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Bis(phosphinoamides) based on sugars for highly enantioselective allylic substitution: inversion of stereocontrol by switching from glucose to mannose

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Abstract—New chiral bis(phosphinoamides) based on glucose **1G** and mannose **1M** have been prepared. Their Pd complexes catalyze the asymmetric desymmetrization of *meso*-cyclopenten-2-ene-1,4-diol biscarbamate in high ee's (up to 97%). Glucose and mannose moieties selectively promote formation of the opposite enantiomers, as a consequence of inverted steric motifs around the metal center.

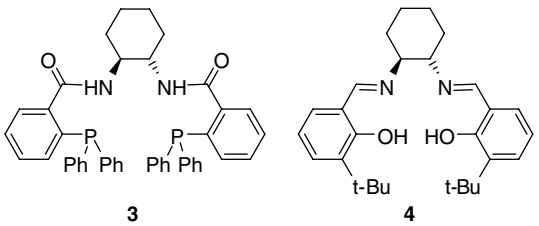
1. Introduction

Sustainable chemistry[1] demands high performance in the manufacture of a given product: valuable reaction outcomes (in terms of activity, productivity, and selectivity), rational choice of resources, use of harmless solvents and reagents, abolition of auxiliaries and undesired by-products. Metal mediated homogeneous catalysis meets these issues, and nowadays is central for the development of innovative industrial processes. Within this frame, enantioselective catalysis is in rapidly expanding in the industrial production of chiral molecules,[2] as demonstrated by Nobel Prizes being assigned in the last four years to scientists of this discipline (Sharpless–Noyori–Knowles in 2001, Schrock–Grubbs in 2005).

High catalyst performance requires careful choice of activating metals and chiral ligands. The central role of the latter components motivated Jacobsen to propose the attribution 'privileged'[3] for ligand structures of wide applicability, used on regular basis for the production of chiral molecules and for discovering new enantioselective processes.

Recently,[4] we developed a strategy aimed at improving the performance of 'privileged' ligands by incorporating their essential functions in a sugar ring. The advantage is that several sugars are easily accessible, and their intrinsic chirality avoids the tedious and often difficult resolution of racemates.[5] In addition, ring sites are available for additional functionalization, without altering the quality of the ligands. This benefit is crucial for application in non-conventional conditions, such as innovative liquid–liquid bi-phasic systems.[6]

The target of our current studies are 'privileged' structures based on *trans*-1,2-cyclohexanediamine **2**, that is, bis-phosphinoamides (e.g., **3**) or salens (e.g., **4** shows the protonated species salenH2), both currently used by industry for the manufacture of fine chemicals (Fig. 1).[7]



3 **4**

Figure 1. Structures of ligands **3** and **4**.

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This approach is inspired by the consideration that 2,3-glucodiamine **5** closely resembles (1*S*,2*S*)-cyclohexanediamine **2**, because both molecules display nitrogen functions in adjacent equatorial positions of a six-membered ring (Fig. 2).

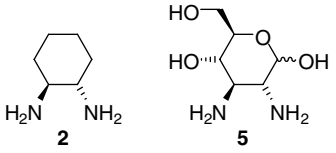


Figure 2. Structures of **2** and **5**.

This strategy has already proven to be feasible, for example, homogeneous[4] and heterogeneous[8] Mn(III) catalysts were successfully prepared with a glucose-based ligand, which mimicked the salen structure **4**.

Herein we report the successful achievement of the sugar-versions of the Trost ligand **3**[9] (**1G** from glucose and **1M** from mannose, Fig. 3), and their use in asymmetric catalysis.

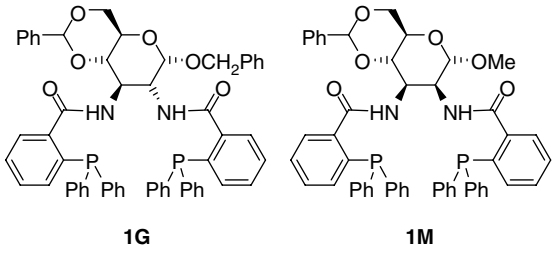
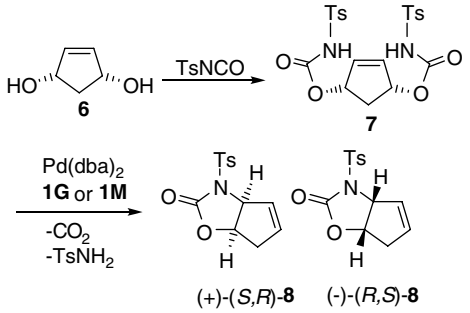


Figure 3. Structures of ligands **1G** and **1M**.

2. Results and discussion

The target ligands were obtained in high yield by reacting the 2,3-sugar diamine precursors[10] with 2-diphenylphosphino benzoic acid in the presence of DCC and DMAP (Scheme 1). After the usual work-up, **1G** and **1M** were characterized through NMR spectroscopy. Typical ring patterns for glucose and mannose rings were observed in the proton spectra of the ligands, along with doublets at high frequency, accounting for the newly formed amido protons.

The chelates were examined in the Pd-catalyzed desymmetrization of *meso*-cyclopenten-2-ene-1,4-diol biscarbamate **7** (Scheme 2). This intramolecular allylic substitution affords the key precursors of mannostatines,[11] and is also a standard test for assessment of the stereo-orienting properties of new ligands.[12]



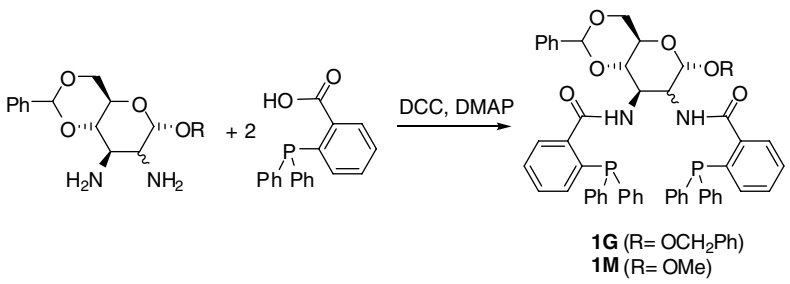
Scheme 2. The asymmetric desymmetrization of *meso*-cyclopenten-2-ene-1,4-diol biscarbamate.

Within this preliminary investigation, the influence of temperature and additives on the catalyst's performance was also assessed (Table 1).

In all cases, product **8** was obtained in high yield within short reaction times. The following was observed:

- glucose and mannose promote preferential formation of the opposite enantiomers;
- the marked beneficial influence of an added base[12f] was demonstrated: in all cases, the ee of the reaction increases in the presence of triethylamine;
- lowering the temperature from 273 to 258 K influences the enantioselectivity, with a favorable effect only if the additive is present. Thus, the optimal reaction conditions were found at 258 K in the presence of triethylamine, which allowed the attainment of the two enantiomers in 97% ee (entries 4 and 8).

In keeping with our initial assumption, **1G** promoted the formation of **8** with the same configuration as ligand **3** based on (1*S*,2*S*)-cyclohexanediamine.[12b,13] This can be reasonably explained by assuming that **3** (Fig. 4a) and **1G** (Fig. 4b) introduce similar steric motifs around Pd, as shown by using the model proposed by Trost[12b,e] for explaining the ligand effect on enantioselectivity.



Scheme 1. Synthesis of **1G** and **1M**.

Table 1. Catalytic reactions according to Scheme 2[a]

Entry	Ligand	T (K)	Additive	Time (min)	Conversion[b] (%)	ee (%) of **8**[c]
1	**1G**	273		30	99	80 (−)-(*R*,*S*)
2	**1G**	258		30	99	68 (−)-(*R*,*S*)
3	**1G**	273	NEt_3	30	99	93 (−)-(*R*,*S*)
4	**1G**	258	NEt_3	30	99	97 (−)-(*R*,*S*)
5	**1M**	273		30	99	91 (+)-(*S*,*R*)
6	**1M**	258		30	99	70 (+)-(*S*,*R*)
7	**1M**	273	NEt_3	30	99	95 (+)-(*S*,*R*)
8	**1M**	258	NEt_3	30	99	97 (+)-(*S*,*R*)

[a] In dry THF, catalyst:substrate 1:20.
[b] Determined by NMR spectra of the crude reaction mixtures.
[c] Determined by HPLC on Chiralcel OD-H, using 2-propanol–hexane 1:10, 1.0 mL/min, UV.

Mannose induces high selectivity in the opposite direction. A reasonable rationalization of this finding is that the chiral environment created by **1M** (Fig. 4c) is enantiomeric to that of **1G** (Fig. 4b). This can happen because the torsional angles N(2)–C(2)–C(3)–N(3) of the chiral backbone are of opposite signs in the two sugars, due to the different orientations of the nitrogen functions, that is, $N(2)_{eq}$–$N(3)_{eq}$ for glucose (Fig. 4b′) and $N(2)_{ax}$–$N(3)_{eq}$ for mannose (Fig. 4c′). As proposed by Trost, this geometrical feature directly correlates[12b] with the stereochemistry of the chiral coordination environment.

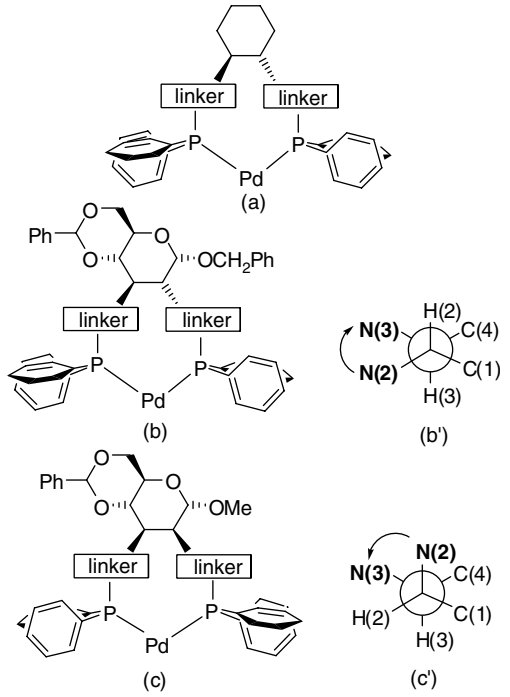


Figure 4. Schematic views of the chiral pockets created by **3** (a), **1G** (b), and **1M** (c) and the torsional angles N(2)–C(2)–C(3)–N(3) for glucose (b′) and mannose (c′).

3. Conclusion

In conclusion, this study clearly demonstrates that simple sugars are versatile scaffolds for building effective chiral ligands. Bis(phosphinoamides) based on glucose and mannose promote the asymmetric desymmetrization of *meso*-cyclopenten-2-ene-1,4-diol biscarbamate in ee's which are among the highest so far described for this reaction.[12]

The adaptability of these structures is clearly proven by the inversion of selectivity observed when switching from glucose to mannose. Future investigations are currently aimed at extending the use of the ligands in innovative conditions,[6] by exploiting the presence of the additional functionalisable groups, for example, 4- and 6-position of the sugar ring. These sites can be easily deprotected and tailored with perfluoroalkyl chains (for use in supercritical or perfluorinated solvents), or employed for anchoring the catalyst to a solid matrix[8] (for application in supported homogeneous catalysis).

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ ($CHCl_3$, δ 7.26, and $^{13}CDCl_3$ δ 77, as internal standards) with a 200 and 300 MHz spectrometers (Varian Model Gemini). The following abbreviations were used for describing NMR multiplicities: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; dt, double triplet; m, multiplet. Optical rotations were measured with a Perkin–Elmer Polarimeter (model 141) at 298 K and 589 nm in dichloromethane (c 1.0 g/100 mL). Benzyl-4,6-*O*-benzylidene-2,3-deoxy-2,3-diamino-α-D-glucoside[10a] and methyl-4,6-*O*-benzylidene-2,3-deoxy-2,3-diamino-α-D-mannoside[10b] were prepared according to the literature methods. THF was distilled from Na/benzophenone, dichloromethane from CaH_2.

4.2. Synthesis of 1G and 1M

A solution of 2-(diphenylphosphino)benzoic acid (1.29 g, 4.2 mmol), 4-dimethylaminopyridine (0.048 g, 0.43 mmol) and 1,3-dicyclohexylcarbodiimide (0.89 g, 4.3 mmol) in dry dichloromethane (7 mL) was added to a solution of the diaminosugar (2.0 mmol) in the same solvent (7 mL). The resulting mixture was stirred for 12 h at room temperature under an inert atmosphere to afford a yellow suspension. The residue was removed by filtration. In the case of **1M**, hexane (10 mL) was carefully added to the resulting

yellow solution. After 24 h white microcrystals of products were separated, washed with hexane and dried under vacuum (yield: 70–75%).

In the case of **1G**, the resulting yellow solution was evaporated under vacuum, and the residue was chromatographed on silica gel (1:5 ethyl acetate–hexane) to afford the pure product as a white solid (yield: 60–65%).

Compound **1G**: Anal. Calcd for $C_{58}H_{50}N_2O_6P_2$: C, 74.67; H, 5.40; N, 3.00. Found: C, 74.88; H, 5.29; N, 2.97. Selected ^{1}H NMR data (200 MHz, $CDCl_3$): δ 6.63 (d, 1H, NH–C2, $^3J_{NH-H2} = 9.9$ Hz), 6.10 (d, 1H, NH–C3, $^3J_{NH-H3} = 9.9$ Hz), 5.18 (s, 1H, PhC*H*O_2), 4.78 (d, 1H, H1, $^3J_{H1-H2} = 3.6$ Hz), 4.70 (q, 1H, H3, $^3J_{H3-H4} = {}^3J_{H3-H2} = 9.9$ Hz), 4.54 (d, 1H, C*H*HPh, $^2J_{gem} = 11.4$ Hz), 4.36 (d, 1H, CH*H*Ph), 4.20 (dt, 1H, H2), 4.05 (dd, 1H, $H6_{eq}$, $^3J_{H6eq-H5} = 4.2$, $^3J_{H6eq-H6ax} = 10.5$ Hz), 3.83 (dt, 1H, H5, $^3J_{H5-H6ax} = {}^3J_{H5-H4} = 9.3$ Hz), 3.58 (t, 1H, $H6_{ax}$), 3.28 (t, 1H, H4). Selected ^{13}C NMR data (50.2 MHz, $CDCl_3$): δ 169.5, 169.1, 101.4, 97.2, 79.7, 70.2, 68.8, 63.9, 53.6, 50.2. $[\alpha]_D = +23$ (*c* 1.0, CH_2Cl_2).

Compound **1M**: Anal. Calcd for $C_{52}H_{46}N_2O_6P_2$: C, 72.89; H, 5.41; N, 3.27. Found: C, 72.56; H, 5.50; N, 3.33. Selected ^{1}H NMR data (200 MHz, $CDCl_3$): δ 6.18 (d, 1H, NH–C2, $^3J_{NH-H2} = 9.3$ Hz), 5.03 5.18 (s, 1H, PhC*H*O_2), 4.82 (m, 2H, H2 and H3), 4.54 (s, 1H, H1), 4.09 (dd, 1H, $H6_{eq}$, $^3J_{H6eq-H5} = 5.0$, $^3J_{H6eq-H6ax} = 9.9$ Hz), 3.83 (dt, 1H, H5, $^3J_{H5-H6ax} = {}^3J_{H5-H4} = 10.1$ Hz), 3.32 (s, 3H, OMe) 3.25 (t, 1H, $H6_{ax}$), 2.98 (t, 1H, H4). Selected ^{13}C NMR data (50.2 MHz, $CDCl_3$): δ 169.5, 169.2, 101.1, 100.5, 76.8, 68.5, 64.0, 54.9, 52.6, 48.3. $[\alpha]_D = -29$ (*c* 1.0, CH_2Cl_2).

4.3. General procedures for catalytic reactions

Without NEt_3: to a solution of *cis*-2,4-cyclopentenediol (0.112 g, 1.00 mmol) in 1.75 mL of dry THF was added tosyl isocyanate (0.404 g, 2.05 mmol). The colorless solution was stirred at room temperature for 15 min and then at 333 K for 30 min. The reaction mixture was cooled to 273 K (or 258 K), and then added dropwise to an orange solution of [Pd(dba)$_2$] (0.050 mmol) and **1G** or **1M** (0.085 mmol) in 1.75 mL of dry THF. The orange reaction mixture was stirred at 273 K (or 258 K) for 30 min. The solvent was removed under vacuum and column chromatography on silica gel (1:10 ethyl acetate–hexane) gave the desired product as a white solid. The enantiomeric excesses were determined by chiral HPLC, Chiralcel OD-H, 1:10 isopropanol–hexane, UV 254 nm, retention times: **8** [(−)-(*R*,*S*)], 22–24 min; **8** [(+)-(*S*,*R*)], 30–32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

With NEt_3: to a solution of *cis*-2,4-cyclopentenediol (0.112 g, 1.00 mmol) in 1.75 mL of dry THF was added tosyl isocyanate (0.463 g, 2.35 mmol). The colorless solution was stirred at room temperature for 15 min and at 333 K for 30 min. The reaction mixture was allowed to cool to room temperature, and triethylamine (0.101 g, 1.00 mmol) was added. The resulting white slurry was cooled at 273 K (or 258 K), and an orange solution of [Pd(dba)$_2$] (0.028 g, 0.050 mmol) and **1G** (or **1M**) (0.085 mmol) in 1.75 mL of THF then added. The orange reaction mixture was stirred at 273 K (or 258 K) for 30 min. The solvent was removed under vacuum and column chromatography on silica gel (1:10 ethyl acetate–hexane) gave the desired product as a white solid. The enantiomeric excesses were determined by chiral HPLC, Chiralcel OD-H, 1:10 isopropanol–hexane, UV 254 nm, retention times: **8** [(−)-(*R*,*S*)], 22–24 min; **8** [(+)-(*S*,*R*)], 30–32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

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References

1. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, 1st ed.; Oxford University Press: New York, USA, 1998.
2. *Asymmetric Catalysis on Industrial Scale*, 1st ed.; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
3. Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.
4. Borriello, C.; Del Litto, R.; Panunzi, A.; Ruffo, F. *Tetrahedron: Asymmetry* **2004**, *15*, 681, and references cited therein.
5. Other categories of ligands based on sugars are known: (a) Steinborn, D.; Junicke, H. *Chem. Rev.* **2000**, *100*, 4283; (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Diaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; (c) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; (d) Diaz, Y.; Castillón, S.; Claver, C. *Chem. Soc. Rev.* **2005**, *34*, 702.
6. *Multiphase Homogeneous Catalysis*, 1st ed.; Cornils, B., Herrmann, W. A., Horvath, I. T., Leitner, W., Mecking, S., Olivier-Borbigou, H., Vogt, D., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
7. Blaser, H.-U.; Pugin, B.; Spindler, F. *J. Mol. Catal. A: Chem.* **2005**, *231*, 1.
8. Borriello, C.; Del Litto, R.; Panunzi, A.; Ruffo, F. *Inorg. Chem. Commun.* **2005**, *8*, 717.
9. Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
10. (a) Meyer zu Reckendorf, W.; Weber, R.; Hehenberger, H. *Chem. Ber.* **1981**, *14*, 1306; (b) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1965**, 6956.
11. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317.
12. (a) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228; (b) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327; (c) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444; (d) Trost, B. M.; Breit, B. *Tetrahedron Lett.* **1994**, *35*, 5817; (e) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386; (f) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339; (g) Lee, S.; Lim, C. W.; Song, C. E.; Kim, K. M.; Jun, C. H. *J. Org. Chem.* **1999**, *64*, 4445; (h) Lim, C. W.; Lee, S. *Tetrahedron* **2000**, *56*, 5131; (i) Trost, B. M.; Zambrano, J. L.; Richter, W. *Synlett* **2001**, *907*; (j) Buschmann, N.; Rueckert, A.; Blechert,

S. *J. Org. Chem.* **2002**, *67*, 4325; (k) Song, C. E.; Yang, J. W.; Roh, E. J.; Lee, S.-G.; Ahn, J. H.; Han, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3852; (l) Trost, B. M.; Pan, Z.; Zambrano, J.; Kujat, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4691; (m) Agarkov, A.; Uffman, E. W.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 2091; (n) Zhao, D.; Wang, Z.; Ding, K. *Synlett* **2005**, 2067.

13. Ref. 12b reports the results obtained with ligands based on (1*R*,2*R*)-cyclohexanediamine. Obviously, specular considerations hold true for (1*S*,2*S*)-cyclohexanediamine.