Published in final edited form as:
Org Lett. 2008 September 18; 10(18): 4133–4135. doi:10.1021/ol8018874.

Catalyst-Directed Diastereoselectivity in Hydrogenative Couplings of Acetylene to α-Chiral Aldehydes: Formal Synthesis of All Eight L-Hexoses

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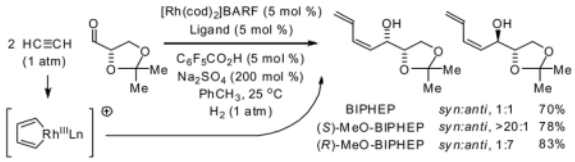
Abstract



Hydrogenative coupling of acetylene to α-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.[1] Beginning with the synthesis of glucose, fructose and mannose from glyceraldehyde reported by Emil Fischer (1890); [2] numerous protocols for the synthesis and interconversion of monosaccharides have appeared.[1] 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.[3] Subsequently, elegant syntheses of various hexose stereoisomers were disclosed based upon catalytic enantioselective alkene dihydroxylation, [4] catalytic enantioselective Payne rearrangement, [5] and catalytic enantioselective aldol addition. [6]

Here, using catalytic enantioselective hydrogenative C-C couplings of acetylene recently developed in our laboratory,[7,8] we report a concise formal synthesis of all eight L-hexoses through *serial catalyst-directed diastereofacial selection*, the sequential use of transformations wherein the stereochemical bias of an enantiomeric catalyst overrides the diastereofacial bias of a chiral nonracemic substrate. [9] Additionally, catalyst-directed diastereofacial selection in hydrogenative couplings of acetylene to α-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 α-chiral aldehyde.

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

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,[7] 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 ≥ 20:1 diastereomeric ratio of adducts **1b** and **1c** is obtained, as determined by ^{1}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 α-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[10] to furnish the corresponding *n*-butyl adducts, which were correlated to authentic samples. [11]

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 terminus of **1b** and **1c** using the Johnson-Lemieux protocol [12] delivers *cis*-enal **5b** and **5c**, respectively. Under the oxidative cleavage conditions, olefin isomerization to form the corresponding *trans*-enals was not detected by ^{1}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 *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,[4e] 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 pseudo-enantiomeric 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgment is made to the Welch Foundation, the NIH-NIGMS (RO1-GM069445) and the ACS-GCI Pharmaceutical Roundtable for partial support of this research. Oliver Briel of Umicore is thanked for the kind donation of $[Rh(cod)_2]BARF$.

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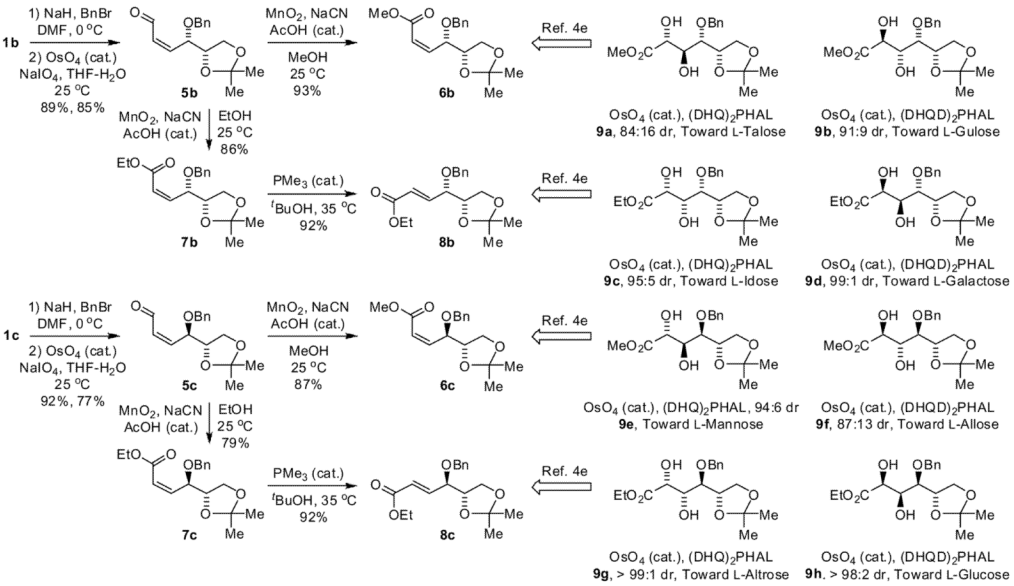


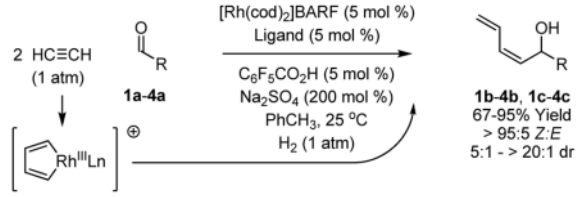
Scheme 1.

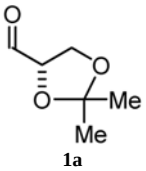
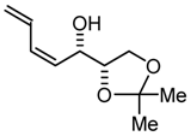
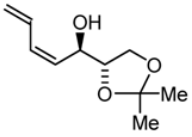
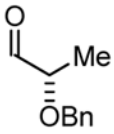
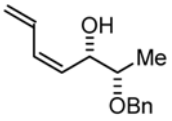
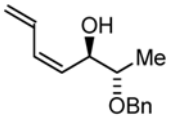
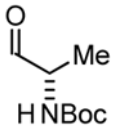
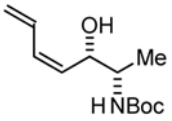
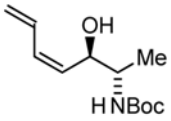
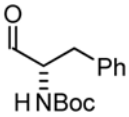
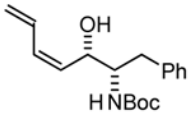
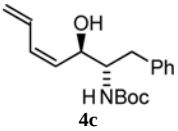
Conversion of D-glyceraldehyde adducts **1b** and **1c** to isomeric enoates **6b**, **8c** and **8b**, **8c** representing a formal synthesis of all eight L-hexoses *via* serial catalyst-directed diastereofacial selection.[a]

[a]Cited yields are of isolated material.

Table 1

Catalyst-directed diastereofacial selection in hydrogenative couplings of acetylene to α-chiral aldehydes.



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

[a] 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.

[b] Reaction was performed at 4 °C.