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1,n-Glycols as Dialdehyde Equivalents in Iridium Catalyzed Enantioselective Carbonyl Allylation from the Alcohol Oxidation Level and Iterative Two-Directional Assembly of 1,3-Polyols**

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Keywords

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Nature's vast collection of polyketide natural products comprises thousands of compounds incorporating polyacetate derived 1,3-diol or higher 1,3-polyol substructures. While numerous protocols for the synthesis of these ubiquitous structural motifs have been advanced,[1] the iterative allylmethallation of aldehydes has found exceptionally broad use.[1–6] For example, asymmetric iterative allylchromation (Nozaki-Hiyama coupling),[2] allyltitanation,[3] allylstannation,[4] allylsilation,[5] and allylboration[6] have been employed in synthetic approaches to 1,3-diols and higher homologues. Brown's allyl borane [$\text{Ipc}_2\text{B}(n\text{-C}_3\text{H}_5)$, Ipc = isopinocampheyl][7] has found the most extensive use in iterative asymmetric carbonyl allylation.[6] While superstoichiometric generation of isopinocampheol poses a barrier to large volume applications,[8] both enantiomers of α -pinene are available at low cost and excellent levels of stereocontrol are observed, making the Brown protocol an attractive method for the academic lab. However, use of traditional allylmethallation protocols in iterative *two-directional* syntheses of 1,3-polyol substructures is prohibited by the instability of malondialdehyde.

In connection with efforts to exploit catalytic hydrogenation in C-C couplings beyond hydroformylation,[9] an enantioselective protocol for carbonyl allylation *from the alcohol oxidation level* was developed in our laboratory under the conditions of iridium catalyzed transfer hydrogenation employing allyl acetate as an allyl donor.[10] Here, the reactant alcohol serves dually as a source of hydrogen and as an aldehyde precursor, enabling formation of highly optically enriched homoallylic alcohols directly from the alcohol oxidation level by way of a transient aldehyde. Whereas reductive coupling of allylic carboxylates, alcohols, or ethers to carbonyl partners is typically achieved using metallic reductants such as SmI_2 , SnCl_2 , Et_2Zn or Et_3B , [11–15] transfer hydrogenative carbonyl allylation precludes the use of any stoichiometric metallic reagents. Here, using a chiral iridium *C,O*-benzoate complex modified by 4-chloro-3-nitrobenzoic acid and (*R*)- or (*S*)-Cl₂MeO-BIPHEP, we report an iterative two-directional *bis*-allylation of glycols, as demonstrated by the rapid assembly of protected 1,3-

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polyol substructures with exceptional levels of enantiocontrol and catalyst-directed diastereoselectivity.[16] Notably, this process successfully exploits 1,3-diols as synthetic equivalents to unstable malondialdehydes.

Although malondialdehyde can be generated through the hydrolysis of 1,1,3,3-tetramethoxypropane, capture of this dialdehyde is impeded by the fact that it is highly unstable and is generated in an aqueous environment, which promotes hydration, oligomerization, self-condensation, which precludes the use of many organometallic reagents. The ability to bypass stoichiometric pre-formation of aldehyde electrophiles, as in carbonyl allylation from the alcohol oxidation level, potentially enables allylation processes that cannot be performed efficiently from preformed aldehyde precursors. We reasoned that 1,3-propanediol **1a** could serve as a synthetic equivalent to malondialdehyde *via* successive generation and capture of mono-aldehyde intermediates. Accordingly, the asymmetric allylation of propylene glycol **1a** was explored. Beyond the variation of standard reaction parameters, our discovery that the active catalyst is an *ortho*-cyclometallated iridium *C,O*-benzoate[10b] offered further opportunity to enhance catalyst performance through structural modification of the benzoate. To our delight, using the cyclometallated catalyst generated *in situ* from [Ir(cod)Cl]₂ (5 mol %), (*S*)-Cl,MeO-BIPHEP (10 mol %), 4-chloro-3-nitrobenzoic acid (20 mol %) and Cs₂CO₃ (40 mol %) in dioxane solvent (0.2 M), the coupling of allyl acetate (1000 mol %) to **1a** at 90 °C delivers the C₂-symmetric homoallylic diol (*S,S*)-**2a** in 70% isolated yield and ≥ 99% enantiomeric excess with ≥ 30:1 diastereoselectivity, as determined by chiral stationary phase HPLC analysis. This transformation was reproducible on 20 mmol scale. A decrease in the loading of allyl acetate from 10 to 5 equivalents diminished the isolated yield of (*S,S*)-**2a** by only 8%. These conditions were applied to propylene glycols **1a–1e**. Although yields were slightly diminished in the case of 2-methyl-1,3-propanediol **1b** and 2,2-dimethyl-1,3-propanediol (neopentyl glycol) **1c**, uniformly high levels of enantioselectivity were observed in all cases (≥99% ee), as the minor enantiomer of the intermediate mono-adduct is converted to the meso product. Efficient *bis*-allylation of 2-methylene-1,3-propanediol **1e** is especially remarkable in view of the exceptional instability anticipated for the corresponding dialdehyde, which, to our knowledge, has not been reported in the literature (Scheme 1).

The step economy associated with the double allylation of propylene glycols is borne out by comparison to known methods for the synthesis of C₂-symmetric homoallylic diols. For example, in the course of a synthetic approach to (+)-phorboxazole A, the mono-TBS-derivative of C₂-symmetric diol (*S,S*)-**2a** was prepared in 7 steps from propylene glycol **1a** (by way of the indicated aldehyde) through successive use of Brown's reagent for asymmetric carbonyl allylation [Ipc₂B(*n*-C₃H₅)].[6e] An improved protocol delivers (*S,S*)-**2a** in 4 steps from acetyl acetone.[17] Additionally, in the synthesis of pismberin, the C₂-symmetric diol (*R,R*)-**2c** was prepared in 5 steps from isobutyraldehyde (by way of the indicated aldehyde) through successive use Leighton's reagent for asymmetric carbonyl allylation.[5a] Under the conditions of iridium catalyzed transfer hydrogenation, the parent C₂-symmetric homoallylic diols (*S,S*)-**2a** and (*R,R*)-**2c** are prepared in highly optically enriched form in a single manipulation from propylene glycol and neopentyl glycol, respectively.

To illustrate the utility of this methodology in the context of "two-directional chain synthesis,"[18] the C₂-symmetric diol (*S,S*)-**2a** prepared from propylene glycol **1a** was subjected to a second round of concomitant two-directional chain elongation. Accordingly, (*S,S*)-**2a** was converted to the corresponding acetonide in 91% isolated yield, which was subjected to ozonolysis. Upon complete consumption of starting material, as revealed by the persistence of a light blue color, the reaction mixture was treated with sodium borohydride to deliver the C₂-symmetric diol (*S,S*)-**3a** in 89% isolated yield. Exposure of diol (*S,S*)-**3a** to the iridium catalyst modified by (*R*)-Cl,MeO-BIPHEP at 110 °C delivers the higher C₂-symmetric diol (*R,S,S,R*)-**4a** in 74% isolated yield, accompanied by 16% of the corresponding mono-

allylation product. Using the enantiomeric catalyst modified by (*S*)-Cl,MeO-BIPHEP, (*S,S,S,S*)-**4a** is obtained in 81% isolated yield, accompanied by 12% of the corresponding mono-allylation product. In both cases, diastereomeric *bis*-adducts could not be detected by ¹H NMR analysis, signifying exceptional levels of catalyst directed diastereoselectivity. [16] The achiral iridium catalyst ligated by BIPHEP converts (*S,S*)-**3a** to a statistical mixture of diastereomeric adducts. The assembly of either (*R,S,S,R*)-**4a** or (*S,S,S,S*)-**4a** in merely four steps from propylene glycol illustrates the power of this protocol for iterative two-directional chain elongation (Scheme 2).

Finally, the iridium catalyzed asymmetric transfer hydrogenative allylation of higher glycols was explored. The outcome of such transformations was rendered uncertain, as 1,4-butanediol **1f** and 1,5-pentanediol **1g** are transformed to γ -butyrolactone and δ -valerolactone, respectively, under transfer hydrogenation conditions. [19] Remarkably, upon exposure to conditions for iridium catalyzed asymmetric transfer hydrogenative allylation, 1,4-butanediol **1f** and 1,5-pentanediol **1g** are transformed to the corresponding the *C*₂-symmetric diols (*R,R*)-**2f** and (*R,R*)-**2g** in 68% and 56% yields, respectively, as single diastereo- and enantiomers, as determined by chiral stationary phase HPLC analysis (Scheme 3).

In summary, under the conditions of iridium catalyzed C-C bond forming transfer hydrogenation, diverse glycols **1a–1g** are subject to highly enantioselective carbonyl allylation from the alcohol oxidation level to furnish the corresponding *C*₂-symmetric diols **2a–2g**. The rapid assembly of 1,3-polyol substructures was demonstrated using iterative two-directional asymmetric carbonyl allylation from the alcohol oxidation level. Remarkably, the stereochemical bias of enantiomeric iridium catalysts modified by (*R*)- or (*S*)-Cl,MeO-BIPHEP was found to override the intrinsic diastereofacial bias of transient β -chiral aldehyde substrates, enabling generation of the acetonide protected *C*₂-symmetric tetraols (*R,S,S,R*)-**4a** and (*S,S,S,S*)-**4a** as single stereoisomers in merely four steps from propylene glycol. Future studies will focus on the development of related C-C bond forming transfer hydrogenations, including imine additions from the amine oxidation level.

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Scheme 1.

Enantioselective allylation of propylene glycols **1a–1e** under the conditions of asymmetric C–C bond forming transfer hydrogenation.^a

^aAll reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography and represent the average of two or more runs.

Enantiomeric excesses and diastereoselectivities were determined by chiral stationary phase HPLC analysis. See supporting information for experimental details.

Scheme 2.
 Enantiospecific two-directional chain elongation *via* transfer hydrogenative carbonyl allylation.

Scheme 3.

Enantioselective allylation of 1,4-butanediol **1f** and 1,5-pentanediol **1g** under the conditions of asymmetric C-C bond forming transfer hydrogenation.^a

^aAll reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography and represent the average of two or more runs.

Enantiomeric excesses and diastereoselectivities were determined by chiral stationary phase HPLC analysis. See supporting information for experimental details.