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Naplephos through the Looking-Glass: Chiral Bis(phosphanylamides) Based on β-1,2-D-Glucodiamine and Their Application in Enantioselective Allylic Substitutions

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The straightforward design of a new library of chiral ligands (elpanphos) based on β-1,2-D-glucodiamine is described, which represents the enantiomeric counterpart of the naplephos library. In this guise, two representative ligands have been successfully applied in the Pd-catalyzed desymmetrization of *meso*-cyclopent-2-ene-1,4-diol, which leads to the expected enantiomer within short times and with high *ee*s in both traditional and unconventional solvents.

Introduction

Homogeneous enantioselective catalysis is central for the production of fine chemicals.[1] In this field, innovative metal catalysts can be rationally prepared by selecting building blocks from the chiral pool.

Within this frame, we recently[2] prepared a library of ligands (naplephos) based on D-glucose[3] (Figure 1). The multifunctional nature of the carbohydrate scaffold is fully employed for a precise tailoring of the ligands: position 2 displays a rigid diphenylphosphanylamide arm, an essential coordination motif of Trost's privileged ligands based on *trans*-cyclohexanediamine.[4] Position 3 is suitable for introducing defined steric hindrance or additional coordinating functions next to the metal centre. Positions 4 and 6 are instead useful for phase-tagging the ligands.

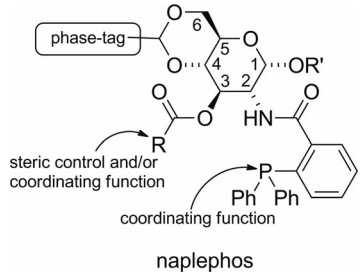
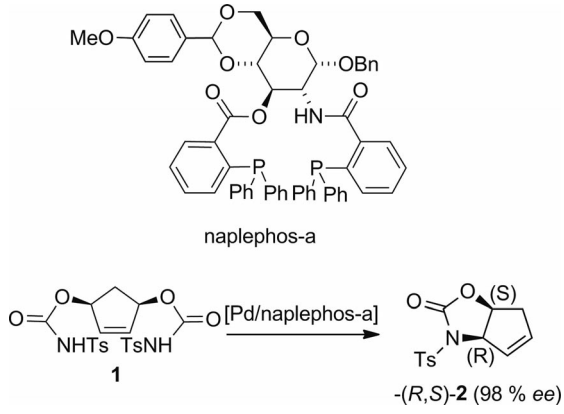


Figure 1. General formula of the naplephos library of ligands.

Accordingly, the ligands were tested[5] in a number of asymmetric reactions in both traditional solvents and ionic liquids, and afford, in several cases, the chiral products in high *ee*s (Scheme 1 shows naplephos-a, one of the best performing ligands, and the corresponding catalysis).



Scheme 1. The desymmetrization of *meso*-cyclopent-2-ene-1,4-diol promoted by naplephos-a.

In order to fully employ the versatility of this strategy, we have rationally designed the related library of ligands (elpanphos),[6] which shows a specular stereochemistry of coordination. This action aims to furnish a complete scenario, in order to perform the same catalytic processes but with the production of the chiral products in opposite configuration.

On the basis of the relative orientations of positions 2 and 3 in the naplephos ligands, this approach has been pursued by introducing the same essential coordinating motifs

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in positions 1 and 2, which clearly provide a pseudo-enantiomeric coordination environment (compare Figures 1 and 2).

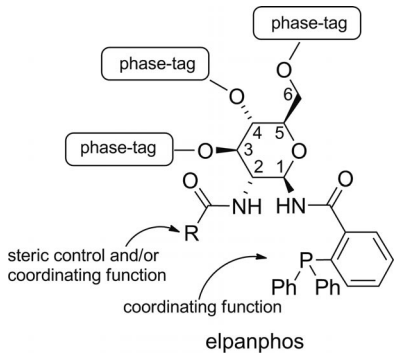
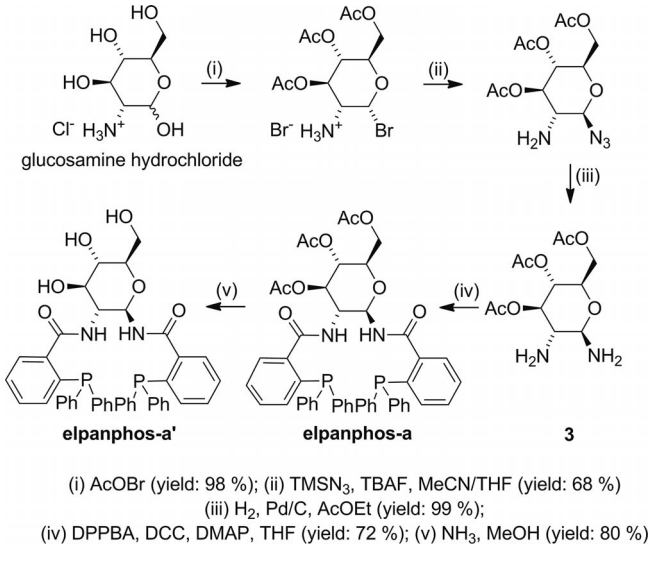


Figure 2. General formula of the elpanphos library of ligands.

In this report, we communicate that this strategy promises to be plainly successful, as newly synthesized elpanphos ligands were applied with full accomplishment of the expectations.

Results and Discussion

The very simple synthesis of the ligands (elpanphos-a and -a′) is reported in Scheme 2.



Scheme 2. Synthesis of elpanphos ligands.

This involves the ready attainment of the known key intermediate 3,4,6-tri-*O*-acetyl-1,2-β-glucodiamine **3**[7] starting from inexpensive glucosamine hydrochloride. Its condensation with two equivalents of diphenylphosphanylbenzoic acid (DPPBA) affords elpanphos-a, which is highly soluble in common organic solvents, such as dichloromethane, THF and methanol. Treatment of the ligand with methanolic ammonia completely deprotects the acetyl groups, and the corresponding polar form of the ligand (elpanphos-a′) could be obtained. This latter molecule is soluble in alcohols and in the most common ionic liquids, a feature particularly attractive as it allows the performing of biphasic asymmetric catalysis[8] (see below).

Both elpanphos ligands represent the specular counterpart of naplephos-a (see Scheme 1), and, therefore, they were examined in the asymmetric desymmetrization of **1** for useful comparison. This intramolecular allylic substitution affords the key precursors of mannostatines and is also a standard test for the assessment of the stereo-orienting properties of new ligands.[9]

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

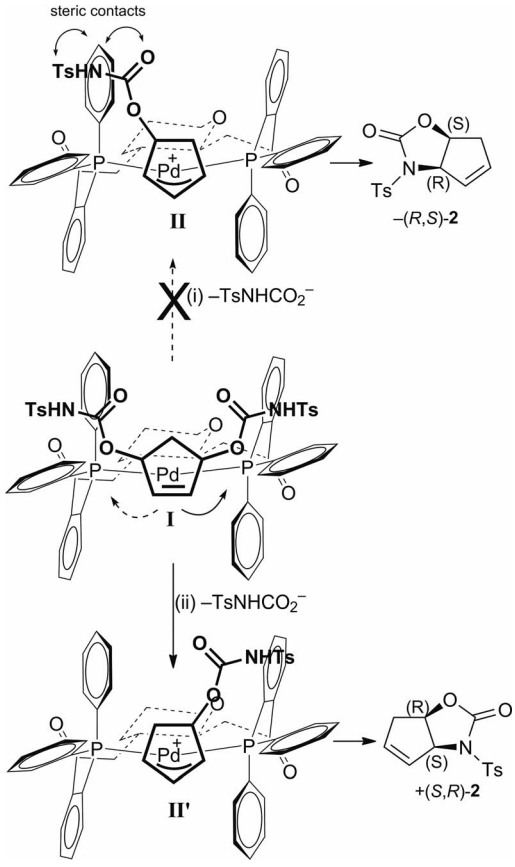
Table 1. Catalytic conversion of **1** to **2**.[a]

	Ligand	*T* [K]	Solvent	Time [min]	Conversion [%][b]	*ee* {+(*S*,*R*)-**2**} [%][c]
1	elpanphos-a	298	THF[d]	5	>99	95
2	elpanphos-a	273	THF[d]	15	>99	95
3	elpanphos-a	258	THF[d]	30	92	96
4	elpanphos-a	298	THF	30	>99	84
5	elpanphos-a	273	THF	30	>99	86
6	elpanphos-a	258	THF	30	>99	86
7	elpanphos-a′	298	THF[d]	5	>99	96
8	elpanphos-a′	298	bmpyBF$_4$[e]	30	>99	94
9	elpanphos-a′	298	bmpyBF$_4$[e] I recycle	30	>99	89
10	elpanphos-a′	298	bmpyBF$_4$[e] II recycle	30	>99	79
11	elpanphos-a′	298	bmimBF$_4$[e]	30	>99	90
12	elpanphos-a′	298	bmimBF$_4$[e] I recycle	30	>99	81
13	elpanphos-a′	298	bmimBF$_4$[e] II recycle	30	>99	77

[a] Catalyst:substrate 1:20. [b] Determined by NMR spectra of the crude reaction mixtures. [c] Determined by HPLC on Chiracel OD-H, by using 2-propanol/hexane, 1:10, 1.0 mL/min, UV (254 nm). [d] Triethylamine as additive. [e] Catalyst:substrate 1:10. Triethylamine as additive.

The following should be observed: (i) in THF (Entries 1–7), the reaction proceeded in high yield within short reaction times; (ii) as desired, the elpanphos ligands produced preferential formation of the opposite enantiomer with respect to the *naplephos* ligands, +(*S*,*R*)-**2** vs. -(*R*,*S*)-**2**; (iii) the marked beneficial influence of an added base was demonstrated:[9e] the *ee* of the reaction increased in the presence of triethylamine (Entry 1 vs. 4, 2 vs. 5, or 3 vs. 6); (iv) lowering the temperature from 298 to 258 K poorly influenced the enantioselectivity, with a small favourable effect. Thus, the optimal reaction conditions were found at 298 K in the presence of triethylamine, which allowed the attainment of the product in only 5 min with a 95–96% *ee* for both ligands (Entries 1 and 7). This also demonstrates that the presence of diverse phase-tags has no effect on the stereochemistry of the reaction.

The stereochemical outcome of the reaction can clearly be explained on the basis of the mechanism proposed by Trost for this reaction.[9a,10] In our case, his cartoon models can be translated as shown in Scheme 3, where, of the sugar moiety, only the chair has been reported for the sake of clarity.



Scheme 3. Model for the enantioselectivity.

The rate-limiting step is the activation of one carbammate in **I** to give a π-allyl intermediate (**II** or **II′**). Activation of the "left" carbammate function (step i) leads to the attainment of **II**, which then results in –(*R*,*S*)-**2**, while activation of the "right" function (step ii) preludes the achievement of +(*S*,*R*)-**2**. Both reactions occur with simultaneous rotation of the five-membered ring, which is clearly inhibited by steric contacts only in the case of the clockwise rotation (i) that accompanies formation of **II**.

Finally, it also should be noted that, according to our assumption, the presence of free hydroxy groups in elpanphos-a′ allowed the catalytic study in ionic liquids,[11,12] where the original Trost ligand based on *trans*-cyclohexanediamine does not show appreciable solubility.

The reactions were performed by adding the substrate and triethylamine to a solution of the catalyst at 298 K. After 30 min, the organic product was extracted with diethyl ether and analyzed. The catalyst phase was recycled for further runs. In $bmpyBF_4$, the first run quantitatively afforded the chiral product in high *ee* (94%, Entry 8), which is the highest value reported so far[2a,5a] for this reaction under unconventional conditions. In subsequent recycles, the conversion was still complete (Entries 9 and 10), while the enantioselectivity only slightly decreased, as rarely observed[13] in ionic solvents for AAA.[14] The observed reduction of enantioselectivity and the simultaneous persistence of activity may be due to a gradual anomerization of the ligand, which is likely more sensitive at position 1. After the second recycle, the catalytic solution was left aside, and 24 h later, fresh substrate was added to the resting catalyst. Notably, the product was again obtained in quantitative yield and with significant *ee* (55%).

A similar general behaviour was observed in $bmimBF_4$, where the values for the *ee* were between 90 and 77%.

Conclusions

This work substantiates the strategy aimed at preparing effective ligands in a simple way from the chiral pool. Thus, the elpanphos library was designed by starting from convenient glucosamine hydrochloride, proving to be much more viable compared to species otherwise accessible only from the expensive L series.

Furthermore, the natural presence of polar phase-tags in the multifunctional[15] sugar structure allows the performing of the same asymmetric process in ionic liquids and with unprecedented enantioselectivity.

Experimental Section

General Considerations: NMR spectra were recorded in $CDCl_3$ ($CHCl_3$, δ = 7.26 ppm, and $^{13}CDCl_3$ δ = 77 ppm, as internal standards) with a 200 MHz (Varian Model Gemini) and a 400 MHz (Bruker DRX-400). ^{31}P NMR experiments were carried out by using aqueous 85% phosphoric acid as external reference (δ = 0 ppm). Specific optical rotatory powers [α] were measured with a Perkin–Elmer Polarimeter (model 141) at 298 K and 589 nm in chloroform or in methanol (c = 1.0 g/100 mL). THF was distilled from $LiAlH_4$, dichloromethane from CaH_2, diethyl ether from Na.

Preparation of 3,4,6-Tri-*O*-acetyl-β-1,2-D-diamineglucose (3): This compound was obtained by adapting a known procedure[7] in order to avoid use of AgN_3: a solution of 1-bromo-3,4,6-tri-*O*-acetyl-α-D-glucosamine hydrobromide[7] (0.90 g, 2.0 mmol) in acetonitrile (10 mL) was treated with $TMSN_3$ (0.24 g, 2.0 mmol) and a 1.0 M solution of TBAF (2 mL, 2.0 mmol) in THF. After stirring for 1 h, the solvent was removed under vacuum, and the residue was dissolved in chloroform (10 mL). The resulting solution was shaken with 2 M aqueous KOH (4 mL), and then washed with water (4 mL). After drying the solution over sodium sulfate, the solvent was evaporated under vacuum, and the residue filtered through a column of silica gel (eluent: ethyl acetate) to afford 1-azido-3,4,6-tri-*O*-acetyl-β-D-glucosamine (0.45 g, 68%). The compound was dissolved in ethyl acetate (10 mL) in the presence of 10% Pd/C (0.18 g) and treated with H_2 (1 atm) for 1.5 h. After filtration, the solvent was removed under vacuum to afford pure 3,4,6-tri-*O*-acetyl-β-1,2-D-diamineglucose in quantitative yield.

Preparation of Elpanphos-a: A solution of 3,4,6-tri-*O*-acetyl-β-1,2-D-diamineglucose (0.61 g, 2.0 mmol), diphenylphosphanylbenzoic acid (1.2 g, 2.0 mmol), 4-dimethylaminopyridine (0.49 g, 4.0 mmol) and 1,3-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry dichloromethane (10 mL) was stirred for 18 h at room temperature under inert atmosphere to afford a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (2:1 ethyl acetate:hexane) to afford the pure product as a white solid (1.2 g, 72%). $C_{50}H_{46}N_2O_9P_2$ (880.87): calcd. C 68.18, H 5.26, N 3.18; found C

68.72, H 5.34, N 3.35. [*a*] = 3.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ_H = 7.85 (m, 1 H), 7.58 (d, $^3J_{NH\text{-}H1}$ = 9.0 Hz, 1 H, N*H*), 7.47 (m, 1 H), 7.36–6.97 (m, 26 H), 6.37 (d, $^3J_{NH\text{-}H2}$ = 8.5 Hz, 1 H, N*H*), 5.29 (t, $^3J_{H1\text{-}NH}$ = $^3J_{H1\text{-}H2}$, 1 H, 1-H), 5.18 (t, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 9.5 Hz, 1 H, 4-H), 5.02 (t, $^3J_{H2\text{-}H3}$ = $^3J_{H3\text{-}H4}$, 1 H, 3-H), 4.47 (q, 1 H, 2-H), 4.17 (dd, $^3J_{H6\text{-}H5}$ = 4.11, $^2J_{H6\text{-}H6'}$ = 12.4 Hz, 1 H, 6-H), 3.94 (dd, $^3J_{H6'\text{-}H5}$ = 1.86 Hz, 1 H, 6′-H), 3.63 (m, 1 H, 5-H), 1.99 (s, 3 H, AcO), 1.96 (s, 3 H, AcO), 1.93 (s, 3 H, AcO) ppm. ^{13}C NMR: δ_C = 172.3, 171.2, 170.8, 169.7, 168.8, 141–127 (aromatics), 80.8, 73.8, 73.3, 68.14, 62.2, 53.9, 21.4, 21.2, 21.0 ppm. ^{13}P NMR: δ = –8.0, –12.0 ppm.

Preparation of Elpanphos-a′: A solution of elpanphos-a (0.44 g, 0.50 mmol) in methanol (5 mL) was saturated with gaseous ammonia. After a few hours, addition of diethyl ether (50 mL) caused precipitation of the product as a white solid, which was filtered, washed with diethyl ether and dried under vacuum (0.30 g, 80%). $C_{44}H_{40}N_2O_6P_2$ (754.76): calcd. C 70.02, H 5.34, N 3.71; found C 69.77, H 5.41, N 3.59. [*a*] = 10.5 (*c* 1.0, MeOH). ^{1}H NMR: δ_H = 7.85 (m, 1 H), 7.70 (m, 1 H), 7.5–6.9 (m, 26 H), 5.09 (d, $^3J_{H1\text{-}H2}$ = 9.7 Hz, 1 H, 1-H), 4.05 (t, $^3J_{H3\text{-}H2}$ = 9.9 Hz, 1 H, 2-H), 3.87 (d, $^2J_{gem}$ = 12.5 Hz, 1 H, 6-H), 3.71 (dd, $^3J_{H6'\text{-}H5}$ = 4.9 Hz, 1 H, 6′-H), 3.65–3.30 (m, 3 H, 3-H, 4-H, 5-H) ppm. ^{13}C NMR: δ_C = 174.6, 172.6, 145–130 (aromatics), 82.8, 81.0, 77.6, 73.2, 64.1, 58.0 ppm. ^{13}P NMR: δ_P = –7.0, –10.5 ppm.

Desymmetrization of meso-2-Cyclopenten-1,4-diol-isocyanate in THF

Without NEt_3: *meso*-2-cyclopenten-1,4-diol-isocyanate (0.10 g, 0.20 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol) and the ligand (0.015 mmol) were dissolved in dry THF (1 mL). The mixture was stirred at the desired temperature, and, after the required reaction time, the solvent was removed under vacuum. Column chromatography on silica gel (1:2 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield.

With NEt_3: *meso*-2-cyclopenten-1,4-diol-isocyanate (0.10 g, 0.20 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol) and the ligand (0.015 mmol) were dissolved in dry THF (1 mL) containing triethylamine (0.030 g, 0.30 mmol). The mixture was stirred at the desired temperature, and, after the required reaction time, the solvent was removed under vacuum. Column chromatography on silica gel (1:2 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield.

In RTIL: *meso*-2-cyclopenten-1,4-diol-isocyanate (0.050 g, 0.10 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol) and elpanphos-a′ (0.012 g, 0.015 mmol) were vigorously stirred in RTIL (1 mL) under an inert atmosphere. After 30 min, the product was extracted with dry diethyl ether (3 × 15 mL) in 70–80% yield and analyzed. Recycling was carried out by adding fresh substrate and triethylamine to the active catalytic solution.

The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:10 2-propanol/hexane, UV 254 nm, retention times: –(*R*,*S*)-**2**: 22–24 min; +(*S*,*R*)-**2**: 30–32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

Supporting Information (see footnote on the first page of this article): Relevant proton and carbon NMR spectra are presented.

Acknowledgments

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