Synthesis of Chiral Enantioenriched Homopropargylic Alcohols from Propargylic Mesylates via Chiral Allenylzinc Intermediates

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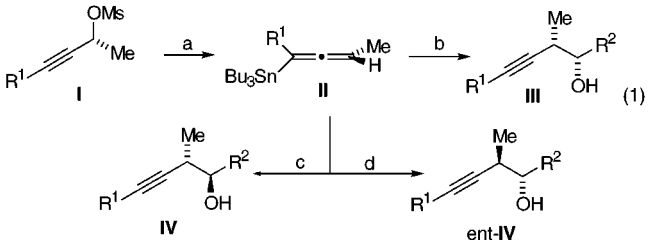
During the past several years, we have prepared chiral allenyl tin and, more recently, indium reagents in connection with the synthesis of stereotriad segments of polypropionate natural products.[1,2] The approach entails the S_N2' displacement of propargylic mesylates **I** with a Bu_3Sn cuprate reagent to afford allenyl $SnBu_3$ intermediates **II** of high ee. These reagents undergo syn-selective S_E2' addition to aldehydes in the presence of $BF_3{\cdot}OEt_2$. Transmetalations with $InBr_3$ or $SnCl_4$ (or $BuSnCl_3$) afford transient $InBr_2$ and $SnCl_3$ (or $BuSnCl_2$) intermediates, which yield anti adducts **IV** or *ent*-**IV**, respectively, upon addition to aldehydes (eq 1).[1] The alkynyl groups of these adducts can be utilized for introduction of additional Me- and OH-substituted stereocenters, as required.

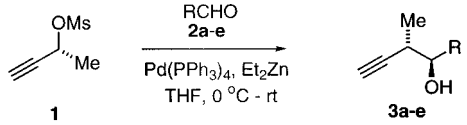


a. Bu_3SnLi, $Me_2S{\cdot}CuBr$; b. R^2CHO, $BF_3{\cdot}OEt_2$; c. InX_3, R^2CHO; d. $SnCl_4$ or $BuSnCl_3$, R^2CHO

Although the foregoing methodology has proven quite useful for the construction of various subunits of polypropionate natural products,[2] the necessary involvement of organotin compounds is viewed as a limitation with regard to large-scale synthesis. Accordingly, we have been exploring alternative allenylmetal reagents that might exhibit similar high levels of enantio- and diastereoselectivity.

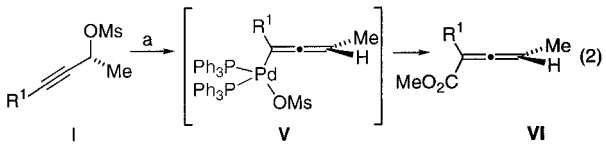
A recent report by Tamaru et al., describing the formation of racemic or achiral allylic zinc species from allylic benzoates or phenyl ethers and catalytic $Pd(PPh_3)_4$ in the presence of excess Et_2Zn, attracted our attention.[3] We have previously shown that propargylic mesylates undergo highly stereoselective alkoxycarbonylation with catalytic $Pd(PPh_3)_4$, CO, and alcohols affording allenic esters **VI** with net inversion of stereochemistry (eq 2).[4] If Zn metathesis of the presumed allenylpalladium intermediate **V** could be effected with comparable regio- and enantioselectivity, it may be possible to produce a chiral allenylzinc reagent that would afford enantioenriched homopropargylic alcohols upon addition to aldehydes. A successful outcome would depend on the (unknown) configurational stability of the transient allenylzinc reagent.

Table 1. Additions of an Allenylzinc Reagent, Generated in Situ from Propargylic Mesylate 1, to Aldehydes 2a−e



R	yield, %	anti:syn[a]	ee,[a−c] %
c-C_6H_{11}, **a**	85	95:5	95
C_6H_{13}, **b**	70	88:12	90
$TBSOCH_2CH_2$, **c**	56	86:14	86[d]
(*E*)-BuCH=CH, **d**	71	77:23	88
1-octynyl, **e**	60	68:32	90

[a] Analysis by gas chromatography. [b] For the anti isomer. [c] Corrected for the ee of the starting material. [d] Analyzed as the diol.



a. $(Ph_3P)_4Pd$, CO, MeOH, THF

To address these issues, we treated the (*R*)-mesylate **1**[5] with 5 mol % of $Pd(PPh_3)_4$, 2.4 equiv of Et_2Zn, and 1 equiv of aldehydes **2a**−**e** in THF at 0 °C to room temperature. This combination led to propargylic adducts **3a**−**e** as the sole products (Table 1). These were analyzed by gas chromatography and identified by comparison with known samples.[6] In all cases, the additions proceeded with good to excellent anti selectivity and acceptable yield. Enantioselectivity was uniformly high, but diastereoselectivity decreased according to the steric requirements of the aldehyde.

A parallel series of additions was carried out starting from the propargylic mesylate **4** (Table 2).[1] The additions followed a trend similar to those of mesylate **1** with regard to diastereo- and enantioselectivity. The yields (unoptimized), however, were somewhat lower in these preliminary experiments.

To probe a potential application of this chemistry to the synthesis of polypropionate subunits,[2] we examined additions of the allenylzinc intermediate from mesylate **4** to the α-methyl-β-benzyloxy aldehydes (*S*)- and (*R*)-**6** (eq 3).[1] In the former case, the anti,syn product **7**[1] was the sole adduct. Addition to (*R*)-**6** afforded the anti,anti adduct **8**[1] in high yield.

We also examined the propargylic acetate, trifluoroacetate, and methyl carbonate analogues of **1** as possible precursors of the allenylzinc intermediate. No products were obtained with the former two esters and cyclohexanecarboxaldehyde. The methyl carbonate derivative gave the propargylic adduct **3a**, but the yield (27%) and ee (29%) were distinctly inferior to results obtained with the mesylate. The mesylate reactions were carried out in several solvents (C_6H_6, MeCN, CH_2Cl_2, and THF), but only MeCN and THF gave homopropargylic alcohol adducts uncontaminated by

(1) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.
(2) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001. Marshall, J. A.; Lu, Z.-H.; Johns, B. *J. Org. Chem.* **1998**, *63*, 817.
(3) Tamaru, Y.; Tanaka, A.; Yasui, K.; Goto, S.; Tanaka S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 787.
(4) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.
(5) The alcohol precursor is available from Aldrich Chemical Co., Milwaukee, WI.
(6) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 8976.

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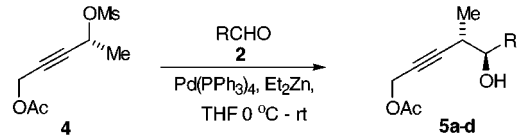
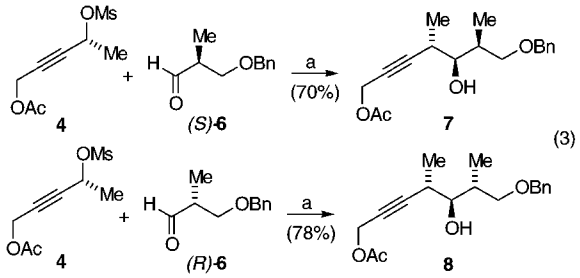
Table 2. Addition of an Allenylzinc Reagent, Generated in Situ from Propargylic Mesylate 4, to Aldehydes 2a−d



R	yield, %	anti:syn[a]	ee,[b,c] %
c-C_6H_{11}, **a**	51	95:5	96
C_6H_{13}, **b**	57	90:10	89
i-Pr, **c**	47	95:5	96
(*E*)-BuCH=CH, **d**	57	70:30	d

[a] ^{1}H NMR analysis. [b] ^{1}H NMR analysis of the *O*-methyl mandelate[8] of the the anti isomer. [c] Corrected for the ee of the starting material. [d] Not determined.



a. $Pd(PPh_3)_4$, Et_2Zn, THF, 0 °C to rt

the regioisomeric allenic products.[7] Reactions in THF gave higher yields of adducts.

The palladation of propargylic mesylates is known to take place with inversion,[4] and the predominant formation of anti adducts **3** strongly implicates a syn addition process (cyclic transition state). It can therefore be surmised that the zincation reaction proceeds with retention of configuration. A possible sequence is depicted in Figure 1. A related pathway has been proposed to account for palladium-catalyzed intramolecular carbozincation of 6-iodo-1-hexenes.[9]

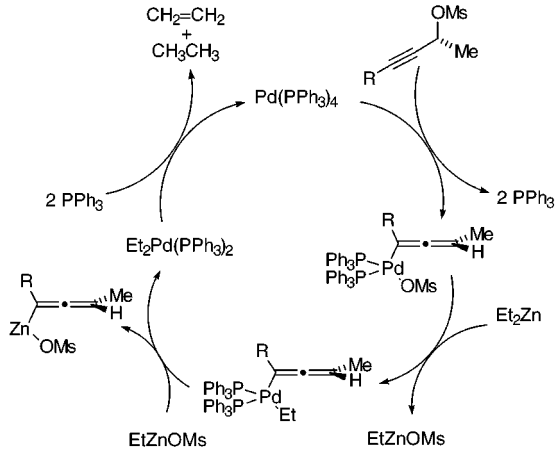


Figure 1. Possible catalytic cycle for Pd(0)-catalyzed zincation of propargylic mesylates.

The present findings show that configurationally stable chiral allenylzinc reagents can be efficiently prepared from propargylic mesylates. These reagents add to a variety of aldehydes to afford anti adducts as major or nearly exclusive products. The ready availability of highly enantioenriched propargylic alcohols[10] and the simplicity of the palladation−zincation process contribute to the appeal of this methodology.

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Supporting Information Available: Procedures for the preparation of all products. ^{1}H NMR spectra of **3a**−**e**, **5a**−**d**, **7**, **8**, and the *O*-methyl mandelates of **5a** and **b** (25 pages).

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(7) Preliminary studies on solvent effects were carried out in these laboratories with a racemic propargylic mesylate by Matt Yanik. Isobutyraldehyde afforded a 70:30 mixture of propargylic and allenic adducts in benzene (91% yield) and a 90:10 mixture in CH_2Cl_2 (67% yield) upon addition of the zinc reagent obtained from the mesylate derivative of 3- undecyn-2-ol. In THF, the propargylic adduct was produced as the sole product in 60% yield.

(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.

(9) Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027.

(10) Yadev, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455. Marshall, J. A.; Jiang, H. *Tetrahedron Lett.* **1998**, *39*, 1493.