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Lipase-Mediated Resolution of 4-TMS-3-butyn-2-ol and Use of the Mesylate Derivatives as a Precursor to a Highly Stereoselective Chiral Allenylindium Reagent

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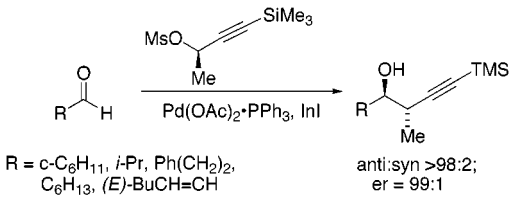
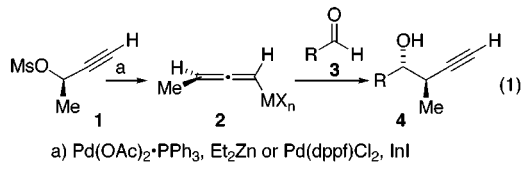
ABSTRACT



An improved procedure for the resolution of 4-trimethylsilyl-3-butyn-2-ol has been developed. The mesylate derivatives of the resolved alcohols have been found to undergo highly enantio-, regio-, and diastereoselective additions to aldehydes, leading to homopropargylic alcohol adducts.

Additions of chiral allenylmetal reagents to aldehydes leading to enantioenriched syn and anti homopropargylic alcohol adducts have played a key role in the synthesis of several polyketide natural products and subunits with potential medicinal applications.[1] One promising variant of the methodology employs enantioenriched propargylic mesylates such as **1** as precursors to enantioenriched allenylzinc or indium reagents.[2] These reagents are generated in situ through "oxidative transmetalation" of transient allenylpalladium intermediates (eq 1).[3]



The alcohol precursors of mesylate (*R*)-**1** and its enantiomer are commercially available.[4] However, the high cost of these alcohols limits widespread utilization of the methodology. For this reason we have been exploring simple and cost-effective preparations. A report by Burgess and Jennings describing the lipase-mediated kinetic resolution of racemic TMS butynol **5** through enantioselective acetylation seemed well suited to this goal (Scheme 1).[5] However, because of

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(1) (a) Zincophorin. Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701. (b) Discodermolide. Marshall, J. A.; Johns. B. A. *J. Org. Chem.* **1998**, *63*, 7885. (c) Callystatin A. Marshall, J. A.; Fitzgerald, R. A. *J. Org. Chem.* **1999**, *64*, 4477. (d) Aplyronine A. Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501. (e) Balifomycin. Marshall, J. A.; Adams, N. D. *Organic Lett.* **2000**, *2*, 2897. (f) Tautomycin. Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, *66*, 1373.

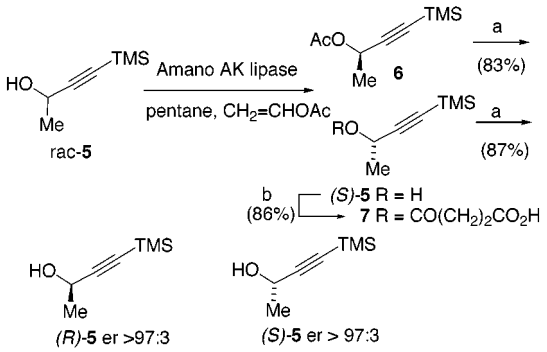
(2) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214.

(3) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

(4) Aldrich Chemical Co., Inc. 1001 West St. Paul Avenue, Milwaukee, WI 53233.

(5) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129. For an application of the lipase resolution methodology to (*E*)-4-diphenylsilyl-3-buten-2-ol and 4-diphenylsilyl-3-butyn-2-ol, see, respectively: Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78. Panek, J. S.; Clark, T. D. *J. Org. Chem.* **1992**, *57*, 4323.

Scheme 1

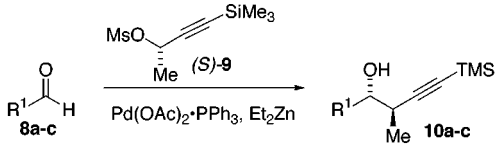


a) DIBAl-H, hexanes; b) succinic anhydride, Et_3N, DMAP.

the high volatility of TMS butynol (*S*)-**5** and its enantiomeric acetate **6**, especially the former, recovery of material after separation by chromatography was low (27% for (*S*)-**5**). Nonetheless, the high efficiency of the resolution (>97:3 er for both (*S*)-**5** and **6** encouraged our investigation of the methodology. To minimize losses of products during initial solvent removal, we conducted the resolution in pentanes rather than hexanes as previously reported.[5] Also, to circumvent material losses and the additional expense of chromatography, we treated the mixture of acetate **6** and alcohol (*S*)-**5** with succinic anhydride to afford a ca. 1:1 mixture of succinate **7** and unchanged acetate **5** which was extracted with $NaHCO_3$ to remove the succinate. Once separated, the esters **6** (ca. 82% yield) and **7** (86% yield) were converted to alcohols (*R*)-**5** and (*S*)-**5** by treatment with excess DIBAL-H in hexanes followed by distillation. The er values of the two alcohols were determined by GC analysis of the acetate derivatives on a β-Dex column.

Rather than desilylate alcohols (*R*)- and (*S*)-**5** to the volatile and water-soluble parent 3-butyn-2-ols, we explored the use of the mesylate derivative (*S*)-**9** for the synthesis of the anti homopropargylic alcohols **10a**−**c** through application of the allenylzinc methodology (Table 1).[2a] We were particularly interested in the regio- and enantioselectivity of these reactions. In fact, the additions proceeded with excellent diastereoselectivity and only slight loss of enantioselectivity,

Table 1. Silylated Allenylzinc Additions to Achiral Aldehydes



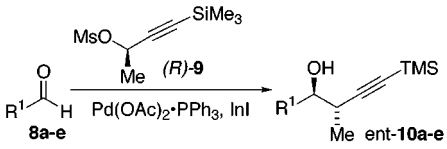
R^1	yield, %	anti:syn[a]	er[a,b]
c-C_6H_{11} (**a**)	84	96:4	97:3
i-Pr (**b**)	86	95:5	98:2
$Ph(CH_2)_2$ (**c**)	78	90:10	99:1

[a] GC analysis on a β-Dex column after cleavage of the silyl group with TBAF. [b] Corrected for the er of the resolved alcohol (*S*)-**5** (97:3).

a phenomenon we ascribe to partial racemization of the allenylpalladium precursor of the chiral allenylzinc reagent.[6] Normant and co-workers have prepared racemic α-TMS allenylzinc bromide reagents and found that they add to chiral imines with high diastereoselectivity and enantiodiscrimination (kinetic resolution).[7] They have found these reagents to be configurationally stable below −10 °C.

It was also of interest to explore additions employing the allenylindium reagent which is derived from mesylate (*R*)-**9** through oxidative transmetalation of the aforementioned allenylpalladium intermediate with InI.[2b] Initial findings with $Pd(dppf)Cl_2$ as the catalyst precursor for the transmetalation were not promising. Only a small amount of adduct was obtained from cyclohexanecarboxaldehyde, even at room temperature over 12 h. In contrast, use of $Pd(OAc)_2$•PPh_3 at 0 °C as the catalyst precursor for the InI exchange reaction led to a remarkable improvement, affording anti adducts with er values of 99:1 or higher and with virtually no trace of syn adducts (Table 2). This selectivity was observed not only

Table 2. Silylaed Allenyulindium Additions to Achiral Aldehydes



R^1	yield, %	anti:syn[a]	er
c-C_6H_{11} (**a**)	75	>99:1	99:1[a]
i-Pr (**b**)	89	98:2	99:1[a]
$Ph(CH_2)_2$ (**c**)	69	>99:1	>99:1[a]
C_6H_{13} (**d**)	80	98:2	99:1[b]
(*E*)-BuCH=CH (**e**)	73	99:1	99:1[b]

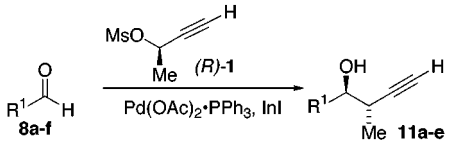
[a] GC analysis on a β-Dex column after cleavage of the silyl group with TBAF. [b] GC analysis on an α-Dex column after cleavage of the silyl group with TBAF.

with branched aldehydes **8a** and **8b** but also with unbranched aldehydes **8c** and **8d**, as well as the conjugated enal **8e**. By comparison, additions of allenylzinc and indium reagents derived from 3-butyn-2-ol mesylate or the 4-acetoxymethyl derivative to unbranched and conjugated aldehydes typically afford anti adducts with 70−85% ds.[2,3] An addition of the TMS reagent to 2-octynal was less satisfactory. A 2:1 mixture of anti and syn diastereomers was obtained in 45% yield along with a chromatographically separable allenylcarbinol isomer in 30% yield. An investigationof this intriguing discrepancy is under investigation. Close inspection of the ^1H NMR spectra of adducts **10a**−**e** revealed signals for traces (5% or less) of comparable adducts.

(6) Chiral allenylpalladium compounds are racemized by Pd(0) catalysts. Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 3042. See also: Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.
(7) Poisson, J.-F.; Chemla, F.; Normant, J.-F. *Synlett* **2001**, 305.

We suspected that the allenyl TMS substituent was responsible for the remarkable selectivity of the allenylindium reagent (2-octynal notwithstanding) but could not exclude the possibility that the $Pd(OAc)_2$·PPh_3 catalyst precursor was a contributing factor. We therefore examined additions of allenylindium reagents derived from mesylate (*R*)-**1** to representative aldehydes with this catalyst precursor (Table 3). In fact, the product ratios were virtually identical to those previously observed with the Pd(dppf) catalyst.[2b]

Table 3. Allenylindium Additions to Achiral Aldehydes

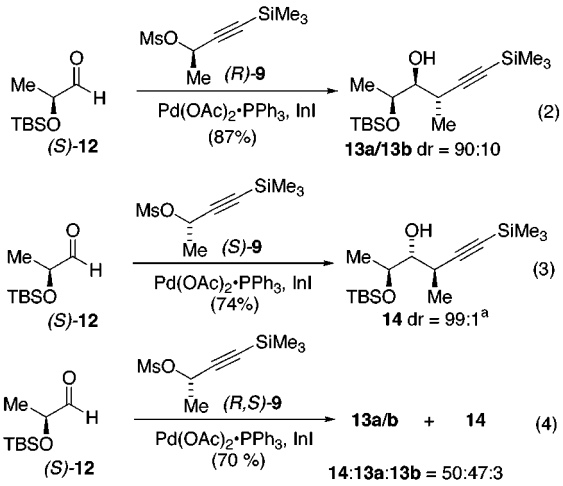


R^1	yield, %	anti:syn[a]	er[b]
c-C_6H_{11} (**a**)	86	95:5	99:1[a]
$Ph(CH_2)_2$ (**c**)	71	77:23	99:1[a]
C_6H_{13} (**d**)	71	93:7	99:1[c]
(E)-BuCH=CH (**e**)	78	60:40	99:1[c]

[a] GC analysis on a β-Dex column. [b] Corrected for the er of the resolved alcohol (*R*)-**5** (97:3). [c] GC analysis on an α-Dex column.

Thus we surmise that the allenyl α-TMS substituent must impose a significant directing effect in these additions. Furthermore, the amount of racemization is lower with the $Pd(OAc)_2$·PPh_3 catalyst system than that of the Pd(dppf) catalyst (<1% vs ~5% with cyclohexanecarboxaldehyde) previously studied.[2c] These results suggest that the former catalyst decreases the rate of allenylpalladium racemization[7] and/or increases the rate of Pd−In exchange to yield a configurationally stable allenylindium reagent. This latter postulate would be consistent with the observed rate difference between additions performed with $PdCl_2$(dppf) vs $Pd(OAc)_2$·PPh_3 as the transmetalation catalysts.

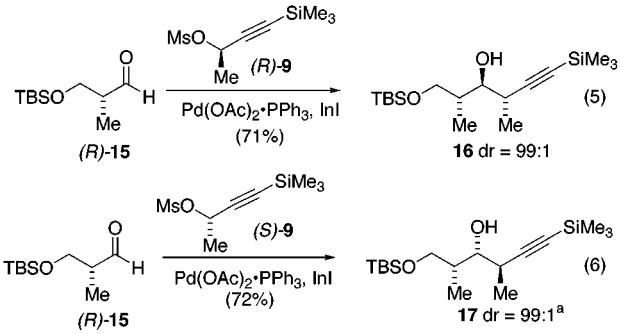
With possible applications to natural product synthesis in mind, we examined additions of allenylindium reagents derived from (*R*)- and (*S*)-**9** to α-oxygenated and α-methyl aldehydes (eqs 2 and 3). We have previously found that nonsilylated allenylindium reagents show significant matching/mismatching with the former but not the latter aldehydes.[8] In fact, addition of the (*R*)-**9**-derived reagent to the TBS ether (*S*)-**12** of (*S*)-lactic aldehyde afforded a 90:10 mixture of the anti adduct **13** and the corresponding syn,syn diastereomer **3b** (not shown). This compares to an 80:20 mixture of the corresponding adducts from the mesylate of 3-butyn-2-ol.[8] As expected, the (*S*)-**9**-derived reagent gave only the anti,-anti adduct **14** with no detectable syn isomer. In both additions, a trace (5%) of the allenylcarbinol byproduct could be seen in the ^{1}H NMR spectrum. To test the configurational stability of the allenylindium reagent, we performed a



[a] corrected for the er of the resolved alcohol *(S)*-**5** (97:3)

"Hoffmann test" [9] with aldehyde (*S*)-**12** and racemic mesylate (*R*,*S*)-**9** (eq 4). In fact, a 50:47:3 mixture of diastereomeric adducts **14**:**13a**:**13b** was produced, indicating that no racemization of the reagent had taken place.

Additions of the (*R*)-**9**-derived reagent to the α-methyl β-OTBS aldehyde (*R*)-**15** afforded the anti,anti adduct **16** as the sole detectable product. Additions of the enantiomeric reagent (*S*)-**9** were equally selective, affording adduct **17** exclusively after correcting for the er (97:3) of the allenylindium precursor (eqs 5 and 6).



[a] corrected for the er of the resolved alcohol *(S)*-**5** (97:3)

The enhanced diastereoselectivity of the α-TMS-substituted allenylindium reagents, particularly with regard to the remarkably high levels observed with unbranched and conjugated aldehydes, is suggestive of a tight transition state for these additions. Such a transition state would place the CH_3 and the nearly eclipsed aldehyde substituent R in close proximity for the syn pathway, whereas these groups are at some distance in the anti array (Figure 1).[10] The precise role (steric or electronic) of the TMS substituent in effecting this perturbation is unclear at present.

The present findings reveal an unprecedented and unexpected TMS effect for enhancing the diastereoselectivity of

(8) Marshall, J. A.; Chobanian, H. R. *J. Org. Chem.* **2000**, *65*, 8357.

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(10) Support for the eclipsed transition states has been obtained for the analogous allenylzinc additions through ab initio calculations at the 3-21G* basis set level. Details of these calculations will be described in a forthcoming publication.

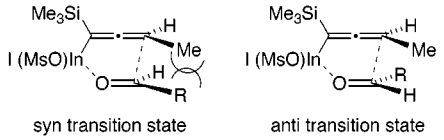

Figure 1. Transition states for additions of allenylindium reagents to aldehydes.

allenylindium additions to aldehydes. The finding that unbranched and conjugated aldehydes respond to this effect considerably broadens the synthetic scope of the methodology. The superiority of the $Pd(OAc)_2 \cdot PPh_3$ catalyst to the previously employed $Pd(dppf)Cl_2$ precursor is also of considerable practical import. An improved, efficient, and inexpensive resolution of the 4-TMS-3-butyn-2-ol precursor of the allenylindium reagents has also been developed. Finally, it should be noted that the alkynyl TMS adducts can be readily desilylated to synthetically useful terminal alkynes[1] with TBAF or used directly in $CuCl_2$-promoted coupling reactions with vinyl and aryl halides, thus further enhancing the utility of the present discovery.[11] Additional seamless methodologies for directly integrating the TMS alkynyl moiety into useful synthetic sequences are currently under investigation.[12]

Acknowledgment. This research was supported by research grants from the National Science Foundation (CHE-9901319) and the National Institutes of Health (R01 CA090383). We thank Professor James Panek for advice and encouragement in connection with the lipase resolution methodology.

Supporting Information Available: Experimental procedures for all new compounds and selected ^1H NMR spectra. This material is available free of charge from the Internet at http://pubs.acs.org.

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(11) Cf. Nishihara, Y.; Ikegashira, K.; Hirabayashi, K. Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780. Results from our laboratory will be described in a forthcoming publication.

(12) **Resolution of 4-TMS-3-butyn-2-ol.** To a solution of racemic 4-trimethylsilyl-3-butyn-2-ol (10.0 g, 69.9 mmol) in pentane (250 mL) were added Amano AK Lipase (2.0 g, Aldrich), freshly distilled vinyl acetate (50 mL), and 1 g of pulverized, activated 4-Å molecular sieves. The reaction progress was monitored by GC (Carbowax, 110 °C, 1 °C ramp/min; acetate, 5.75 min; alcohol, 8.22 min). After 72 h, the ratio of acetate to alcohol was 48:52. The mixture was filtered through a medium scintered glass funnel, washed with additional pentane, and concentrated via rotary evaporation, affording 11.5 g of a nearly 1:1 mixture of alcohol and acetate by ^1H NMR analysis. To this mixture of **6** and (*S*)-**5** in THF (50 mL) were added Et_3N (9.1 mL, 65.0 mmol), DMAP (92 mg, 0.75 mmol), and succinic anhydride (4.15 g, 41.1 mmol) successively. The mixture was heated to reflux for 4 h, cooled, and quenched with 30 mL of $NaHCO_3$. The solution was stirred vigorously for 1 h and diluted with Et_2O. The Et_2O solution was separated and washed with 10% HCl and brine. The Et_2O solution was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The resulting oil was purified by bulb-to-bulb distillation (50 °C at 0.5 mmHg) to yield 5.31 g (82%) of acetate **6** as a clear oil: $[\alpha]^{20}_D$ +117.5 (c = 2.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.45 (d, J = 7.2 Hz, 3H), 2.08 (s, 3H), 5.42 (q, J = 7.2 Hz, 1H). Analysis by GC on a β-Dex column showed a single peak. The aqueous phase was carefully acidified with 12.0 M HCl to pH ~1.0 and extracted with EtOAc. The extracts were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation, affording 7.35 g (86%) of the succinate **7** as a light yellow oil which solidified upon cooling to 0 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 0.15 (s, 9H), 1.45 (d, J = 7.2 Hz, 3H), 2.62 (m, 4H), 5.47 (q, J = 7.2 Hz, 1H). This acid was carried on without further purification. To a solution of acetate **6** (4.22 g) in 30 mL of hexanes at −78 °C was added 35 mL of DIBAL-H (1.0 M in hexanes). The solution was stirred for 10 min and poured into a rapidly stirred mixture of 300 mL of aqueous Rochelle's salt and 200 mL of Et_2O. Once the Et_2O layer clarified, it was separated, dried over $MgSO_4$, filtered, and concentrated at atmospheric pressure to yield an oil. The oil was purified by bulb-to-bulb distillation (65 °C at 0.5 mmHg) to yield 2.70 g (83%) of alcohol (*R*)-**5**: $[\alpha]^{20}_D$ +23.8 (c = 2.02, $CHCl_3$); IR (film) υ 3335, 2173 cm $^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.44 (d, J = 6.6 Hz, 3H), 4.51 (q, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.6, 88.4, 58.7, 24.2, −0.96. To a solution of (*S*)-succinate **7** (2.92 g) in 30 mL of CH_2Cl_2 at −78 °C was added 28 mL of DIBAL-H (1.0 M in hexanes). The solution was stirred for 10 min, and the product was isolated as described above. The resulting oil was purified by bulb-to-bulb distillation (65 °C/0.5 mmHg) to yield 1.49 g (87%) of alcohol (*S*)-**5**: $[\alpha]^{20}_D$ −22.6 (c = 2.29, $CHCl_3$); lit. (−25.9, c = 3.12).[5] A portion of the alcohol was acetylated with excess acetic anhydride, NEt_3, and DMAP (catalytic) in CH_2Cl_2. GC analysis of the crude acetate on a β-Dex column indicated a 97:3 enantiomeric ratio.