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Efficient Pseudo-enantiomeric Carbohydrate Olefin Ligands

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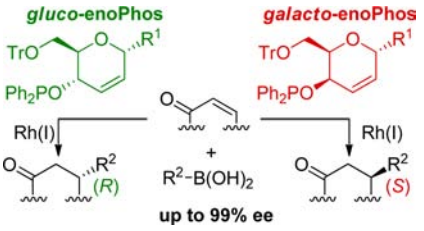
ABSTRACT

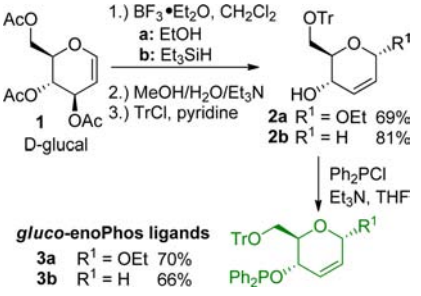


Highly efficient pseudo-enantiomeric olefin ligands were designed from D-glucose and D-galactose. These ligands yield consistently excellent levels of enantioselectivity in Rh(I)-catalyzed 1,4-additions of aryl- and alkenylboronic acids to achiral enones and high diastereoselectivity with chiral substrates. Contrary to established olefin ligands, they are obtained enantiomerically pure via short syntheses without racemic resolution steps, making them a valuable addition to the arsenal of chiral ligands with olefinic donor sites.

Asymmetric catalysis using metal complexes of chiral ligands is of great importance in the synthesis of natural products, pharmaceuticals, and drug candidates. Unsurprisingly, the design of new chiral ligands is a very active field of research. Amino acids, terpenes, and alkaloids from the *chiral pool* are important enantiomerically pure starting materials useful in ligand design.

Chiral bidentate olefins[1] are a highly useful addition to the arsenal of tools for asymmetric catalysis and have become ligands of choice for rhodium-catalyzed 1,4-additions.[2−4] The first examples were bicyclic diolefins developed independently by Hayashi[5] and Carreira.[6] Olefin−phosphine hybrids were first described by Grützmacher,[7] and shortly afterward, Hayashi[8] published further examples. Today, many structurally diverse olefin ligands are known and used,[9,10] but only a few are derived from *chiral pool* compounds (e.g., from the terpenes carvone[6] and α-phellandrene[9d]). Most are prepared as racemates and have to be resolved by chiral HPLC making their synthesis tedious.

Scheme 1. Synthesis of *gluco*-enoPhos Ligands from Glucal **1**



Carbohydrates have long been avoided as starting materials for ligand design. Even as the first ligands based on

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(3) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

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(5) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.

(6) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873.

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monosaccharides were reported over 30 years ago,[11] only now the potential of carbohydrates in asymmetric synthesis is broadly exploited.[12] We have developed carbohydrate bis(oxazolines) that gave excellent results in copper-catalyzed reactions.[13,14] The design of novel olefin hybrid ligands based on carbohydrates is attractive, as unsaturated monosaccharide derivatives are easily available and phosphorus donor sites can be conveniently incorporated into the pyranoside framework by phosphinite formation.[11,15] Starting from commerically available glucal **1**, we recently prepared new olefin–phosphinite hybrid EtO-*gluco*-enoPhos (**3a**) which gave the (*R*)-configured 1,4-addition product of cyclohexenone with phenylboronic acid.[16,17] After this initial success, we aimed for both a broad application of the new ligand and a possibility to obtain enantiomeric addition products.

To explore the influence of the anomeric substituent on stereoselectivity, simplified ligand H-*gluco*-enoPhos (**3b**) was prepared via a Ferrier rearrangement[18] with triethylsilane[19] (Scheme 1). First trials of **3b** in 1,4-additions with phenyboronic acid (**7a**) and cyclohexenone **6a** or cyclopentenone **6b** gave > 90% yield of the (*R*)-configured products **8aa** and **8ba** in 98% ee and 99% ee, respectively. These results were almost identical to those obtained with EtO-*gluco*-enoPhos (**3a**) (Table 1, entries 2 and 6 vs entries 1 and 5). Thus, the anomeric substituent is not essential for an efficient asymmetric induction.

To access the (*S*)-enantiomers of the 1,4-addition products **8aa** and **8ba**, the enantiomeric ligands to **3a**,**b** are necessary, which poses a considerable obstacle, as L-glucose derivatives are prohibitively expensive and therefore not an option for ligand synthesis. As D- and L-arabinose are available at reasonable price, we explored an olefin phosphinite ligand based on this monosaccharide. Unfortunately, this ligand led to the formation of product **8aa** in 76% ee and 92% yield,[16b] which made arabinose unsuitable for the preparation of an enantiomeric hybrid ligand pair.

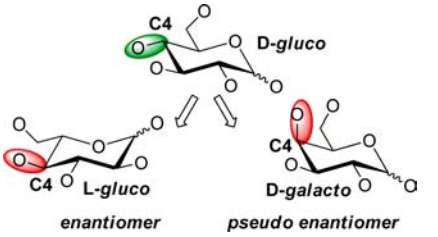


Figure 1. D-*gluco*- and D-*galacto*-configured carbohydrate scaffolds as pseudo-enantiomers.

The application of a pseudo-enantiomeric carbohydrate scaffold is an option to avoid ligand syntheses from expensive L-carbohydrates. This strategy has been successfully employed by Kunz and RajanBabu for chiral carbohydrate auxiliaries[20] and ligands.[21] The synthesis of such pseudo-enantiomeric ligands uses diastereomeric compounds as starting materials.[22] Elegant and attractive as this approach is, the development of an efficient pseudo-enantiomeric ligand is by no means a trivial feat. The challenge lies in finding a carbohydrate scaffold which reverses the asymmetric induction and does this with the same high level of enantioselectivity as the original ligand. Therefore, the development of pseudo-enantiomers is a process of trial and error, just as any design of a new ligand, and not necessarily successful. We decided to explore D-galactose, the C4-epimer of D-glucose (Figure 1), as a candidate for the preparation of pseudo-enantiomeric olefin hybrid ligands.

The synthesis of *galacto*-configured olefin–phosphinite ligands from commercially available D-galactal **4** (Scheme 2) was done analogous to the preparation of the *gluco*-ligands. The Ferrier rearrangement of **4** with alcohols leads to notoriously unsatisfactory yields;[23] therefore,

(9) Selected examples for diolefins: (a) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (b) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (c) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (d) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387. (e) Nishimura, T.; Nagaosa, M.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 860. (f) Hu, X.; Zhuang, M.; Du, H. *Org. Lett.* **2009**, *11*, 4744. (g) Li, Q.; Dong, Z.; Yu, Z.-X. *Org. Lett.* **2011**, *13*, 1122. (h) Trost, B. M.; Burns, A. C.; Tautz, T. *Org. Lett.* **2011**, *13*, 4566.

(10) Selected examples for olefin–phosphine hybrids: (a) Kasák, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084. (b) Stremmler, R. T.; Bolm, C. *Synlett* **2007**, 1365. (c) Mariz, R.; Briceño, A.; Dorta, R.; Dorta, R. *Organometallics* **2008**, *27*, 6605.

(11) (a) Cullen, W. R.; Sugi, Y. *Tetrahedron Lett.* **1978**, *19*, 1635. (b) Jackson, R.; Thompson, D. J. *J. Organomet. Chem.* **1978**, *159*, C29. (c) Selke, R. *React. Kinet. Catal. Lett.* **1979**, *10*, 135. (d) Sinou, D.; Descotes, G. *React. Kinet. Catal. Lett.* **1980**, *14*, 463.

(12) For reviews, see: (a) Lehnert, T.; Özüduru, G.; Grugel, H.; Albrecht, F.; Telligmann, S. M.; Boysen, M. M. K. *Synthesis* **2011**, 2685. (b) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007. (c) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390. (d) Boysen, M. M. K. *Chem.—Eur. J.* **2007**, *13*, 8648. (e) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189. (f) Hale, K. J. In *Second Supplement to the Second ed. of Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1993; Vol. 1E/F/G, Chapter 23b, p 273.

(13) (a) Irmak, M.; Groschner, A.; Boysen, M. M. K. *Chem. Commun.* **2007**, 177. (b) Minuth, T.; Irmak, M.; Groschner, A.; Lehnert, T.; Boysen, M. M. K. *Eur. J. Org. Chem.* **2009**, 997.

(14) Irmak, M.; Boysen, M. M. K. *Adv. Synth. Catal.* **2008**, *350*, 403.

(15) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 5593.

(16) (a) Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212. (b) Grugel, H.; Minuth, T.; Boysen, M. M. K. *Synthesis* **2010**, 3248.

(17) Bidentate coordination of **5a** to Rh(I) was unequivocally established by ^{1}H and ^{31}P NMR spectroscopy (ref 16a). The data are in good agreement with those reported for an achiral allyl phosphinite: Curtis, J. L. S.; Hartwell, G. E. *J. Organomet. Chem.* **1974**, *80*, 119.

(18) (a) Ferrier, R. J.; Overend, W. G.; Ryan, A. E. *J. Chem. Soc.* **1962**, 3667. (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570.

(19) (a) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040. (b) Takahashi, K.; Masumura, T.; Ishihara, J.; Hatakeyama, S. *Chem. Commun.* **2007**, 4158.

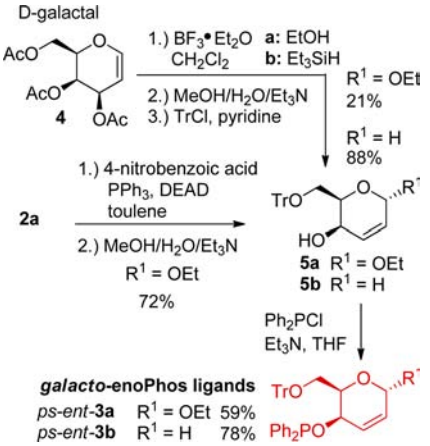
(20) Kunz, H.; Pfrengle, W.; Rück, K.; Sager, W. *Synthesis* **1991**, 1039.

(21) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; K. K. You, Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012.

(22) The most prominent example of pseudo-enantiomeric ligands are probably the ones employed in the Sharpless asymmetric dihydroxylation, which are derived from diastereomeric cinchona alkaloids: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Am. Chem. Soc.* **1992**, *57*, 2768.

(23) Ciment, D. M.; Ferrier, R. J. *J. Chem. Soc. C* **1966**, 441.

Scheme 2. Synthesis of Pseudo-enantiomeric Olefin–Phosphinite Ligands *galacto*-enoPhos from Galactal **4**



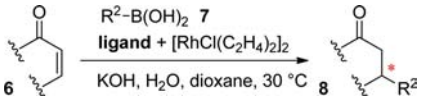
ligand EtO-*galacto*-enoPhos (*ps-ent*-**3a**) was obtained only in modest overall yield, while H-*galacto*-enoPhos (*ps-ent*-**3b**) was isolated in good overall yield. An efficient access to *ps-ent*-**3a** was established via alcohol **2a** from the synthesis of EtO-*gluco*-enoPhos. A known[24] Mitsunobu epimerization produced *galacto*-configured alcohol **5a** which was transformed into ligand *ps-ent*-**3a** in high yield. This approach renders the route via galactal **4** redundant and gives access to both *gluco*- and *galacto*-configured ligands from D-*gluco* alcohol **2a** as a single key intermediate.

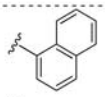
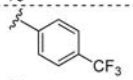
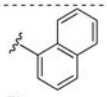
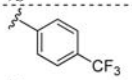
The new ligands EtO-*galacto*-enoPhos (*ps-ent*-**3a**) and H-*galacto*-enoPhos (*ps-ent*-**3b**) were then evaluated in the 1,4-addition of boronic acid (**7a**) to cyclohexenone **6a**. Independently of the anomeric substituent, *ps-ent*-**3a** and *ps-ent*-**3b** gave product **8aa** in >90% yield and excellent 99% ee (Table 1, entries 3 and 4). Most importantly, both produced the (*S*)-enantiomer, completely reversing the asymmetric induction. Thus, *gluco*- and *galacto*-configured olefin–phosphinite hybrids **3a**,**b** and *ps-ent*-**3a**,**b**, derived from inexpensive D-carbohydrate scaffolds, act as highly efficient pseudo-enantiomeric ligand pairs.

Next the substrate spectrum of the new pseudo-enantiomeric ligands **3a**,**b** and *ps-ent*-**3a**,**b** was evaluated in 1,4-additions of various aryl and alkenyl boronic acids (**7b**–**e**) to enones **6a**,**b** and enoate **6c** (Table 1, entries 7–21). All reactions were carried under mild conditions with only a small excess of the boronic acid component (1.5 equiv). Regardless of the boronic acid, ligands **3a**,**b** and *ps-ent*-**3a**,**b** consistently yielded the respective products in opposite configuration and, in all but three cases, with excellent ee, even for sterically demanding aryl boronic acids (**7b**,**c**) and the more labile alkenyl boronic acid **7e**. As a general trend, *galacto*-configured ligands *ps-ent*-**3a**,**b** produced higher yields than their *gluco*-configured counterparts, always giving >90% ee. In case of *gluco*-ligands **3a**,**b**, the additions of *ortho*-substituted aryl boronic acid **7c** and

(24) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Georges, M.; Mackay, D.; Fraser-Reid, B. *Can. J. Chem.* **1984**, *62*, 1539.

Table 1. Rhodium-Catalyzed 1,4-Additions with *gluco*-enoPhos (**3a**,**b**) and *galacto*-enoPhos (*ps-ent*-**3a**,**b**)*



entry	ligand	substrate	R^2	product 8	yield [%][a]	*ee* [%][b]
1	**3a**[c]			**8aa**	80	99 (*R*)
2	**3b**				79	98 (*R*)
3	*ps-ent*-**3a**				99	99 (*S*)
4	*ps-ent*-**3b**				92	99 (*S*)
5	**3a**[c]			**8ba**	82	99 (*R*)
6	**3b**				91	99 (*R*)
7	*ps-ent*-**3b**				90	96 (*S*)
8	**3a**			**8ab**	85	96 (*R*)
9	*ps-ent*-**3a**				85	98 (*S*)
10	**3b**			**8ac**	94	60 (*R*)
11	*ps-ent*-**3b**				96	93 (*S*)
12	**3a**			**8ad**	84	99 (*R*)
13	*ps-ent*-**3a**				86	99 (*S*)
14	**3a**			**8ae**	54	78 (-)
15	*ps-ent*-**3b**				90	96 (+)
16	**3a**			**8bb**	37	89 (*R*)
17	*ps-ent*-**3b**				77	94 (*S*)
18	**3a**			**8bd**	34	79 (*R*)
19	*ps-ent*-**3b**				66	92 (*S*)
20	**5a**[c]			**8ca**	48	94 (*R*)
21	*ps-ent*-**3b**				42	93 (*S*)

* Ligand (3.3 mol %), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), **6** (1 equiv), **7** (1.5 equiv). [a] Isolated yield after chromatography. [b] Determined by GC or HPLC. [c] Results from ref 16.

alkenylboronic acid **7e** to cyclohexenone **6a** led to less than 80% ee (entries 10 and 18), while the other reactions produced the products in high enantioselectivity. For enoate **6c** and phenylboronic acid (**7a**) the corresponding product **8ca** was obtained in high enantioselectivity (entries 20 and 21).

(25) For diastereoselective 1,4-additions of boronic acids to racemic 6-alkyl cyclohexenones, see: (a) Mediavilla Urbaneja, L.; Krause, N. *Tetrahedron: Asymmetry* **2006**, *17*, 494. (b) Chen, Q.; Soeta, T.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Adv. Synth. Catal.* **2006**, *348*, 2604. (c) Bürgi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.; Blumentritt, S.; Linden, A.; Dorta, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2768.

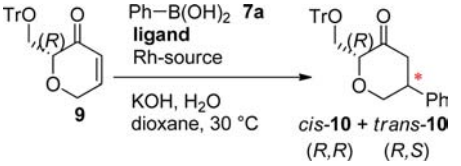
In order to demonstrate the efficiency of the pseudo-enantiomeric olefin−phosphinite ligands in the reactions of chiral substrates,[25] diastereoselective 1,4-additions to (6*R*)-2-trityloxymethyl-6*H*-pyran-3-one (**9**) were tested. Enone **9**[26] is accessible in enantiomerically pure form by oxidation of alcohol **2b** with TPAP/NMO[27] in 59% yield. The results of the diastereoselective reactions with **9** are summarized in Table 2. First, the 1,4-addition was conducted with achiral catalyst $[Rh(cod)OH]_2$ in the absence of any chiral ligand. Under these substrate-controlled conditions, the diastereomeric products **10** were obtained in 93% yield and a ratio of 20:80 in favor of the *trans*-**10** with (*S*)-configuration at the newly formed stereocenter (entry 1). As can be seen from Table 1, *gluco*-configured ligands **3a**,**b** give (*R*)-configured products without exception. Therefore, substrate control of **9** and catalyst control of EtO-*gluco*-enoPhos (**3a**) work against each other in reaction entry 2. However, ligand **3a** smoothly overrode the substrate control in this *mismatched* case, giving a diastereomeric ratio of 89:11 in favor of *cis*-**10**. The reaction of **9** in the presence of H-*galacto*-enoPhos (*ps-ent*-**3a**), which constitutes the *matched* combination of substrate and catalyst control, led to an improved diastereomeric ratio of 6:94 in favor of *trans*-**10** (entry 3). These exellent results show, that the new ligands are suitable for the highly diastereoselective conversion of complex chiral substrates.

In summary, we have designed the diastereomeric carbohydrate-based ligands *gluco*-enoPhos **3a,b** and *galacto*-enoPhos *ps-ent*-**3a**,**b** which give excellent results in rhodium-catalyzed asymmetric 1,4-additions and act as two pairs of highly efficient pseudo-enantiomers. The ligands achieve excellent levels of enantioselectivity with achiral enones and enoates in the reactions of a broad number of boronic acids. Further, they lead to highly diastereoselective reactions with complex chiral substrates, efficiently overriding substrate control. Generally, the rhodium catalysts derived from *galacto*-configured ligands gave higher stereoselectivity than their *gluco*-configured counterparts.

(26) Benko, Z.; Fraser-Reid, B.; Mariano, P. S.; Beckwith, A. L. J. *J. Org. Chem.* **1988**, *53*, 2066.

(27) Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; Puccioni, L. *J. Carbohydr. Chem.* **2000**, *19*, 79.

Table 2. Diastereoselective 1,4-Additions of Phenylboronic Acid (**7a**) to Chiral Enone **9**[*]



			product **10**	
entry	ligand	Rh source	yield[a] (%)	*cis*/*trans* ratio[b]
1	none	$[Rh(cod)OH]_2$	93	20:**80**
2	**3a**	$[RhCl(CH_2{=}CH_2)_2]_2$	78	**89**:11
3	*ps-ent*-**3b**	$[RhCl(CH_2{=}CH_2)_2]_2$	86	6:**94**

[*] Ligand (3.3 mol %), Rh(I) (3.3 mol %), **9** (1 equiv), **7a** (1.5 equiv). [a] Combined yield after chromatography. [b] Determined by ^{1}H NMR.

The reason for this finding is yet unknown, but experiments toward an elucidation are in progress.

The *gluco*-configured ligands **3a**,**b** are accessible from glucal **1** in just four simple steps via alcohols **2a**,**b**. As *galacto*-alcohol **5a** can be prepared via the epimerization of *gluco*-alcohol **2a** as key intermediate, the synthesis of pseudo-enantiomer *ps-ent*-**3a** takes only three additional steps. With this convenient ligand synthesis and the high stereoselectivities obtained, even on complex substrates, our new carbohydrate olefin ligands are attractive alternatives to many of the currently employed ligands.

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Supporting Information Available. Experimental details for ligand syntheses and rhodium-catalyzed 1,4-additions, full characterization of all products, and data for the determination of all enantiomeric excesses. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.