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Iterative Synthesis of (Oligo)deoxypropionates via Zinc-Catalyzed Enantiospecific sp^3-sp^3 Cross-Coupling

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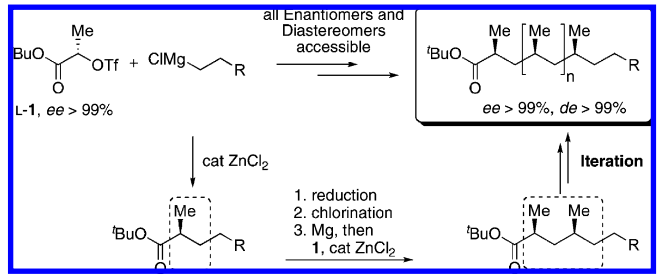
ABSTRACT



This group's recently reported mild zinc-catalyzed enantiospecific sp^3-sp^3 cross-coupling of lactic acid *tert*-butylester triflate with Grignard reagents was now applied to an iterative approach in the synthesis of a series of all four possible diastereomers of the shown trideoxypropionate. Oligodeoxypropionate structures are a common motif in a large number of biologically relevant natural products of polyketide origin thus making our approach a versatile tool in their synthesis.

(Oligo)deoxypropionate structures are common motifs in a large number of biologically relevant natural products of polyketide origin.[1] Several iterative methods[2] have been reported on their synthesis to date. Most strategies rely on asymmetric induction resulting from either chiral auxiliaries (e.g., the alkylation of enolates,[3] amide enolates,[4] or aza-enolates[5]) or resident chirality as in the case of the conjugate addition disclosed by Hanessian[6] or the allylic alkylation developed in our own group.[7] In the past few years, iterative catalytic asymmetric approaches reported by Negishi[8] and Feringa[9] have further advanced this field.

However, the development of simple and highly flexible procedures to access deoxypropionate units with complete control of their relative and absolute configuration still remains a challenging task.

Recently, we have reported a new method that allows for the mild zinc-catalyzed enantiospecific sp^3-sp^3-coupling of

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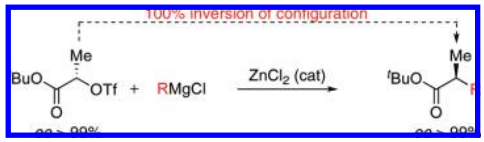
a great variety of Grignard reagents with different α-hydroxy ester triflates derived from the chiral pool.[10] Starting from enantiopure lactic acid *tert*-butyl ester triflate affords chiral α-methyl-substituted esters with complete inversion of configuration (Scheme 1).

Scheme 1. Zn-Catalyzed sp^3-sp^3 Cross-Coupling

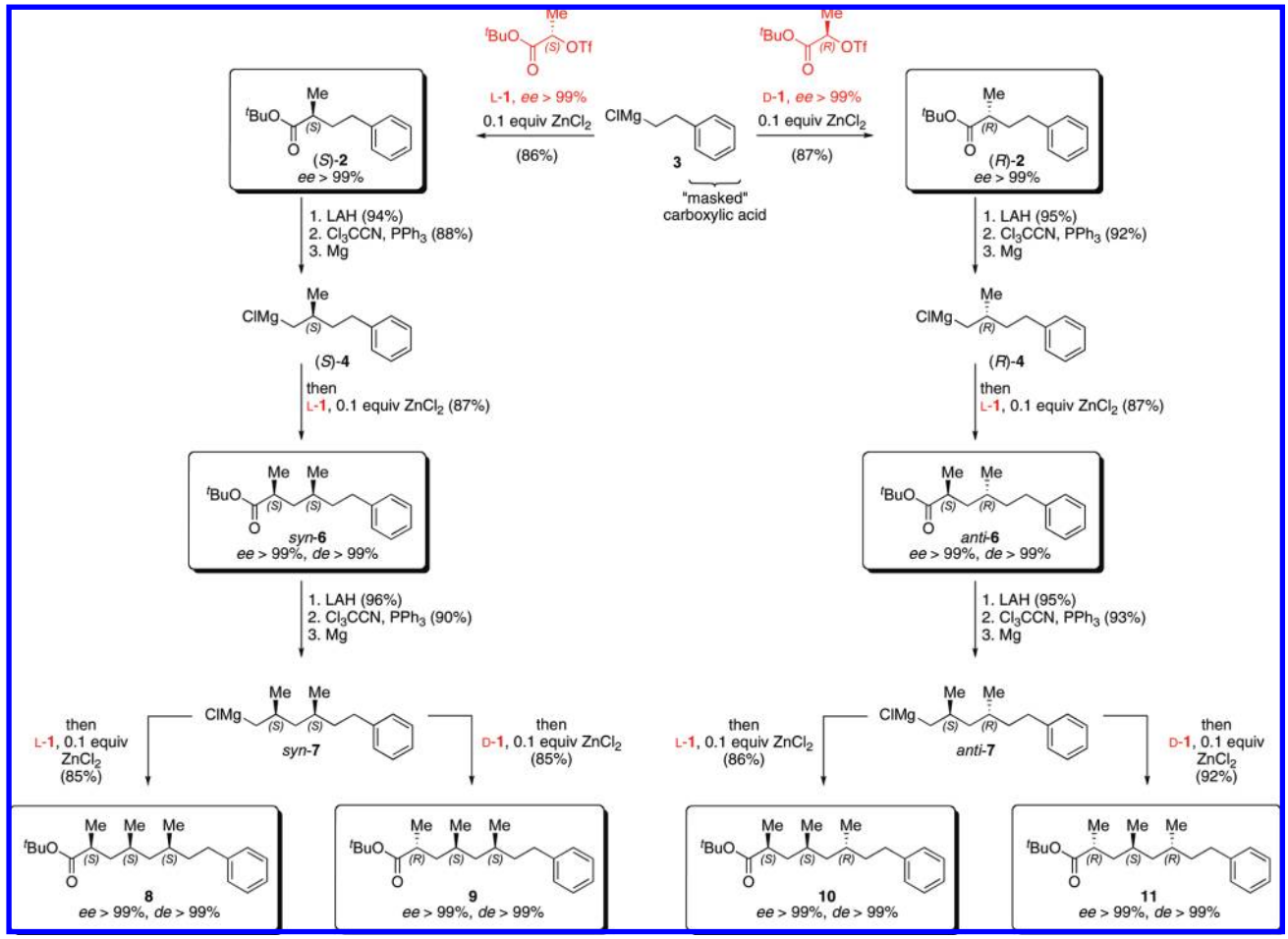


In an extension of this versatile method, we report herein on a new practical strategy for the iterative synthesis of (oligo)deoxypropionates. This approach allowed us to synthesize all four possible diastereoisomers of trideoxypropionates without the need of any chiral auxiliary or ligand, relying simply on readily available lactic acid. Their subsequent conversion to highly functionalized (e.g., biscarboxylic acid) substrates is also shown.

The synthesis of trideoxypropionates (Scheme 2) started with a coupling reaction of phenylethyl Grignard (**3**) to lactic acid *tert*-butyl ester triflate (L- or D-**1**) in the presence of a catalytic amount of $ZnCl_2$ affording products (*S*)-**2** and (*R*)-**2** in high yield (up to 87%) as single enantiomers as determined by chiral HPLC. This reaction set the first deoxypropionate unit. We chose the phenyl moiety as a "masked" carboxylic acid, which at a later stage of the synthesis can easily be transformed by using oxidizing conditions.[11]

Iteration for dideoxypropionate construction began with the reduction of the esters **2** with LAH yielding the corresponding alcohols (up to 95%) which were transformed by a Mukaiyama redox condensation[12] to the corresponding chlorides (up to 92%). From these, the Grignard reagents (*S*)-**4** and (*R*)-**4** were generated and coupled once again under the above-mentioned conditions with L-**1** and D-**1**, respectively. This afforded in excellent yield diastereoisomers *syn*-**6**

Scheme 2. Enantioselective Iterative Synthesis of Di- and Trideoxypropionates on the Basis of a Zinc-Catalyzed sp^3-sp^3 Cross-Coupling[a]

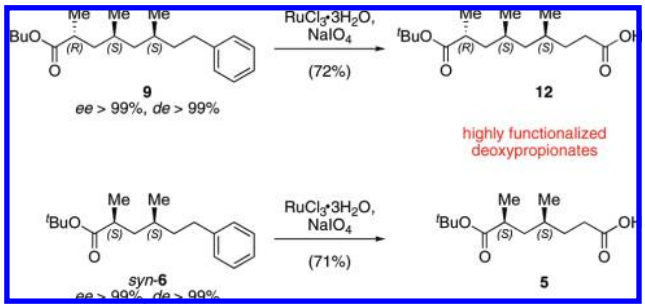


[a] Reagents and general conditions: (1) LAH, Et_2O, 0 °C, 30 min; (2) Cl_3CCN, PPh_3, DCM, 0 °C to rt, 3 h; (3) Mg, THF, reflux 3 h; **1**, $ZnCl_2$ (0.10 equiv), THF, 0 °C, overnight. All ee and de determined by HPLC.

and *anti*-**6** (87%, up to 10 mmol scale) as well as the enantiomers (not shown). All ee and de were determined by chiral HPLC to be >99%. Now the above-mentioned reduction/chlorination/Grignard formation procedure could be repeated to construct *syn*-**7** and *anti*-**7** which were coupled again to either L-**1** or D-**1** giving rise to all four diastereoisomers **8**−**11** of trideoxypropionates in excellent yield (up to 92%, de > 99%).

To further demonstrate the power of our synthesis we derivatized the trideoxypropionate **9** by converting the phenyl moiety via oxidative cleavage with $RuCl_3/NaIO_4$ to the carboxylic acid[11] giving rise to highly substituted monoprotected biscarboxylic acid **12** in good yield (72%) (Scheme 3).

Scheme 3. Functionalization of the Phenyl Moiety to a Carboxylic Acid



Dideoxypropionate *syn*-**6** was subjected to the same procedure furnishing substrate **5** (71%).

As a plausible reaction mechanism for our mild coupling reaction we postulate the following catalytic cycle[13] shown in Figure 1. In an initial step the addition of Grignard reagent RMgCl to the zinc chloride generates a neutral, linear diorganozinc species (R_2Zn). This compound then reacts with a third Grignard reagent to give a triorganozincate species ($R_3ZnMgCl$). Calculations suggest that this molecule has a trigonal planar structure[14] in which the hybridization state of the zinc−carbon bond has changed from sp to sp^2. The higher degree of p character now polarizes the electron density in the bond toward the carbon atom resulting in an increased nucleophilicity of the alkyl substituents. This in turn facilitates an S_N2 substitution of the triflate by the alkyl group. Furthermore, experimental data suggest a coordination of the magnesium ion to the triflate to occur and to be essential since triorganozincates generated from organolithium reagents do not lead to the desired product.[10] Therefore, the combination of transmetalation and Lewis acid activation through magnesium ions seems to be the key to this highly efficient coupling.

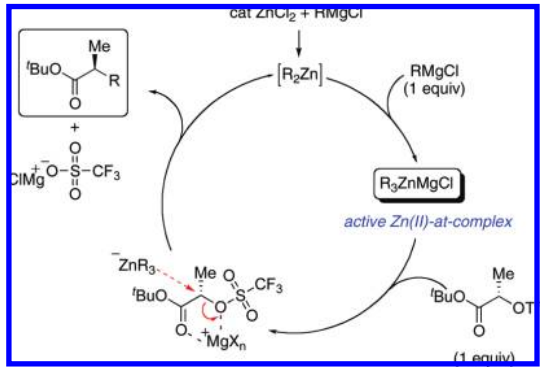


Figure 1. Postulated catalytic cycle.

In summary, we have demonstrated that our recently developed mild zinc-catalyzed enantiospecific sp^3-sp^3-coupling of Grignard reagents with α-hydroxy ester triflates is a very powerful method in the synthesis of (oligo)deoxypropionate structures. Enantiopure lactic acid *tert*-butyl ester triflate, easily accessible from the chiral pool, has proven to be a practical building block that allowed us to synthesize all four diastereoisomers with perfect stereocontrol in very high yield. Subsequent conversion of the phenyl moiety to a carboxylic acid led to highly functionalized (oligo)deoxypropionate units, making this versatile methodology a valuable and efficient tool in organic synthesis.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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