starting propargylic mesylate would undergo S_N2 or S_N2' displacement by a Cl_3Si cuprate (formally *i*-$Pr_2NEt{\cdot}HCl{\cdot}CuSiCl_3$) to afford the intermediate chlorocuprates **VI** or **VII**.[11] Conversion to the trichlorosilanes by reductive elimination then occurs with retention of configuration. Chlorosilanes **VIII** and **IX** and the chlorosilylcuprate precursors (by analogy to allylic cuprates) may exist as an equilibrating mixture.[1,2,5,11] Addition to the aldehyde can be envisioned to take place through transition states **A** or **B**, analogous to those proposed for the propargyl/allenylstannane counterparts.[1,2]

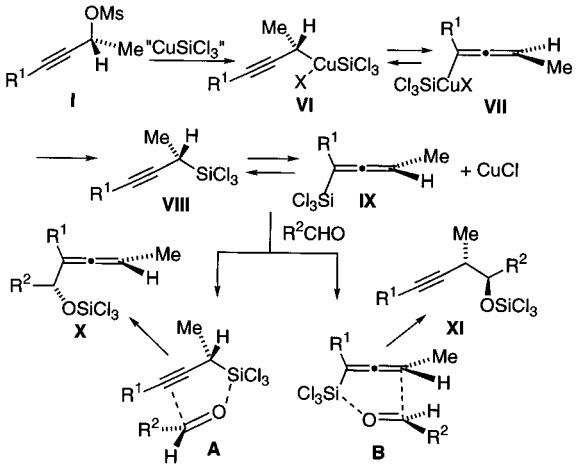


Figure 1. Possible reaction pathways for S_E2' additions of allenyl/propargyl trichlorosilanes to aldehydes.

The foregoing studies establish the potential of nonracemic propargylic and allenic chlorosilanes as reagents for the production of homopropargylic alcohols and allenylcarbinols with high diastereoselectivity and chirality transfer. These reagents offer a useful alternative to their stannane counterparts for the synthesis of potential precursors to polypropionate and polyether natural products. Our findings also establish a possible reaction pathway for these transformations, which should be of predictive value for regio- and stereoselective synthesis.

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Supporting Information Available: ^{1}H NMR spectra and experimental procedures for key intermediates, the ^{13}C NMR spectrum of allenylcabinol **4c**, and GC traces for **6b**,**c** (25 pages).

JO971853L

(9) Lowe, G. *J. Chem. Soc., Chem. Commun.* **1965**, 411. Brewster, J. H. *Topics Stereochem.* **1967**, *2*, 1. The assumption is made that TMS is more polarizable than CH(OH)R and Me is more polarizable than H.

(10) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

(11) Cf. Marshall, J. A. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 1503. Goering, H. L.; Kanter, S. S. *J. Org. Chem.* **1983**, *48*, 721.