Synthetic Methods

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

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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. Although numerous procedures for the synthesis of these ubiquitous structural motifs have been advanced,[1] the iterative allylmetallation 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 allylborane (n-C_3H_5)Ipc_2B (Ipc = isopinocampheyl)[7] has found the most extensive use in iterative asymmetric carbonyl allylation.[6] Although 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 method attractive for use in academic laboratories. However, use of traditional allylmetallation procedures 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] we have developed an enantioselective method for carbonyl allylation from the alcohol oxidation level under the conditions of iridium-catalyzed transfer hydrogenation that employ allyl acetate as an allyl donor.[10] The reactant alcohol serves both 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*)-Cl,MeO-biphep (2,2′-bis(diphenylphosphino)-5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl), we report an iterative two-directional bis allylation of glycols. The method is demonstrated by the rapid assembly of protected 1,3-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 under aqueous conditions, which promote hydration, oligomerization, and self-condensation, and preclude the use of most 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 certain unstable aldehydes. 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 **1a** was explored. Beyond the variation of standard reaction parameters, our observation 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}$_2$], (*S*)-Cl,MeO-biphep, 4-chloro-3-nitrobenzoic acid, and Cs_2CO_3 in dioxane solvent (Scheme 1), the coupling of allyl acetate to **1a** at 90 °C delivers the C_2-symmetric homoallylic diol (*S*,*S*)-**2a** in 70% yield and more than 99% *ee* and with better than 30:1 diastereoselectivity, as determined by chiral stationary-phase HPLC analysis. This transformation was reproducible on a 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 **1b**–**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 into the *meso* product.[18] Efficient bis allylation of

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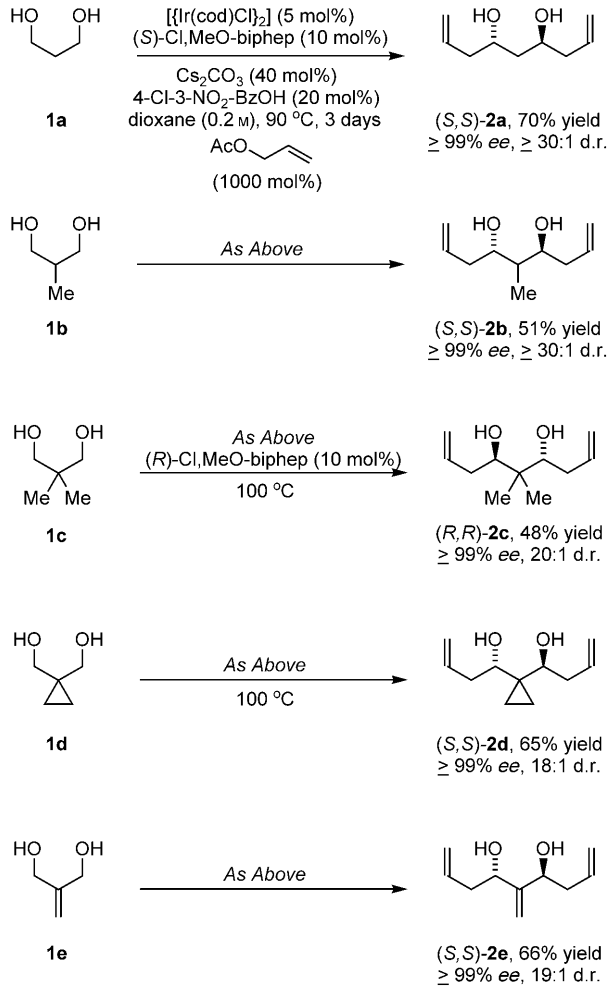


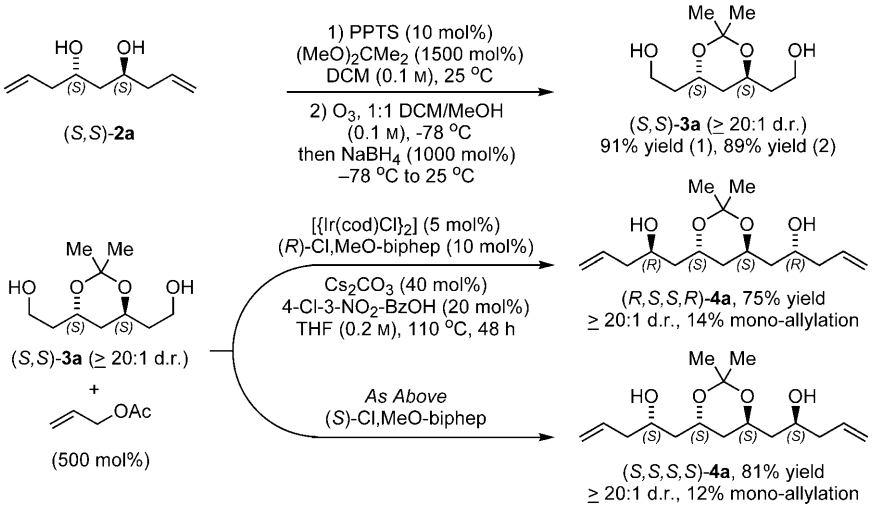
Scheme 1. Enantioselective allylation of propylene glycols **1a**–**1e** under the conditions of asymmetric C–C bond-forming transfer hydrogenation. All reactions were performed in 13×100 mm pressure tubes. The cited yields are of material isolated by silica-gel chromatography and are the average of two or more runs. Enantiomeric excesses (*ee*) and diastereomeric ratios (d.r.) were determined by chiral stationary-phase HPLC analysis. cod = cyclooctadiene, Bz = benzoyl. See the Supporting Information for experimental details.

2-methylene-1,3-propanediol **1e** is especially remarkable in view of the exceptional instability anticipated for the corresponding dialdehyde, which has not been reported to date.

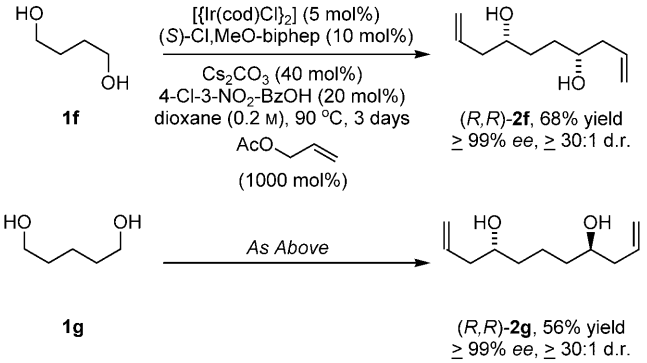
The step economy associated with the double allylation of propylene glycols is borne out by comparison to known methods for the synthesis of C_2-symmetric homoallylic diols. For example, in the course of a synthetic approach to (+)-phorboxazole A, the mono-TBS (*tert*-butyldimethylsilyl) derivative of C_2-symmetric diol (*S*,*S*)-**2a** was prepared in 7 steps from propylene glycol **1a** through successive use of Brown's reagent for asymmetric carbonyl allylation, $Ipc_2(n\text{-}C_3H_5)B$.[6e] An improved procedure delivers (*S*,*S*)-**2a** in 4 steps from acetylacetone.[17] Additionally, in the synthesis of pysmberin, the C_2-symmetric diol (*R*,*R*)-**2c** was prepared in 5 steps from isobutyraldehyde through successive use of Leighton's reagent for asymmetric carbonyl allylation.[5a] Under the conditions of iridium-catalyzed transfer hydrogenation, the parent C_2-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 method in the context of two-directional chain synthesis,[18] the C_2-symmetric diol (*S*,*S*)-**2a** prepared from propylene glycol **1a** was subjected to a second round of concomitant two-directional chain elongation (Scheme 2). Accordingly, (*S*,*S*)-**2a** was converted into the acetonide in 91% isolated yield, and was then 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 C_2-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 delivered the higher C_2-symmetric diol (*R*,*S*,*S*,*R*)-**4a** in 75% isolated yield, accompanied by 14% 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 ^{1}H NMR analysis, signifying exceptional levels of catalyst-directed diastereoselectivity.[16] The achiral iridium catalyst ligated by biphep converts (*S*,*S*)-**3a** into a statistical mixture of diastereomeric adducts. The assembly of either (*R*,*S*,*S*,*R*)-**4a** or (*S*,*S*,*S*,*S*)-**4a** in only four steps from propylene glycol illustrates the power of this new protocol for iterative two-directional chain elongation.

Finally, the iridium-catalyzed asymmetric transfer-hydrogenative allylation of higher glycols was explored (Scheme 3). The outcome of such transformations was uncertain, as 1,4-



Scheme 2. Enantiospecific two-directional chain elongation by transfer-hydrogenative carbonyl allylation. PPTS = pyridinium *p*-toluenesulfonate.



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. All reactions were performed in 13×100 mm pressure tubes. The cited yields are of material isolated by silica-gel chromatography and are the average of two or more runs. Enantiomeric excesses and diastereomeric ratios were determined by chiral stationary-phase HPLC analysis. See the Supporting Information for experimental details.

butanediol **1f** and 1,5-pentanediol **1g** are transformed into 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 into 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.

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 overrides the intrinsic diastereofacial bias of transient β-chiral aldehyde substrates. Thus, the generation of the acetonide-protected C_2-symmetric tetraols (*R*,*S*,*S*,*R*)-**4a** and (*S*,*S*,*S*,*S*)-**4a** as single stereoisomers is enabled 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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