ORGANIC LETTERS

2008
Vol. 10, No. 18
4133−4135

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

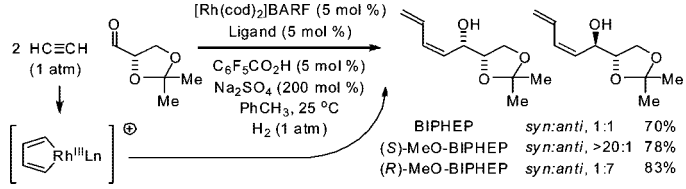
Soo Bong Han, Jong Rock Kong, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, Texas 78712

mkrische@mail.utexas.edu

Received August 12, 2008

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

(1) For selected reviews encompassing *de novo* synthetic approaches to monosaccharides, see: (a) Zamoiski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1. (b) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195. (c) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443. (d) Vogel, P. In *Glycoscience*; Fraser-Reid, B. O., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, 2001; Vol. II, Chapter 4.4, p 1023.

(2) (a) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 370. (b) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 799.

(3) For monosaccharide synthesis employing alkene enantioselective epoxidation, see: Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, 949. Also see ref 9a.

(4) For monosaccharide synthesis employing enantioselective alkene dihydroxylation, see: (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982. (b) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **1999**, 341. (c) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17. (d) Ahmed, Md. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745. (e) Ermolenka, L.; Sasaki, N. A. *J. Org. Chem.* **2006**, *71*, 693.

(5) For monosaccharide synthesis employing enantioselective Payne rearrangement, see: Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217.

(6) For monosaccharide synthesis employing enantioselective organocatalyzed aldol addition, see: (a) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752. (b) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210.

10.1021/ol8018874 CCC: $40.75
Published on Web 08/26/2008

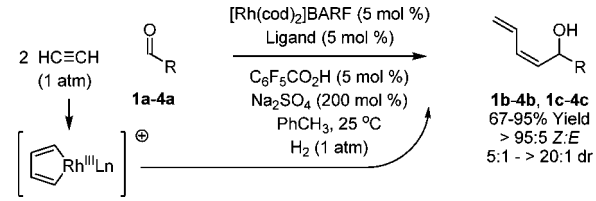
stereochemical bias of an enantiomeric catalyst overrides the diastereofacial bias of a chiral nonracemic substrate.[9] Additionally, catalyst-directed diastereofacial selection in hydrogenative couplings of acetylene to α-chiral aldehydes **1a**−**4a** is described. In each case, the stereochemical bias of the catalyst was found to override the inherent diastereofacial bias of the α-chiral aldehyde.

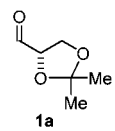
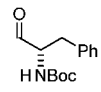
Initial studies focused on catalyst-directed stereoinduction in the hydrogenative coupling of acetylene to L-glyceraldehyde **1a**. Under previously disclosed conditions using the achiral ligand BIPHEP,[7] an equimolar distribution of diastereomers **1b** and **1c** is formed. This absence of substrate-directed 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 termini of **1b** and **1c** using the Johnson-Lemieux protocol[12] delivers *cis*-enals **5b** and **5c**, respectively. Under the oxidative cleavage

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**	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**	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**	BIPHEP	**3b**:**3c**, 2:1	73%
		(*S*)-MeO-BIPHEP	**3b**:**3c**, 16:1	75%
		(*R*)-MeO-BIPHEP	**3b**:**3c**, 1:5	67%
4	 **4a**	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.

(7) For hydrogen-mediated couplings of acetylene to carbonyl compounds and imines, see: (a) Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16040. (b) Skucas, E.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242.

(8) For selected reviews of hydrogenative C−C coupling, see: (a) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007**, *279*, 77. (c) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394.

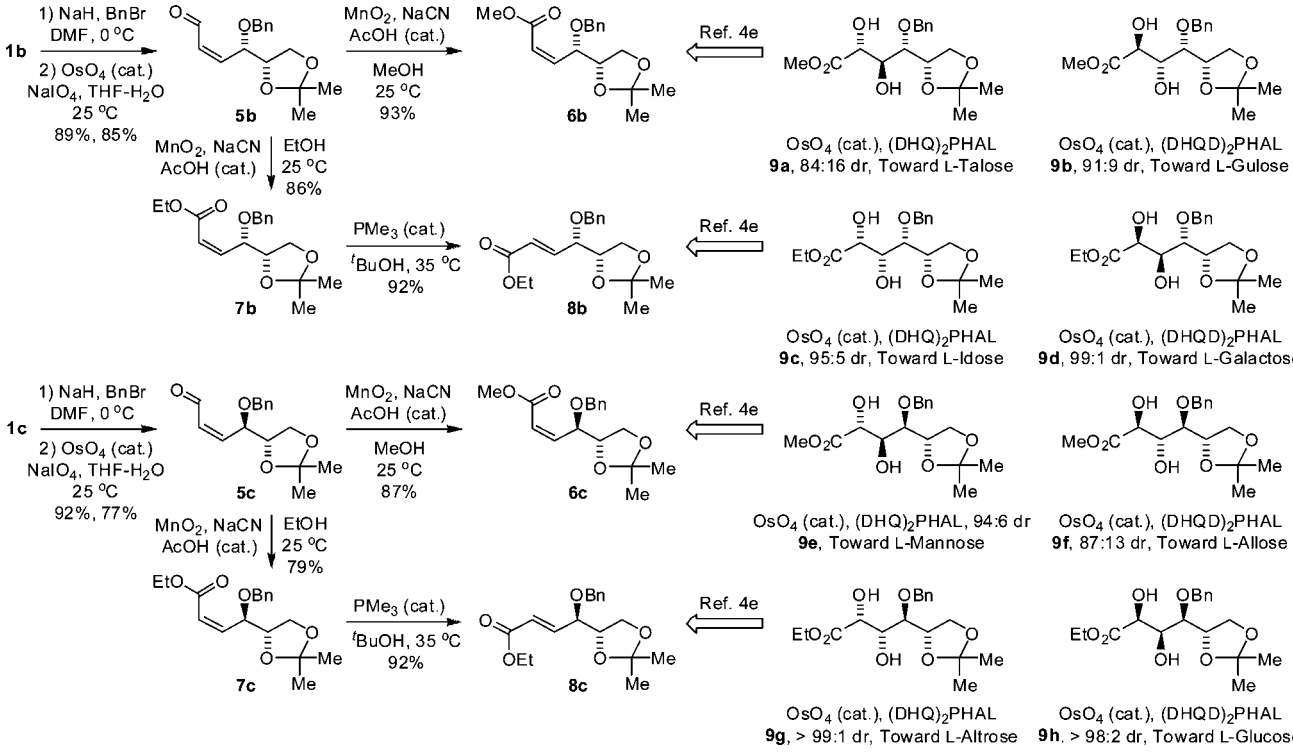
(9) For selected examples of catalyst directed diastereofacial selection, see: (a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (b) Kobayashi, S.; Ohtsubo, A.; Mukaiyama, T. *Chem. Lett.* **1991**, 831. (c) Hammadi, A.; Nuzillard, J. M.; Poulin, J. C; Kagan, H. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1247. (d) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837. (e) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713. (f) Balskus, E.; E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736. Also, see ref 3.

(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.

(11) *O*-Benzyl derivative of adduct **1b**: (a) Ito, M.; Kibayashi, C. *Tetrahedron* **1991**, *45*, 9329. Adduct **2c**: (b) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415. Adduct **3b**: (c) Reetz, M. T.; Rolfing, K.; Greibenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969. Adduct **4b**: (d) Barrow, J. C.; Coburn, C. A.; Nantermet, P. G.; Selnick, H. G.; Stachel, S. J.; Stanton, M. G.; Stauffer, S. R.; Zhuang, L.; Davis, J. R. International Patent WO 2005/065195, 2005.

(12) For Johnson-Lemieux reaction of conjugated dienes, see: (a) Sakya, S. M.; Suarez-Contreras, M.; Dirlam, J. P.; O'Connell, T. N.; Hayashi, S. F.; Santoro, S. L.; Kamicker, B. J.; George, D. M.; Ziegler, C. B. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2751. (b) Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 891.

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.

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 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,[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 pseudoenantiomeric 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.

Acknowledgment. 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.

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.

OL8018874