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Catalytic, Efficient, and *syn*-Selective Construction of Deoxypolypropionates and Other Chiral Compounds via Zr-Catalyzed Asymmetric Carboalumination of Allyl Alcohol

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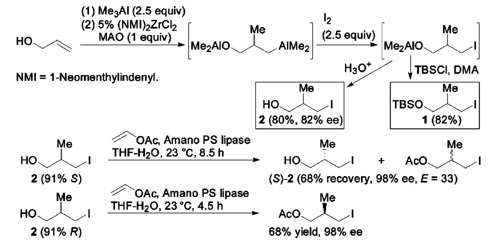
Herein reported is an all-catalytic *syn*-selective asymmetric protocol for the synthesis of deoxypolypropionates, especially those that are α,ω-diheterofunctional, and other chiral compounds. The crucial transformation involves a novel "one-pot" conversion of inexpensive allyl alcohol to TBS-protected (*R*)- or (*S*)-3-iodo-2-methyl-1-propanol (**1**)[1] via (i) Zr-catalyzed asymmetric carboalumination[2] (ZACA reaction hereafter), (ii) in situ iodinolysis, and (iii) in situ protection with ^{t}BuMe$_2$SiCl. The entire one-pot reaction proceeds to give either *R* or *S* isomer of **1** in 82% isolated yield by using (−)- or (+)-(NMI)$_2$ZrCl$_2$,[3] respectively. (*R*)- or (*S*)-3-Iodo-2-methyl-1-propanol (**2**) can also be readily isolated, and its Mosher ester analysis has indicated its enantiomeric purity to be 91% (or 82% ee). Treatment of (*S*)-**2** with vinyl acetate in THF−H$_2$O in the presence of Amano PS lipase (32 mg/mmol of **2**)[4] at 23 °C for 8.5 h readily improved the stereoisomeric purity to 98% ee (68% recovery at 25% conversion). It was also practical to convert (*R*)-**2** of 82% ee into its acetate of 98% ee in 68% recovery (75% conversion) by using the same procedure. The results discussed above are summarized in Scheme 1.

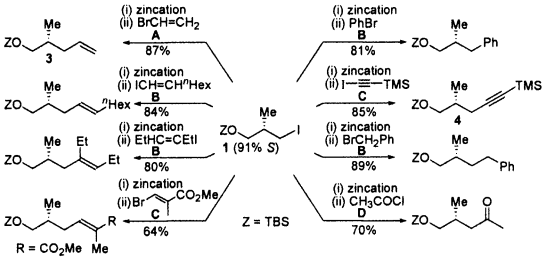
For the synthesis of deoxypolypropionates and other chiral compounds containing two or more asymmetric carbon centers, crudely isolated **1** may be used without purification for the synthesis of isomerically pure compounds, as reported earlier[1,5] and further elaborated later in this paper. In addition to the Pd-catalyzed vinylation of **1** to give **3** in 87 or 71% in two steps from allyl alcohol, several additional Pd-catalyzed cross-coupling reactions[7] with differently substituted alkenyl, aryl, trimethylsilylethynyl (to give **4**), benzyl, and acyl halides have been achieved in high yields, as shown in Scheme 2. No stereoisomerization has been detected in these transformations.

Behind all these favorable results are numerous unsatisfactory reactions, of which the following are worth mentioning. (1) Iodinolysis of the in situ generated isoalkylalane leading to the synthesis of **1** and **2** in high yields was a crucial finding since neither oxidation nor protonolysis of the isoalkylalane intermediate would lead to chiral products. To avoid the loss of chirality, TBS- or TBDPS-protected allyl alcohol was initially used. The four-step synthesis of **3** shown in eq 1 of Scheme 3 is not only cumbersome but of lower stereoselectivity (74−75% ee), suggesting that the Me$_2$AlO group in the allylic position (Scheme 1) must exert a minor but unmistakably favorable effect on stereoselectivity. (2) Attempts to prepare **3** via one-pot ZACA-Pd-catalyzed vinylation[6] of allyl alcohol without going through iodinolysis and zincation have thus far failed to yield useful results. (3) Also attempted was a one-step synthesis of 2-methyl-4-penten-1-ol (**5**) from 1,4-pentadiene. The use of a 5-fold excess of 1,4-pentadiene in the ZACA reaction with Me$_3$Al and either (+)- or (−)-(NMI)$_2$ZrCl$_2$ followed by oxidation with O$_2$ did produce **5** in 80% yield based on Me$_3$Al. To our surprise, however, it was found to be ***0% ee***,[8] even though several other 1,4-diene derivatives had reacted normally to produce the corresponding 2-methyl-4-alken-1-ols of about 75% ee.[9] It then occurred to us that the unsubstituted and symmetrical parent 1,4-pentadiene could undergo facile racemization via cyclic intramolecular carbometalation to generate an unstable and achiral cyclobutylcarbinylmetal derivative **6**.[10] Accordingly, (1*E*,4*E*)-1,5-dideuterio-1,4-pentadiene (ca. 80−85% D incorporation) was prepared and subjected to the ZACA reaction. Scrambling of only the D atom of that vinyl group which participated in the ZACA reaction was observed to a considerable extent, and it was more or less evenly distributed at C1 and C3, even though the starting diene was only 80−85% dideuterated and ^{13}C NMR analysis of C1 was not very accurate due to signal overlapping. It is nevertheless unmistakably clear that the ZACA reaction is accompanied by a skeletal rearrangement that is consistent with the mechanism proposed in Scheme 4.

Scheme 1

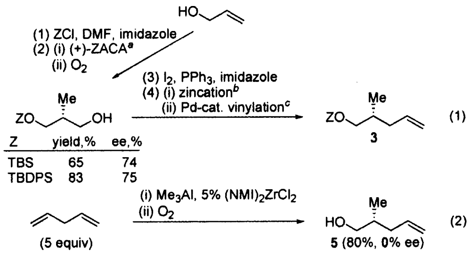


Scheme 2 ^{a,b}



^{a}**A**: 5% Pd(DPEphos)Cl$_2$, 10% DIBAL-H, THF-ether, 23 °C, 12 h; **B**: 5% Pd(PPh$_3$)$_4$, THF-ether, 23 °C, 12 h; **C**: 5% Pd(DPEphos)Cl$_2$, DMF-THF-ether, 23 °C, 12 h; **D**: 5% Pd(DPEphos)Cl$_2$, THF, 23 °C, 12 h. ^{b}Zincation: ^{t}BuLi (2.1 equiv), and then dry ZnBr$_2$ (0.6 equiv)

Scheme 3



Z	yield,%	ee,%
TBS	65	74
TBDPS	83	75

^{a}(+)-ZACA: Me$_3$Al and 5% (+)-(NMI)$_2$ZrCl$_2$. ^{b}Zincation: ^{t}BuLi (2.1 equiv), and then dry ZnBr$_2$ (0.6 equiv). ^{c}Pd-cat. vinylation: BrCH=CH$_2$ (6 equiv), 5 mol% Pd(PPh$_3$)$_4$.

Although some promising routes to deoxypolypropionates and other related chiral compounds via catalytic asymmetric C−C bond

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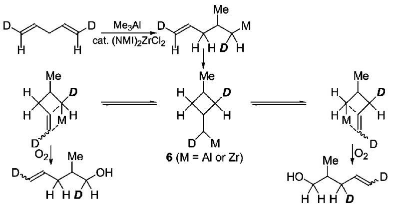
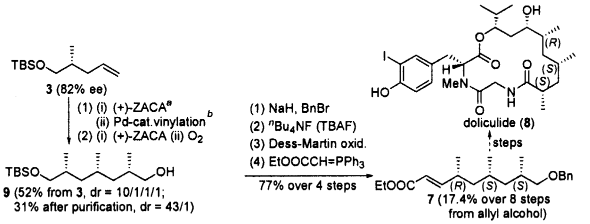
Scheme 4

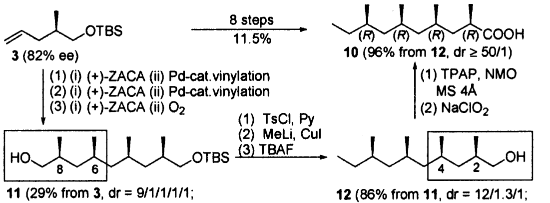


Scheme 5



^{a}(+)-ZACA: Me_3Al (3 equiv) and 5% (+)-$(NMI)_2ZrCl_2$. ^{b}Pd-cat. vinylation: (i) dry $Zn(OTf)_2$ (1-1.5 equiv) in DMF, (ii) $BrCH{=}CH_2$ (6 equiv), 3 mol% $Pd(DPEphos)Cl_2$, 6 mol% DIBAL-H.

Scheme 6 ^{a}



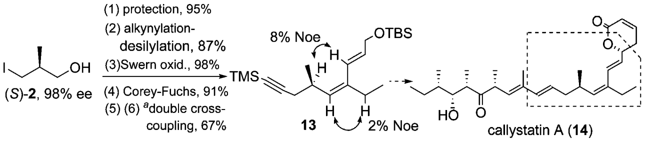
^{a}See footnote in Scheme 5.

formation have recently been developed,[11−13] the great majority of widely used and satisfactory methods known at present require at least the stoichiometric amounts of chiral reagents.[14,15] Moreover, the protocol herein described has effectively provided a critically missing piece for rounding out the development of the ZACA-based *all*-catalytic asymmetric method for the synthesis of deoxypolypropionates and many other related chiral organic compounds developed over the past several years.[5,6,16,17] Since the ZACA reaction of **3** has recently been shown to be more *syn*-selective (*syn*/*anti* = 13/1) than *anti*-selective (*anti*/*syn* = 8/1),[1] the new protocol herein reported nicely complements an *anti*-selective styrene-based protocol reported recently.[6]

To demonstrate its synthetic utility, a key intermediate **7** in a recently reported synthesis[18b] of doliculide (**8**)[18] preparable via **9**[1] and a major acid component of a preen-gland wax of the graylag goose, *Anser anser*, that is, *all*-(*R*)-2,4,6,8-tetramethyldecanoic acid (**10**),[19] were chosen, and their syntheses were performed as summarized in Schemes 5 and 6, respectively. In our previously reported partially catalytic synthesis of **9**,[1] methyl (*S*)-3-hydroxy-2-methylpropionate was converted to **9** in 11.5% yield over eight steps and two chromatographic operations. The same compound **9** (dr = 43/1, >99% ee) can now be prepared in mere four isolation steps and one chromatographic purification from allyl alcohol in 25% overall yield (Scheme 5).

For the synthesis of the tetramethyldecanoic acid (**10**), **3** (82% ee) was subjected to two rounds of the (+)-ZACA-Pd-catalyzed vinylation followed by the third (+)-ZACA reaction and oxidation with O_2. The crudely isolated **11** (29% from **3**) could only be partially purified at C6 and C8 by a single round of chromatography to give a 12/1.3/1 diastereomeric mixture in 20% yield from **3**. After its tosylation, methylation with MeLi−CuI, TBAF desilylation, and another single round of chromatography produced stereoisomerically pure **12** (dr ≥ 50/1) in 59% yield or 12% yield from **3**. After two successive oxidation steps, **10** was obtained in 96% from **12** (11.5% over eight steps from **3**).

Scheme 7



^{a} (5) Zn(OTBS)$_2$, cat. $Pd(DPEphos)Cl_2$, 75%. (6) Et_2Zn, cat. $Pd(DPEphos)Cl_2$, 1:1 THF-DMF, 89%.

Although the ZACA reaction by itself has failed to provide convenient routes to enantiomerically pure chiral compounds of ≥98−99% ee containing just one asymmetric carbon atom, the ZACA-lipase-catalyzed acetylation tandem protocol (Scheme 1) has now provided a convenient solution to this pending issue, as exemplified by the synthesis of ≥98% pure **13**, which can serve as a potential intermediate for the synthesis of callystatin A (**14**),[20] from (*S*)-**2** of 98% ee in 49% yield over six steps (Scheme 7).[21]

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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