Formation of Transient Chiral Allenylindium Reagents from Enantioenriched Propargylic Mesylates through Oxidative Transmetalation. Applications to the Synthesis of Enantioenriched Homopropargylic Alcohols

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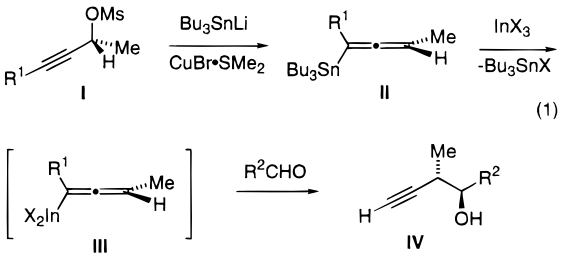
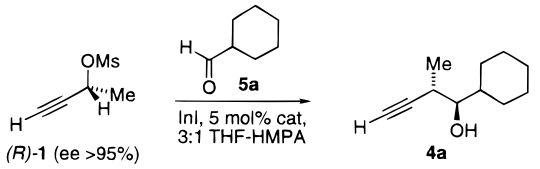
Reactions of allenylmetal compounds with aldehydes and ketones have been the subject of a number of investigations over the past half-century.[1] Early work addressed the issues of regiochemistry (propargyl vs allenyl) and relative stereochemistry (syn and anti). In recent years attention has been directed to the synthesis and utility of chiral nonracemic allenylmetal compounds as reagents for enantioselective synthesis.[2,3] We have described a simple, direct route to chiral allenylstannanes through S_N2' displacement of enantioenriched secondary propargylic mesylates with Bu_3SnCu reagents.[2] Lewis-acid promoted additions of these reagents to aldehydes lead to syn homopropargylic alcohols whereas *anti* adducts are obtained through transmetalation of the chiral allenic Bu_3Sn intermediates with $SnCl_4$, $BuSnCl_3$, or InX_3 compounds, followed by addition of the aldehyde (eq 1).[4] These reactions are capable of outstanding levels of enantio- and diastereoselectivity, especially in additions involving α-branched aliphatic aldehydes. However, the inevitable formation of toxic Bu_3SnX byproducts presents a significant obstacle to their widespread usage.



The low toxicity of organoindium compounds stimulated our interest in the use of allenylindium reagents for these additions.[5] As noted above, the indium reagents have previously been prepared in nonracemic form from allenyltin intermediates. We now describe alternative routes that do not involve tin compounds.

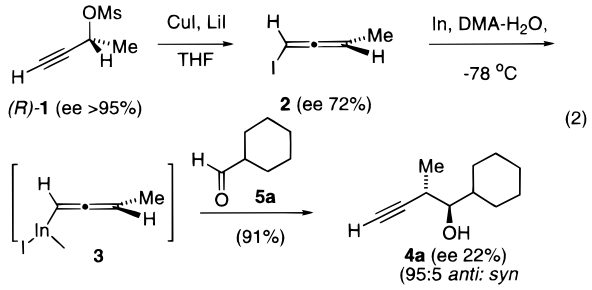
Propargylic mesylates have been shown to undergo efficient *anti* S_N2' displacement with LiX/CuX reagents to afford allenic halides.[6] We envisioned an in situ preparation of chiral allenylindium reagents from these halides by reaction with indium metal. As a test of concept we prepared the known allenyl iodide **2**[6] from mesylate (*R*)-**1** of >95% ee. Sequential addition of the iodide and aldehyde to a stirred suspension of indium powder in various solvents afforded the homopropargylic alcohol **4a**. Of the solvents examined (EtOH, EtOH−H_2O, THF, THF−H_2O, DMF, DMF−H_2O, DMA, DMA−H_2O), the combination of DMA and 5−10% H_2O gave the best overall results.[7] However, while the yield and diastereoselectivity of the addition were excellent, the enantioselectivity was poor (eq 2). This result could reflect partial racemization during metalation and/or the configurational lability of the intermediate allenylindium reagent.[3]

Table 1. Variation of Catalyst and Solvent in Additions of Allenylindium Reagents Derived From Mesylate (*R*)-1 to Cyclohexanecarboxaldehyde



catalyst	yield, %	*anti*:*syn*[a]	ee, %[a]
none	66	96:4	0
$Pd(dppf)Cl_2$	76	95:5	95
$Pd(dppf)Cl_2$[b]	63	87:13	87
$Pd(dppf)Cl_2$[c]	80	91:9	90
$Pd(dppf)Cl_2$[d]	66	93:7	91
$Pd(OAc)_2$•PPh_3	75	95:5	91

[a] Ratios and ee values were determined by GC analysis. [b] 3:1 THF−DMPU as the solvent. [c] 1:1 THF−DMPU as the solvent.[d] 20:1 THF−HMPA as the solvent.



Attempted formation of an allenylindium intermediate from the propargyl mesylate (*R*)-**1** and indium powder in the presence of aldehyde was not successful. The aldehyde was recovered. However, when InI was employed, metalation of the mesylate took place, and the adduct **4a** was produced in 66% yield as a 95:5 mixture of *anti* and *syn* isomers (Table 1). Unfortunately, the adduct was racemic. We then explored the possible transmetalation of an allenylpalladium intermediate with InI, a process that we perceived to be conceptually related to a Pd−Zn metathesis of recent interest for the in situ formation of chiral allenylzinc reagents.[8,9] In fact, the reaction proceeded as planned. Adduct **4a** (95:5 anti: syn) of 95% ee was obtained in 76% yield from mesylate (*R*)-**1** and InI in the presence of 5 mol % $Pd(dppf)Cl_2$ as the catalyst

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(3) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001. Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817. Marshall, J. A.; Johns, B. A.; *J. Org. Chem.* **1998**, *63*,
(4) Cf. Marshall, J. A.; Perkins, J. F.; Wolf, M. A.; *J. Org. Chem.* **1995**, *60*, 5556.
(5) Marshall, J. A.; *Chemtracts − Organic Chemistry* **1997**, *10*, 481.
(6) Elsevier: C. J.; Vermeer, P.; Gedanken, A.; Runge, W. *J. Org. Chem.* **1985**, *50*, 364.
(7) DMA = *N*,*N*-dimethylacetamide, DMPU = *N*,*N*-dimethylpropyleneurea, DPS = diphenyl-*tert*-butylsilyl.
(8) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812. Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 878.
(9) A reviewer called our attention to a report of Trost and co-workers who found that 10 mol % of $In(acac)_3$ in the presence of 5 mol % $Pd(OAc)_2$ and various phosphine ligands causes the reagent $TMSCH_2(C{=}CH_2)CH_2$-OAc to undergo 1,2- as opposed to 1,4-additions to conjugated aldehydes and ketones. Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7903.

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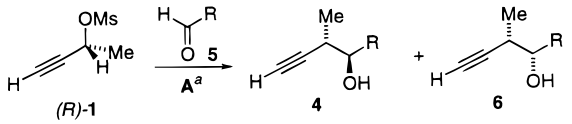
Table 2. Additions of Transient Chiral Allenylindium Reagents from Mesylate (*R*)-1 to Representative Achiral Aldehydes



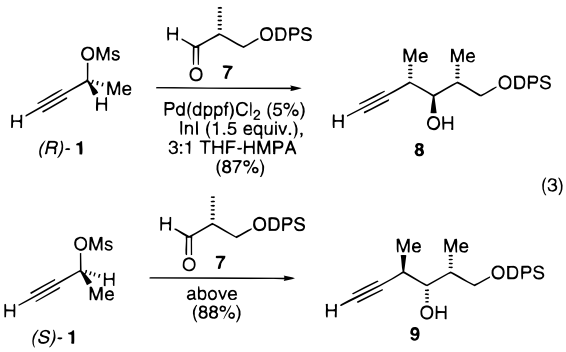
R	yield, %	*anti*:*syn*	ee, %
c-C_6H_{11} (**5a**)	76	95:5[b]	95[b]
C_6H_{13} (**5b**)	73	82:18[b]	96[b]
$DPSOCH_2CH_2$ (**5c**)	88	88:12[c]	*d*
(E)-BuCH=CH (**5d**)	68	71:29[b]	96[b]
1-heptynyl (**5e**)	62	72:28[b]	95[b]
Ph (**5f**)	85	45:55[b]	92[b]

[a] 5 mol % Pd(dppf)Cl_2, 1 equiv of InI, 3:1 THF−HMPA, room temp. [b] Analysis by gas chromatography on a β-cyclodextrin column. [c] Calculated from the ^{1}H NMR spectrum. [d] Not determined.

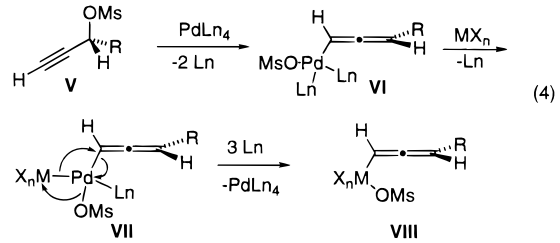
precursor (Table 1).[10] The addition was most efficient in 3:1 THF−HMPA, although as little as 5% HMPA in THF could be employed. The use of 3:1 THF−DMPU[7] led to lower yield, diastereoselectivity, and enantioselectivity. However, 1:1 THF−DMPU was quite satisfactory. $Pd(OAc)_2$·PPh_3[11] also served as an efficient catalyst precursor. As expected, no addition took place when the foregoing experiments were performed in the absence of InI.

The scope of the new process was examined with a number of representative achiral aldehydes and the mesylate (*R*)-**1** (Table 2). In all cases the addition afforded adducts of high ee, as determined by GC analysis. *Anti*:*syn* ratios were excellent with the α-branched aldehyde **5a** but only modest with unbranched and conjugated aldehydes **5b**−**e**.[12] Addition to benzaldehyde (**5f**) afforded a nearly 1:1 mixture of *anti* and *syn* adducts.[8] All reactions were conducted with 5 mol % of catalyst precursor and 1.5 equiv of InI at room temperature.

The matched/mismatched characteristics of the reagent derived from mesylate **1** were examined with the (*R*)-α-methyl-*β*-ODPS aldehyde **7**[13] (eq 3). The *anti*, *anti* adduct **8** was obtained in 87% yield from (*R*)-**1**, and the *anti*, *syn* adduct **9** was formed in 88% yield from (*S*)-**1**.[14] Only trace amounts of diastereomeric products (<5%) could be detected by ^{1}H NMR analysis. Evidently these additions are strongly reagent controlled.



The foregoing additions are easily performed and employ a readily available propargylic alcohol of high ee as starting material.[8] The current application is well suited to the synthesis of polypropionate subunits.[3] Extension to other propargylic alcohols will be examined in future studies. The overall process of "oxidative transmetalation" may be generalized as shown in eq 4. Other lower valent metals such



as Sn(II), Pb(II), Ti(II), Cu(I), and the like may follow a similar course,[15] thus providing access to chiral allenylmetal reagents that would not be available by existing methodology. Studies on these systems will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data, and GC traces for all adducts.

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(10) [1, 1′-Bis(diphenylphosphino)ferrocene]dichloropalladium [Pd(dppf)Cl_2], InI, and the alcohol precursor of mesylate **1** are available from the Aldrich Chemical Co., Milwaukee, WI.

(11) $Pd(OAc)_2$·PBu_3 has been employed for the preparation of allylic zinc intermediates. Oppolzer, W.; Flachsmann, F. *Tetrahedron Lett.* **1998**, *39*, 5019. The Ph_3P analogue was first examined in our laboratory by N. D. Adams.

(12) The stereochemistry of the adducts was established by comparison to authentic samples. Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 8976.

(13) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987**, *52*, 316.

(14) The structure of these adducts is assigned by comparison with authentic samples prepared from aldehydes **7** and *ent*-**7** by N. D. Adams as described in ref 12.

(15) A similar concept has been employed for the conversion of achiral or racemic allylic acetates, carbonates, and alcohols to allylic stannanes from Sn(II) salts[16] or $Et_2AlSnBu_3$,[17] and allylic zinc intermediates from Zn[18] with $Pd(PPh_3)_4$ as the catalyst. However, in situ additions of these allylmetal compounds to aldehydes typically proceed in low to moderate yield to afford homoallylic alcohol adducts with low diastereoselectivity. Allenylsamarium intermediates have also been prepared through use of propargylic esters, $Pd(PPh_3)_4$, and SmI_2. Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2275. Aurrecoechea, J. M.; Fañanás-San Antón, R. *J. Org. Chem.* **1994**, *59*, 702.

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(18) Masuyama, Y.; Kinugawa, N.; Kurusu, Y. *J. Org. Chem.* **1987**, *52*, 3702. Zhang, P.; Zhang, W.; Zhang, T.; Wang, Z.; Zhore, W. *J. Chem. Soc., Chem. Commun.* **1991**, 491.