

# Catalyst-Directed Diastereoselectivity in Hydrogenative Couplings of Acetylene to $\alpha$ -Chiral Aldehydes: Formal Synthesis of All Eight L-Hexoses

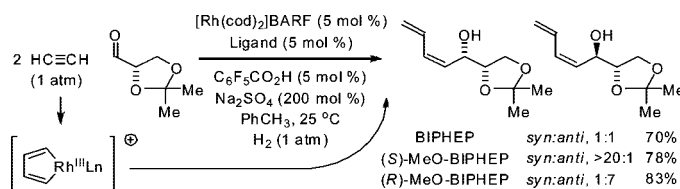
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## ABSTRACT



Hydrogenative coupling of acetylene to  $\alpha$ -chiral aldehydes 1a–4a using enantiomeric rhodium catalysts ligated by (S)-MeO-BIPHEP and (R)-MeO-BIPHEP delivers the diastereomeric products of carbonyl-(Z)-butadienylation 1b–4b and 1c–4c, respectively, with good to excellent levels of catalyst directed diastereofacial selectivity. Diastereomeric L-glyceraldehyde acetonide adducts 1b and 1c were converted to the four isomeric enoates 6b, 8b, 6c, and 8c, representing a formal synthesis of all eight L-hexoses.

The broad role of carbohydrates in diverse biological processes evokes a persistent need for efficient synthetic strategies toward natural and unnatural monosaccharides.<sup>1</sup> Beginning with the synthesis of glucose, fructose, and mannose from glyceraldehyde reported by Emil Fischer (1890),<sup>2</sup> numerous protocols for the synthesis and interconversion of monosaccharides have appeared.<sup>1</sup> However, nearly a century elapsed before the first enantioselective de novo synthesis of a monosaccharide was reported by Sharpless and Masamune (1983), who prepared all eight L-hexoses through asymmetric epoxidation.<sup>3</sup> Subsequently, elegant syntheses of various hexose stereoisomers were disclosed based upon catalytic enantioselective alkene dihydroxylation,<sup>4</sup> catalytic enantioselective Payne rearrangement,<sup>5</sup> and catalytic enantioselective aldol addition.<sup>6</sup>

Here, using catalytic enantioselective hydrogenative C–C couplings of acetylene recently developed in our laboratory,<sup>7,8</sup> we report a concise formal synthesis of all eight L-hexoses through *serial catalyst-directed diastereofacial selection*, the sequential use of transformations wherein the

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stereochemical bias of an enantiomeric catalyst overrides the diastereofacial bias of a chiral nonracemic substrate.<sup>9</sup> Additionally, catalyst-directed diastereofacial selection in hydrogenative couplings of acetylene to  $\alpha$ -chiral aldehydes **1a–4a** is described. In each case, the stereochemical bias of the catalyst was found to override the inherent diastereofacial bias of the  $\alpha$ -chiral aldehyde.

Initial studies focused on catalyst-directed stereoinduction in the hydrogenative coupling of acetylene to L-glyceraldehyde **1a**. Under previously disclosed conditions using the achiral ligand BIPHEP,<sup>7</sup> an equimolar distribution of diastereomers **1b** and **1c** is formed. This absence of substrate-directed diastereofacial selectivity suggested the feasibility of catalyst-directed diastereofacial selection. Indeed, employing a chiral rhodium catalyst ligated by (*S*)-MeO-BIPHEP, a  $\geq 20:1$  diastereomeric ratio of adducts **1b** and **1c** is obtained, as determined by <sup>1</sup>H NMR. Using the enantiomeric rhodium catalyst ligated by (*R*)-MeO-BIPHEP, a 1:7 diastereomeric ratio of adducts **1b** and **1c** is obtained, representing an inversion in diastereofacial selectivity (Table 1, entry 1).

Based on these results, catalyst-directed diastereofacial selection was explored in hydrogenative couplings of acetylene to aldehydes **2a–4a** using enantiomeric rhodium catalysts ligated by (*S*)-MeO-BIPHEP and (*R*)-MeO-BIPHEP. For each aldehyde, good to excellent levels of catalyst-directed stereoinduction are observed in both the matched and mismatched cases. For  $\alpha$ -alkoxy aldehydes **1a** and **2a** and *N*-Boc-L-alaninal **3a**, anti-Felkin-Anh addition represents the matched mode of C–C coupling. In the case of *N*-Boc-L-phenylalaninal **4a**, equivalent levels of diastereofacial selectivity are observed in additions employing enantiomeric rhodium catalysts. To corroborate the relative stereochemical assignment of adducts **1b**, **2c**, **3b**, and **4b**, the diene side chain of these materials was exhaustively hydrogenated under the conditions of iridium catalysis<sup>10</sup> to furnish the corresponding *n*-butyl adducts, which were correlated to authentic samples.<sup>11</sup>

To showcase the utility of this methodology, the L-glyceraldehyde acetonide adducts **1b** and **1c** were transformed to *cis*-enoates **6b** and **6c** and *trans*-enoates **8b** and **8c**, representing a formal synthesis of all eight L-hexoses (Scheme 1). Oxidative cleavage of diene termini of **1b** and

**Table 1.** Catalyst-Directed Diastereofacial Selection in Hydrogenative Couplings of Acetylene to  $\alpha$ -Chiral Aldehydes

entry	substrate	ligand	diastereomeric products, dr	yield <sup>a</sup>
1		BIPHEP ( <i>S</i> )-MeO-BIPHEP ( <i>R</i> )-MeO-BIPHEP	  <b>1b:1c</b> , 1:1 <b>1b:1c</b> , > 20:1 <b>1b:1c</b> , 1:7	70% 78% 83% <sup>b</sup>
2		BIPHEP ( <i>S</i> )-MeO-BIPHEP ( <i>R</i> )-MeO-BIPHEP	  <b>2b:2c</b> , 1.5:1 <b>2b:2c</b> , 11:1 <b>2b:2c</b> , 1:5	76% 95% 92%
3		BIPHEP ( <i>S</i> )-MeO-BIPHEP ( <i>R</i> )-MeO-BIPHEP	  <b>3b:3c</b> , 2:1 <b>3b:3c</b> , 16:1 <b>3b:3c</b> , 1:5	73% 75% 67%
4		BIPHEP ( <i>S</i> )-MeO-BIPHEP ( <i>R</i> )-MeO-BIPHEP	  <b>4b:4c</b> , 1:1 <b>4b:4c</b> , 12:1 <b>4b:4c</b> , 1:12	70% 80% 73%

<sup>a</sup> Cited yields are of isolated material. Best results are obtained using an apparatus in which mixtures of hydrogen and acetylene are delivered from a gas bag via cannula. See Supporting Information for detailed experimental procedures. <sup>b</sup> Reaction was performed at 4 °C.

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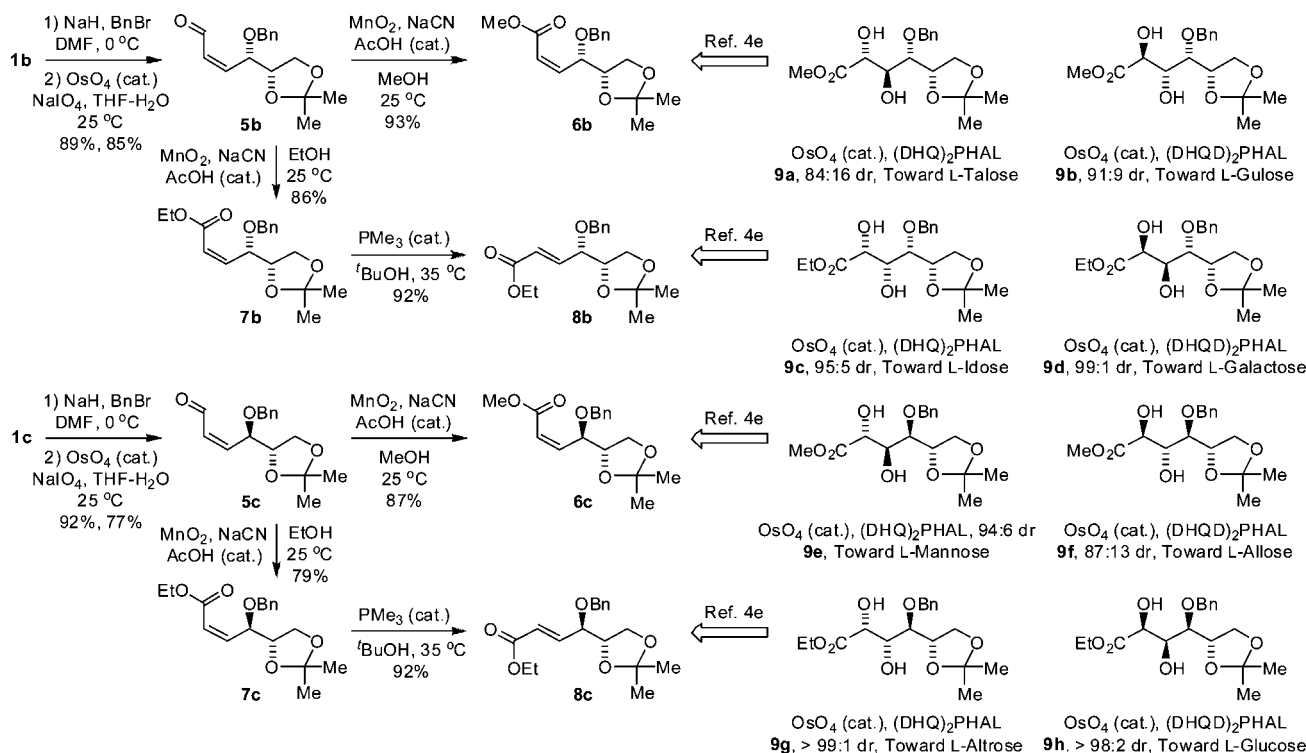
(10) For exhaustive hydrogenation of conjugated dienes catalyzed by iridium, see: Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 14212, and references therein.

**1c** using the Johnson-Lemieux protocol<sup>12</sup> delivers *cis*-enals **5b** and **5c**, respectively. Under the oxidative cleavage

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**Scheme 1.** Conversion of D-Glyceraldehyde Adducts **1b** and **1c** to Isomeric Enoates **6b**, **8c** and **8b**, **8c** Representing a Formal Synthesis of All Eight L-Hexoses via Serial Catalyst-Directed Diastereofacial Selection<sup>a</sup>



<sup>a</sup>Cited yields are of isolated material.

conditions, olefin isomerization to form the corresponding *trans*-enals was not detected by <sup>1</sup>H NMR. Exposure of *cis*-enals **5b** and **5c** to manganese oxide in the presence of sodium cyanide in methanol provides the methyl *cis*-enoates **6b** and **6c**, respectively. The stereochemical integrity of the *cis*-olefin moieties of **6b** and **6c** is retained in the presence of cyanide, a nucleophilic catalyst. The corresponding ethyl *trans*-enoates **8b** and **8c** were prepared in a similar fashion. Exposure of *cis*-enals **5b** and **5c** to manganese oxide in the presence of sodium cyanide in ethanol provides the ethyl *cis*-enoates **7b** and **7c**, respectively. Exposure of **7b** and **7c** to trimethylphosphine in dilute butanol results in formation of the corresponding ethyl *trans*-enoates **8b** and **8c**.

As reported by Sasaki,<sup>4e</sup> Sharpless asymmetric dihydroxylation of the diastereomeric methyl *cis*-enoates **6b** and **6c** delivers diols **9a**, **9b**, **9e**, and **9f**, which have been transformed to L-talose, L-gulose, L-mannose and L-allose, respectively. Sharpless asymmetric dihydroxylation of the diastereomeric ethyl *trans*-enoates **8b** and **8c** delivers diols **9c**, **9d**, **9g**, and **9h**, which have been transformed to L-idose, L-galactose, L-altrose, and L-glucose, respectively. Diastereofacial selectivities obtained using the indicated pseudoenantimeric osmium-based catalysts are indicated explicitly for the convenience of the reader.

In summary, we report catalyst-directed diastereoselectivity in the hydrogenative coupling of acetylene to aldehydes **1a–4a**. Further, through sequential catalyst-directed diastereoselective hydrogenative carbonyl-(*Z*)-butadienylation-olefin asymmetric dihydroxylation, a concise formal synthesis of all eight L-hexoses is achieved from L-glyceraldehyde acetonide **1a**. These studies demonstrate the utility of serial catalyst-directed diastereofacial selection as a means for the controlled preparation of contiguous stereochemical arrays.

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**Supporting Information Available:** Experimental procedures and tabulated spectral data and scanned images of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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