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Novel, Efficient Alkene-Phosphinite Hybrid Ligand Based on D-Glucose

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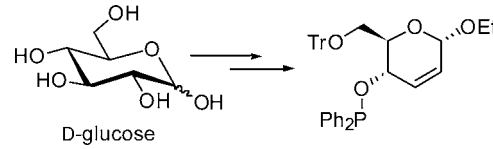
ABSTRACT



A commercially available 2,3-unsaturated pyranoside, derived from D-glucose, was converted into a new type of olefin phosphorus chelate ligand in only three steps. Application in rhodium catalyzed conjugate additions of phenylboronic acid to enones led to excellent levels of stereoinduction for several cyclic substrates. The easy preparation and the high efficiency of this ligand make it an interesting and promising alternative to established systems.

During recent years, chiral olefins have emerged as novel and exciting ligands for metal catalyzed asymmetric transformations.[1] While simple alkenes coordinate metals only weakly, the enhanced stability of complexes with novel olefin ligands stems from chelation of the metal by either two alkene moieties as in chiral dienes[2] or by an olefin in combination with phosphorus or nitrogen donor centers. Prominent examples of alkene-phosphorus hybrid ligands are shown in Figure 1. The first reports on this type of ligand by Grützmacher[3] described **1**, based on a 5*H*-dibenzo[a,d]-cycloheptene backbone. Hayashi introduced norbornene-based **2**,[4] which is one of the most successful alkene-phosphorus ligands. Later Grützmacher published **3** as a variant of **1**.[5] Ligands **4** and **5**, containing a binaphthyl scaffold were reported by Widhalm[6] and Carreira,[7] respectively. Bolm[8] and Stepnicka[9] described several examples of planar chiral hybrid ligands, among them **6** and **7**.

These ligands have been employed in iridium catalyzed hydrogenation of imines (**1**)[3b] and acrylic acid derivatives (**3**),[5] iridium catalyzed amination of allylic alcohols (**5**)[7] and palladium catalyzed allylic substitutions[10] (**2** and **6**).[9b,11] Their most important application, however, is the rhodium catalyzed conjugate addition of boronic acids to enones (Hayashi−Miyaura reaction),[12,13] with Hayashi's ligand **2**

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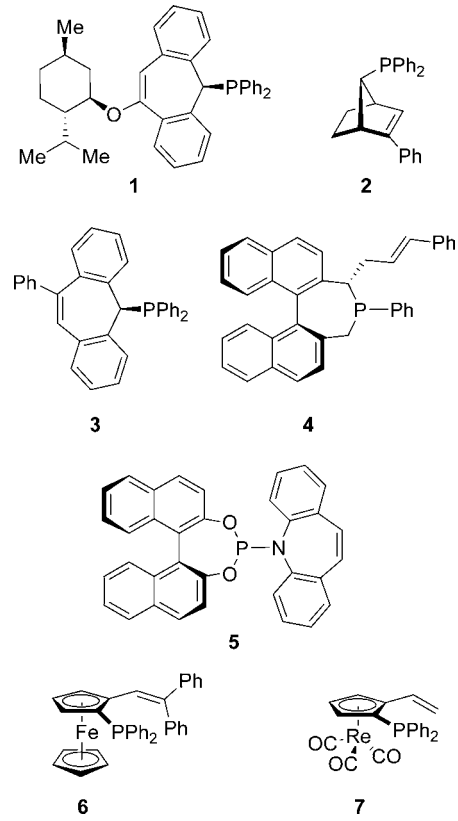


Figure 1. Chiral alkene-phosphine hybrid ligands.

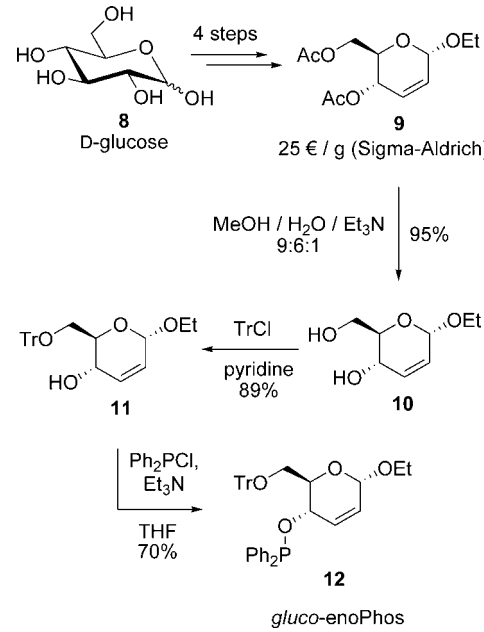
giving excellent results.[4,14] Ligands **3**, **4**, **5** and **7** have also been successfully employed for this reaction.[5,6,8,15]

Despite its high efficiency, ligand **2** suffers from the drawback of a laborious preparative route which includes an enantiomeric resolution by preparative HPLC.[4,14] The preparation of **1** and **3** is fraught with similar difficulties. Only the synthesis of **4** and **5** makes use of enantiomerically pure binaphthyl precursors[6,7] and until today no example of an alkene-phosphine ligand based on compounds from the *chiral pool* has been reported.

Carbohydrates are attractive, if comparatively rarely used, starting materials for the design of chiral complex ligands.[16] The first examples of this type were reported independently by Cullen,[17] Thompson,[18] Selke,[19] and Descotes[20] who prepared bidentate phosphinite ligands by the simple reaction of carbohydrate diols with diphenyl chlorophosphine. Since this pioneering work a large number of carbohydrate ligands, featuring a wide range of donor atoms, have appeared in the literature. Many of these ligands contain at least one phosphorus-based donor center, as found in the more recent examples of phosphinite ligands reported by RajanBabu,[21] Uemura and Ohe.[22]

In the course of our work, we have introduced new bis(oxazolines) derived from D-glucosamine,[23] which have proven to be very efficient in asymmetric cyclopropanation[23a,d] and imine alkynylation.[23b] We have now become interested in the preparation of a novel type of alkene-phosphinite hybrid ligand based on carbohydrates for two reasons: as described above, phosphorus-based donor centers can be easily introduced into a carbohydrate framework by phosphinite formation, and a number of unsaturated carbohydrate derivatives are accessible by well established synthetic methods or even commercially available at reasonable pricing.

Scheme 1. Preparation of a Novel Carbohydrate Alkene-Phosphinite-Hybrid Ligand from Commercially Available 2,3-Unsaturated Pyranose **9**



Our ligand synthesis (Scheme 1) started from ethyl-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (**9**), which was purchased from Sigma-Aldrich (approximately 25 Euros/g, May 2009). This 2,3-unsatur-

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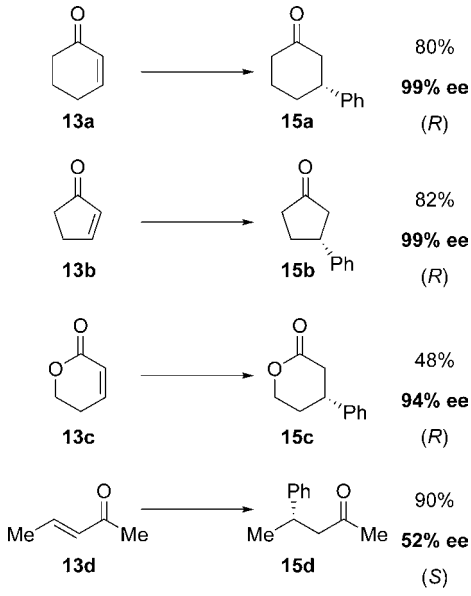
ated pyranose can also be prepared from D-glucose (**8**) via D-glucal using a Ferrier rearrangement[24] as the key step. Basic deprotection[25] of **9** with subsequent regioselective tritylation[26] led to alcohol **11**. Reaction with diphenyl chlorophosphine under conditions described previously for the preparation of carbohydrate-based oxazoline-phosphinite hybrid ligands[22] yielded the desired hybrid ligand *gluco*-enoPhos (**12**), which was thus obtained in only three steps and good overall yield.

Next we tested the new alkene-phosphinite hybrid ligand in asymmetric conjugate additions of boronic acids to enones (Hayashi−Miyaura reaction).[12,13] To our delight, the reaction of 2-cyclohexene-1-one (**13a**) with phenylboronic acid (**14**) in the presence of 1.5 mol % $[RhCl(H_2C{=}CH_2)_2]_2$ and 3.3 mol % **12** under Hayashi's conditions[27] furnished the 1,4-addition product **15a** in good yield and excellent enantioselectivity of 99% ee.

The same yield and excellent level of stereoinduction were obtained for 2-cyclopentene-1-one **13b**, while lactone **13c** was converted to **15c** in moderate yield and 94% ee. Due to its conformational flexibility and the absence of large substituents at the termini, acyclic enone **13d** represents a challenging substrate for stereoselective conjugate addition. With the new ligand **12**, addition product **15d** was obtained in good yield and 52% ee which, for this substrate, is still encouraging. The results of the conjugate additions are summarized in Scheme 2.

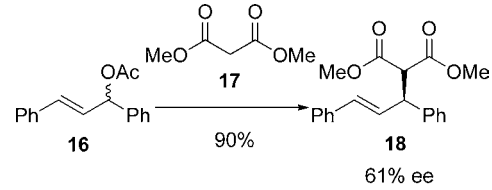
Scheme 2. Application of *gluco*-enoPhos (**12**) in Conjugate Additions of Phenylboronic Acid to Enones



Evidence for the bidentate coordination of *gluco*-enoPhos (**12**) to rhodium(I) through both the alkene and the phosphinite was obtained from NMR studies. The complex formed from $[Rh(acac)(H_2C{=}CH_2)_2]$ with 1 eq of **12** in $CDCl_3$ showed significant upfield shifts for the olefinic pyranose protons [^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.34 ppm for H-2; δ = 4.47 ppm for H-3] compared to free ligand **12** [^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 ppm for H-2; δ = 5.92 ppm for H-3]. The phosphinite resonance in compexed *gluco*-enoPhos (**12**) experienced a downfield shift and was split up to a doublet due to $^{31}P-^{103}Rh$ coupling [^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 159.0 ppm, d, $^1J_{P,Rh}$ = 193.7 Hz] while free **12** gave a singlet further upfield [^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 113.3 ppm, s]. These findings correlate with those reported for olefin-phosphine ligands and their rhodium complexes.[4−6]

gluco-enoPhos (**12**) was also employed in a palladium catalyzed asymmetric allylic alkylation reaction.[10,28] When racemic 1,3-diphenyl-2-propenyl acetate (**16**) was treated with dimethylmalonate (**17**) in the presence of a palladium complex of **12** under known conditions,[29] the allylation product was formed in good yield and 61% ee (Scheme 3).

Scheme 3. Application of *gluco*-enoPhos (**12**) in an Asymmetric Allylic Alkylation Reaction



gluco-enoPhos (**12**) (0.55 mol %)
$[Pd(\eta^3\text{-}C_5H_5)Cl]_2$ (0.25 mol %)
N,*O*-bis(trimethylsilyl) acetamide, KOAc
CH_2Cl_2, 0 °C, 16 h

Although only a moderate level of stereoinduction was achieved in this transformation, it clearly shows that the new ligand **12** is able to exert asymmetric induction in combination with other metal centers in different reactions.

In conclusion, with *gluco*-enoPhos, we have introduced a novel type of alkene-phosphinite hybrid ligand, accessible in three simple steps from a commercially available unsaturated pyranose derivative. As this precursor is derived from D-glucose, time-consuming and laborious enantiomeric resolution steps are not necessary for the preparation of this new ligand. First applications in asymmetric catalysis led to excellent levels of stereoselectivity in 1,4-additions of boronic acids to enones and moderate selectivity in asymmetric allylic

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alkylations. These results together with the facile preparation of the ligand make it a very attractive and promising candidate for future applications in catalysis. Studies concerning the scope of the new ligand and its optimization are currently underway.

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Supporting Information Available: Experimental details and analytical data for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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