Communication

All-Catalytic, Efficient, and Asymmetric Synthesis of □,□-Diheterofunctional Reduced Polypropionates via "One-Pot" Zr-Catalyzed Asymmetric Carboalumination–Pd-Catalyzed Cross-Coupling Tandem Process

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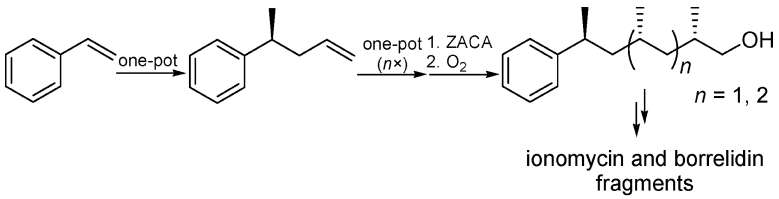

One pot = 1. Zr-catalyzed asymmetric carboalumination (ZACA)
2. Pd-catalyzed vinylation

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All-Catalytic, Efficient, and Asymmetric Synthesis of α,ω-Diheterofunctional Reduced Polypropionates via "One-Pot" Zr-Catalyzed Asymmetric Carboalumination−Pd-Catalyzed Cross-Coupling Tandem Process

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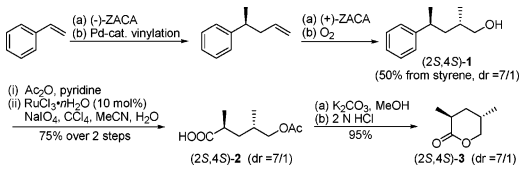
We report herein a highly efficient method for the synthesis of stereoisomerically pure (≥99% ee and >50/1 dr) α,ω-diheterofunctional reduced polypropionates, the essential features of which are represented by the conversion of inexpensive (<$1/mol) styrene into 2-methyl-4-phenyl-1-pentanol[1] (**1**) in 50% yield over two steps from styrene via Zr-catalyzed asymmetric carboalumination[2,3] (ZACA reaction) and Pd-catalyzed vinylation of the in situ generated isoalkylalanes[4] promoted by $Zn(OTf)_2$ (Scheme 1). Since oxidation of the first ZACA reaction with O_2 gave 2-phenyl-1-propanol of 89% ee by HPLC analysis of the urethane obtained by treating the alcohol with 1-α-naphthylethyl isocyanate, the diastereomeric ratio (dr) of 7.0/1 observed by ^{13}C NMR spectroscopy for **1**, before purification, indicated that the enantioface selectivity in the second ZACA reaction was 92% and that **1** should be 99% ee. The undesired diastereomers of **1** could be separated by ordinary column chromatography. For synthetic applications of **1**, however, diastereomeric separation may be more efficiently and profitably performed after the conversion of the phenyl group into COOH and OH (vide infra).

To demonstrate the feasibility of using terminally phenyl-substituted methyl-branched alcohols as intermediates for the synthesis of α,ω-diheterofunctional polypropionates, a 7/1 diastereomeric mixture of **1** was acetylated first in quantitative yield and then subjected to Ru-catalyzed oxidation with $NaIO_4$[5] to give 5-acetoxy-2,4-dimethylpentanoic acid (**2**) in 75% yield over two steps. Hydrolysis of a 7/1 diastereomeric mixture of **2** with methanolic K_2CO_3 followed by acidification with 2 N HCl produced **3**[6] as a 7/1 diastereomeric mixture in quantitative yield. Thus, conversion of **1** to **3** via **2** proceeded without epimerization. Comparison of the ^1H and ^{13}C NMR spectral data with the reported values in conjunction with the previously established absolute stereochemistry for the first ZACA reaction[2a,3] has firmly established that the major stereoisomers of **1**−**3** are the expected (2*S*,4*S*) isomers, as shown in Scheme 1. Similarly, a syn isomer of **1**, i.e., (2*S*,4*R*)-**1**, was prepared in 47% yield over two steps as a 4.6/1 diastereomeric mixture by using (+)-$(NMI)_2ZrCl_2$[7] for both ZACA reaction steps. It is noteworthy that the diastereomeric ratio is higher for the formation of the anti isomer of **1**, i.e., (2*S*,4*S*)-**1** (dr = 7.0/1), than that of the syn isomer of **1**, i.e., (2*S*,4*R*)-**1** (dr = 4.6/1).[8] In all previous cases, where 1-alkenes containing chiral alkyl groups were subjected to the ZACA reaction, there was either a minor preference for the formation of the syn isomers or essentially no internal asymmetric induction.[2e−g]

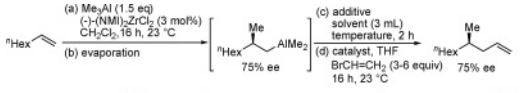
The high efficiency in the conversation of styrene into **1** is also critically dependent on the development of a satisfactory Pd-catalyzed vinylation of the in situ generated isoalkyldimethylalanes without oxidation to alcohols and/or conversion to iodides, the latter of which is to be subsequently lithiated with the use of 2 equiv of ^{t}BuLi before generation of alkylzinc derivatives to be vinylated. The use of (i) $Zn(OTf)_2$ as an additive, (ii) $Pd(DPEphos)Cl_2$[9] and

Scheme 1 [a]



[a] ZACA = Me_3Al (2−5 equiv), MAO (≤0.1 equiv), or H_2O (1 equiv), 3−5 mol % (+)- or (−)-$(NMI)_2ZrCl_2$ for (+) or (−)-ZACA, respectively, CH_2Cl_2. Pd-cat. vinylation = (a) evaporation of volatiles, (b) $Zn(OTf)_2$ (1−1.5 equiv), DMF, 70 °C, (c) 3% $Pd(DPEphos)Cl_2$, 6% DIBAL−H, $BrCH{=}CH_2$ (5−6 equiv).

Scheme 2



additive (equiv)	solvent	temp. (°C)	catalyst (%)	yield (%)
$ZnBr_2$ (1)	THF	60	$Pd(PPh_3)_4$ (5)	14
$ZnBr_2$ (1)	DMF	120	$Cl_2Pd(DPEphos)$ (5) + ^{i}Bu$_2$AlH (10)	36
$ZnBr_2$ (3)	DMF	120	$Cl_2Pd(DPEphos)$ (5) + ^{i}Bu$_2$AlH (10)	63
$Zn(OTf)_2$ (1)	DMF	70	$Cl_2Pd(DPEphos)$ (3) + ^{i}Bu$_2$AlH (6)	71

^{i}Bu$_2$AlH (DIBAL−H) in a 1:2 molar ratio as a catalyst system, and (iii) DMF as a solvent was critically important (Scheme 2). The ZACA reaction of 1-octene proceeded in 75% ee (Mosher ester analysis[10] of 2-methyl-1-octanol). After Pd-catalyzed vinylation at elevated temperature (120 °C used), the product was oxidatively cleaved[11] to produce 3-methylnonanoic acid. Analysis by HPLC of the amide obtained by treating the acid with (*S*)-1-(α-naphthyl)-ethylamine, $NCP(O)(OEt)_2$, Et_3N, and DMF[12] indicated the carboxylic acid to be 75% ee. Thus, no racemization took place under the conditions of the Pd-catalyzed vinylation.

Ionomycin[13] (**4**) and borrelidin[14] (**5**) are representative examples of natural products containing reduced polypropionate moieties that have been synthesized via α,ω-diheterofunctional tri- and tetramethyl-branched intermediates, respectively. Although reported syntheses appear satisfactory, all require at least in some steps the stoichiometric amounts or even excesses of enantiometrically pure starting materials and/or chiral auxiliaries. To demonstrate the feasibility of constructing some of the key intermediates employed in the previous syntheses in an "all-catalytic" manner, **6**[13] was chosen for the synthesis of ionomycin (Scheme 3). For the synthesis of borrelidin (**5**), **7a** used by Kuwajima and Omura[14d] and **7b** used by Theodorakis[14c] were chosen (Scheme 4).

In the synthesis of **6** shown in Scheme 3, the most sluggish first ZACA reaction was promoted by the use of 5 equiv of Me_3Al and in situ generation of MAO by addition of 1 equiv of H_2O.[3] For the other cases, 2 equiv of Me_3Al were sufficient, and 0.1 equiv of MAO was used as a promoter only in the third step. Crude **8** thus obtained in 39% yield over three steps was a mixture of the desired isomer and the three major diastereomers containing minor amounts

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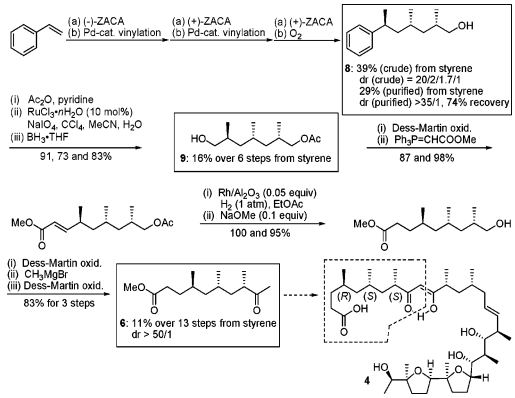
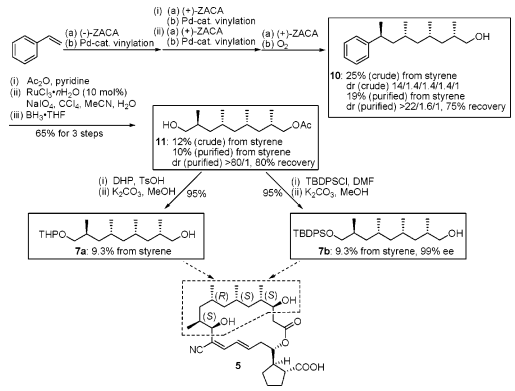
Scheme 3 [a]



[a] See Scheme 1 for the ZACA and Pd-catalyzed vinylation conditions.

Scheme 4 [a]



[a] See Scheme 1 for the ZACA and Pd-catalyzed vinylation conditions.

of their enantiomers in a 20/2/1.7/1 ratio by ^{13}C NMR spectroscopy. After one round of chromatography (silica gel, 2/98 EtOAc−hexanes), pure **8** of dr >35/1 was obtained in 74% recovery (out of the maximum possible 81%). After acetylation in 91% yield, oxidation with $NaIO_4$ with cat. $RuCl_3 \cdot nH_2O$[5] followed by reduction with $BH_3 \cdot THF$[15] provided **9** in 55% yield over three steps or 16% yield over six steps from styrene. There was no sign of epimerization throughout these steps. Conversion of **9** into **6** (dr >50/1) in 67% yield over seven steps was achieved through the use of well-documented reactions including Dess−Martin oxidation, olefination with $Ph_3P{=}CHCOOMe$, and catalytic hydrogenation over 5% $Rh-Al_2O_3$.[16]

For the preparation of the borrelidin intermediates **7a** and **7b** (Scheme 4), all that was required to prepare the first key intermediate **10** was to repeat the ZACA−Pd-catalyzed vinylation (the second step in Scheme 3). The enantioselectivity in each of these two steps was estimated to be 90−91%. After the fourth ZACA reaction and oxidation with O_2, **10** was obtained in 25% yield over four steps from styrene as a mixture of the desired compound and four major diastereomers containing minor amounts of their enantiomers in a 14/1.4/1.4/1.4/1 ratio. Some other very minor isomers were also detectable by ^{13}C NMR spectroscopy. After one round of chromatographic purification (silica gel, 2/98 EtOAc−hexanes) a 22/1.6/1 mixture was obtained in 75% recovery. Evidently, two of the four asymmetric carbon centers, most probably at C2 and C4, had become essentially pure, while the C6 chiral center must have been partially purified. After acetylation, Ru-catalyzed oxidation with $NaIO_4$ and reduction with $BH_3 \cdot THF$, as described above, the second key intermediate **11** was obtained in 65% yield over three steps from **10** (dr = 22/1.6/1 by ^{13}C NMR). As expected, its purity was readily improved to dr >80/1 (80% recovery) by chromatography (silica gel, 5/95 EtOAc−hexanes). Thus, pure **11** was prepared in 10% yield over seven steps and two chromatographic operations. Protection of **11** with dihydropyran and TsOH followed by ester hydrolysis with methanolic K_2CO_3 gave **7a**,[13d] while protection of **11** with $^tBuPh_2SiCl$ followed by deacetylation provided **7b** (99% ee by NMR analysis of the Mosher esters).[13c]

In summary, an *efficient all-catalytic asymmetric protocol* for the synthesis of α,ω-diheterofunctional reduced polypropionates represented by **6** and **7** (dr ≥50/1) has been developed perhaps for the first time. Although there is room for further improvements, the protocol presented herein promises to make the synthesis of α,ω-diheterofunctional reduced polypropionates more efficient and satisfactory.

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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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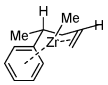
(8) The observed anti preference may be rationalized in terms of preferred equatorial disposition of the preexisting Me group in a putative pseudo-chairlike conformation arising from double π-complexation of a 14-electron $MeZr(NMI)_2$ complex.



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