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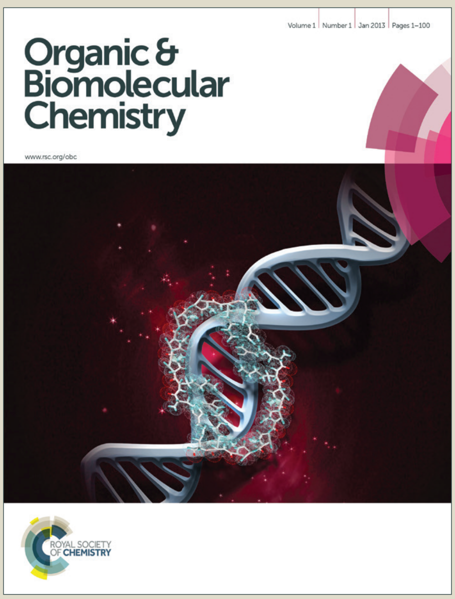

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ARTICLE

D-Glucosamine as a novel chiral auxiliary for the stereoselective synthesis of P-stereogenic phosphine oxides

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D-Glucosamine was successfully employed as a chiral auxiliary for the enantioselective synthesis of phosphine oxides. The influence of the anomeric position was also investigated and revealed the excellent ability of the α-anomer to perform this transformation in a highly selective fashion. The methodology employed consisted in three steps: diastereoselective formation of the oxazaphospholidine followed by subsequent selective cleavage of P-N and P-O bonds by reaction with two Grignard's reagents. P-epimers oxazaphospholidines were prepared switching from a P(V) to a P(III) precursor, thus allowing for the synthesis of enantiomeric phosphine oxides. In addition, the chiral auxiliary could be recovered and efficiently recycled.

Introduction

The asymmetric synthesis of P-stereogenic molecules has interested scientists because of their important use as chiral ligands and organocatalysts.[1-2] Since the first synthesis of the chiral ligand DIPAMP by Knowles and coworkers,[3] various methodologies have been developed such as the resolution of racemic and diastereoisomeric mixtures,[4] the enantioselective deprotonation of phosphine-boranes,[5-7] and the use of a chiral auxiliary.[8-15] Many studies have been devoted to the discovery of novel chiral scaffolds that would allow the synthesis of a large range of variously substituted P-stereogenic molecules. The major contributions in this area come from the use of optically pure amino alcohols-derived scaffolds. These templates allow for the preparation of chiral cyclic aminophosphinites which are subjected to the addition of various nucleophiles. Representative examples (Figure 1) include Jugé's strategy with the efficient use of ephedrine for the preparation of several P-stereogenic ligands,[11] and Verdaguer's strategy involving the *cis*-1-amino-2-indanol was employed for the preparation of P-stereogenic bulky aminophosphines.[13] More recently, Han et al. designed a chiral scaffold in which the reactivities of the P-O and P-N bonds are differentiated by the introduction of an arylsulfonyl group, thus allowing for the introduction of bulky nucleophiles.[14]
Recent studies from our laboratory revealed the possible use of (1*S*,2*S*)-2-aminocyclohexanol for the asymmetric synthesis of phosphine oxides.[16] The efficiency of this *trans* chiral amino alcohol led us to consider the use of the bio-sourced D-glucosamine as a novel chiral scaffold to achieve this transformation. Indeed, D-glucosamine displays a skeleton resembling the (1*S*,2*S*)-2-aminocyclohexanol with the presence of a 6-membered backbone ring, and the *trans* conformation of the 1,2-amino alcohol.

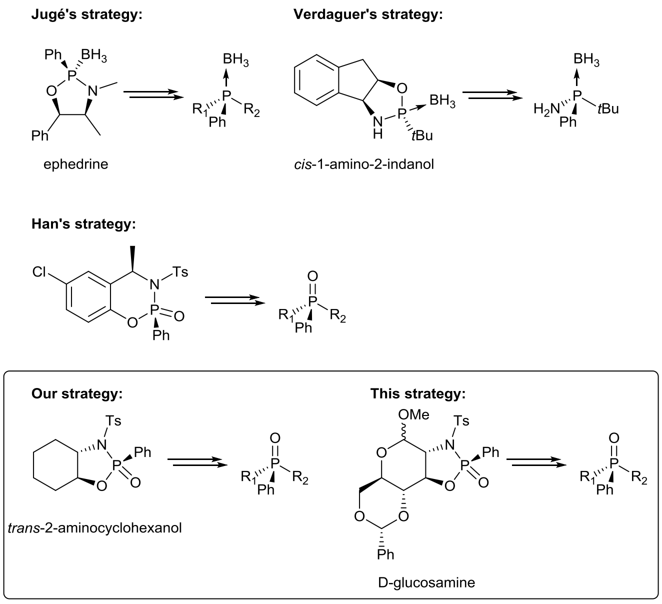

Figure 1. Synthesis of P-stereogenic phosphines and phosphine oxides using various chiral auxiliaries

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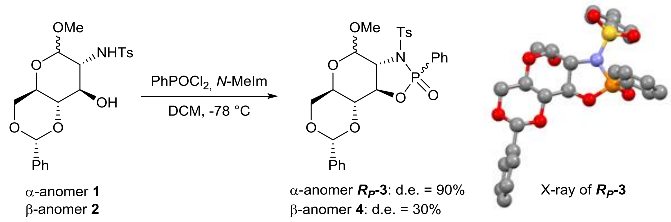
D-Glucosamine is one of the most abundant monosaccharides and has thus been widely valorized as a synthetic tool for many organometallic[17] and organocatalytic[18] transformations. However, as far as we know, P-stereogenic compounds using D-glucosamine as chiral auxiliary have been synthesized only once by Inch and coworkers.[19] The scope of this transformation was not explored as the obtained ethyl methyl phosphonates only served as proof of the configuration at phosphorous in the corresponding oxazaphospholidines. Various other carbohydrates have been tested, albeit with moderate yields and/or selectivities.[10,20-22] In this communication, we wish to report the first use of D-glucosamine as a chiral auxiliary for the efficient synthesis of optically pure phosphine oxides.

Results and discussion

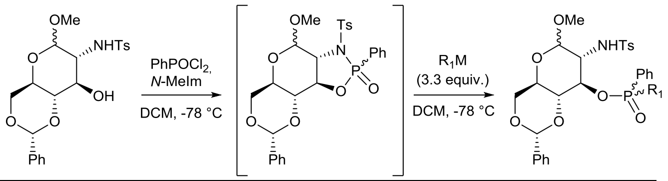
Following the P(V) strategy recently developed by our group,[16] benzylidene acetals **1**[23] and **2**[24] were both cyclized to the corresponding oxazaphospholidines **3** and **4** by reaction with phenylphosphonic dichloride and *N*-methylimidazole in DCM at -78 °C (Scheme 1). The diastereoselectivity of the cyclization was evaluated by ^{31}P NMR, and the α-anomer **1** proved to be more suitable for this transformation. Indeed, while the β-anomer **2** provided a low selectivity (d.e. 30%), the α-anomer afforded the desired oxazaphospholidine ***R*$_P$-3** with a high diastereoselectivity of 90%.[25] X-Ray analysis of the corresponding major diastereoisomer, crystallized by slow evaporation of chloroform, permitted to reveal the *R* absolute configuration at the phosphorus atom (Scheme 1).[26]



Scheme 1. Diastereoselective formation of oxazaphospholidine starting from a phosphine oxide precursor (P(V) strategy)

As these cyclized products appeared difficult to purify,[16] crude oxazaphospholidines ***R*$_P$-3** and **4** were directly engaged into the selective cleavage of P-N bond. The conditions previously optimized[16] were thus applied, and upon treatment with 3.3 equiv. of Grignard reagents (*o*-anisylmagnesium bromide and methylmagnesium chloride) at -78 °C in DCM, the expected phosphinates were both formed in 83% yield with satisfying diastereoselectivities (90% and 94% respectively – Table 1, entries 1 and 2).

Table 1. Diastereoselective ring opening of oxazaphospholidine.



Entry	Anomer	R_1M	d.e. of the crude[a]	Isolated phosphinate		
				yield	d.e.[a]	
1	α	*o*-AnMgBr	90%	83%	>99%	***S*$_P$-5**
2	α	MeMgCl	94%	83%	>99%	***R*$_P$-6**
3	β	*o*-AnMgBr	14%	/	/	**7**

[a] Determined by ^{31}P NMR

Phosphinates ***S*$_P$-5** and ***R*$_P$-6** were crystallized (see supp. Info.) and analyzed by X-Ray diffraction. It appeared that the inversion of configuration at the phosphorus atom, already observed during our previous study,[16] was also confirmed in the ring opening of oxazaphospholidine ***R*$_P$-3**.[27] In addition, the X-Ray structure (Figure 2) highlighted the presence of an intramolecular H-bond between the N-H of the glucopyranoside derivative and the oxygen of phosphine oxide (distance = 2.0 Å).

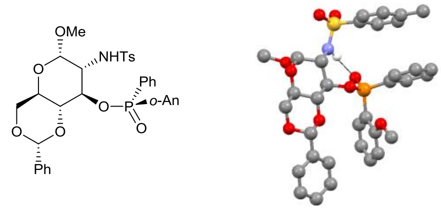


Figure 2. X-ray crystal structure of phosphinate ***S*$_P$-5**

The same methodology was applied to the β-anomer (Table 1, entry 3) but the desired phosphinate **7** was formed with a low selectivity (d.e. = 14%). This lack of selectivity might be explained by a high steric hindrance between the tosyl group and the methoxy in the β-position. At this stage, it was decided that the study would be carried on the α-anomer only.

The preparation of phosphine oxides by cleavage of the P-O bond was next attempted. We were pleased to observe that the previously optimized conditions[16] proved once again successful on glucopyranoside derivatives ***S*$_P$-5** and ***R*$_P$-6**. Indeed, 6.0 equiv. of nucleophiles, like methylmagnesium chloride and ethylmagnesium bromide, reacted successfully at 40 °C with phosphinate ***S*$_P$-5** with very good yields and enantioselectivities (Table 2, entries 1 and 2). Unfortunately, more sterically hindered nucleophiles such as *i*-propylmagnesium chloride failed to furnish the expected phosphine oxide (Table 2, entry 3). However, the use of the smaller phosphinate ***R*$_P$-6** allowed for the reaction with a larger range of nucleophiles with excellent enantioselectivities (Table 2, entries 4-6), notwithstanding that yields diminished when the steric hindrance of nucleophiles increased. As expected, HPLC analysis confirmed that the P-O bond cleavage occurred with inversion of configuration at the phosphorous atom.[27]

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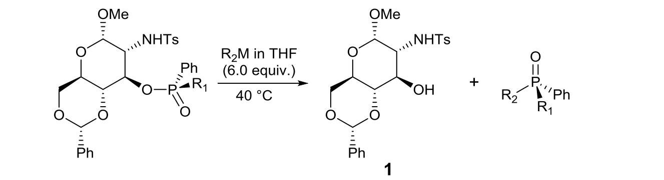
Interestingly, the chiral auxiliary could be recovered almost quantitatively[28] and successfully re-engaged in the strategy without any loss of the efficiency and selectivity.[29]

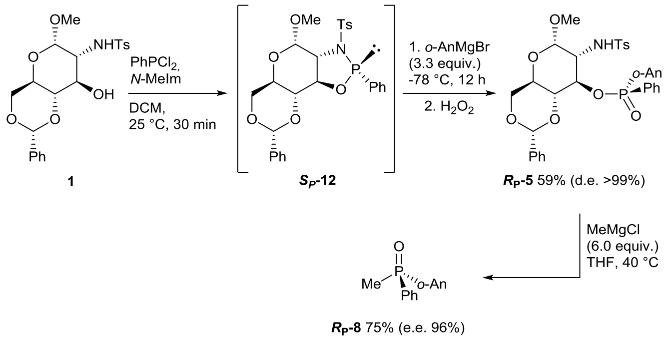
Table 2. Synthesis of phosphine oxides by cleavage of P-O bond



Entry	R_1	R_2M	Isolated yield	e.r.[a]	Phosphine oxide
1[b]	*o*-An	MeMgCl	75%	90%	***S***$_P$**-8**
2	*o*-An	EtMgBr	85%	92%	***S***$_P$**-9**
3	*o*-An	*i*-PrMgCl	No reaction	No reaction	**/**
4	Me	EtMgBr	99%	94%	***S***$_P$**-10**
5	Me	*o*-AnMgBr	84%	98%	***R***$_P$**-8**
6	Me	*i*-PrMgCl	34%	90%	***S***$_P$**-11**

[a] Determined by HPLC. [b] The optically pure glucopyranoside **1** was recovered in 95% yield.

Our group previously demonstrated that the use of a P(III) precursor for the cyclization step afforded a P-epimer oxazaphospholidine, and thus enantiomeric phosphine oxides after cleavage of P-N and P-O bonds.[16] This method was then applied to glucopyranoside **1** (Scheme 2). Chiral auxiliary **1** was then reacted with dichlorophenylphosphine in the presence of *N*-methylimidazole. After 30 minutes at room temperature, oxazaphospholidine ***S***$_P$**-12** was formed and was directly engaged in the P-N bond cleavage. *o*-Anisylmagnesium bromide was thus reacted with oxazaphospholidine under the conditions previously described (see Table 1). The phosphinite obtained was oxidized *in situ* upon treatment with hydrogen peroxide to afford phosphinate ***R***$_P$**-5** in a good yield and excellent diastereoselectivity[30] (Scheme 2). Addition of methylmagnesium chloride afforded the final phosphine oxide ***R***$_P$**-8** in excellent yield and enantioselectivity (Scheme 2). HPLC data confirmed that the P(III) and P(V) strategy led to the formation of enantiomeric phosphine oxides (see Supp. Info.).



Scheme 2. Formation of phosphine oxide starting from a phosphine precursor (P(III) strategy)

Conclusions

In conclusion, we have reported the successful use of D-glucosamine as the chiral auxiliary for the preparation of enantiopure phosphine oxides. Two strategies starting from either a P(V) or a P(III) precursor were successfully employed, thus allowing for the easy preparation of enantiomeric phosphine oxides in very high enantioselectivities. The influence of the anomeric position was also demonstrated, and the α-anomer proved to be the most efficient affording excellent selectivities for the three key steps of the process: the formation of oxazaphospholidine and the cleavage of P-N and P-O bonds. Interestingly, the chiral auxiliary could be recovered and recycled without any loss of efficiency or selectivity. This study highlighted a novel application of D-glucosamine in stereoselective synthesis. This bio-sourced amino alcohol can serve as an efficient chiral auxiliary for the asymmetric synthesis of P-stereogenic phosphine oxides.

Experimental section

General

All reactions were performed under an argon atmosphere using Schlenk techniques. THF was freshly distilled over sodium/benzophenone. Dry dichloromethane stabilized on amylene was purchased from Aldrich and used as received. Phenylphosphonic dichloride and *N*-methylimidazole were freshly distilled under reduced pressure before use. Organometallics reagents were ordered from Aldrich or Acros® as solutions in THF unless otherwise specified, and used as received.

Analytical TLC was performed on ready-made plates coated with silica gel on aluminium (Merck 60 F_{254}). Products were visualized by ultraviolet light and treatment with permanganate stain followed by gentle heating. Flash chromatography was performed using silica gel (60 Å, particle size 40-63µm).

NMR spectra were recorded on a Bruker ALS-300 MHz spectrometer with a QNP probe in $CDCl_3$. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) downfield to tetramethylsilane using the residual solvent signal as internal standard. ^{31}P spectra are decoupled ^{1}H and referenced to H_3PO_4. Proton (^{1}H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal), coupling constant (*J*) in Hertz (Hz), number of protons. UV spectra were recorded on a Shimadzu UVmini-1240. High resolution mass spectrometry spectra are recorded on BruckerMicrOQTOF-Q II XL. The enantiomeric excess was determined by chiral HPLC using a Chiralpack AD column (4.6mm x 25cm) or a Cellulose OD-H column (4.6mm x 20cm).

Synthesis of oxazaphospholidine *R*$_P$-3. In a dried and inert Schlenk tube, sulfonylated dervivative **1** (100 mg, 0.23 mmol) was dissolved into anhydrous dichloromethane (1 mL). *N*-Methylimidazole (41 mg, 0.50 mmol) was then added, and the mixture was cooled to -78°C. After 15 minutes of stirring, dichlorophenylphosphine oxide (49 mg, 0.25 mmol) was added dropwise, and the reaction mixture was stirred for 2 hours at -

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78°C, and then 1 hour at room temperature. Only the 31P NMR of the crude was recorded. 31P NMR (121 MHz, CDCl3), δ(ppm) = 28.7 (0.05P), 24.0 (0.95P). In the NMR tube, a crystal was formed and was isolated offering the possibility to have a X-ray structure of the derivative **3**.

General procedure for the cleavage of P-N bond with P(V)-strategy from sulfonylated derivatives 1 and 2. In a dried and inert Schlenk tube, sulfonylated derivative **1** or **2** (100 mg, 0.23 mmol) and anhydrous dichloromethane (1 mL) were placed. After the addition of of *N*-Methylimidazole (41 mg, 0.50 mmol), the mixture was cooled down to -78°C. After 15 minutes of stirring, dichlorophenylphosphine oxide (49 mg, 0.25 mmol) was added dropwise, and the reaction mixture was stirred for 2 hours at -78°C, and then 1 hour at room temperature. The mixture was cooled down to -78°C, and the Grignard reagent *o*-AnMgBr 1M in THF (800 µL, 0.80 mmol) or MeMgCl 3M in THF (270 µL, 0.81 mmol) was slowly added. The reaction mixture was stirred for 2 hours at -78°C, and allowed to reach room temperature overnight. The reaction was diluted with dichloromethane (5 mL), quenched with an aqueous saturated ammonium chloride solution (5 mL). The organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The diastereoisomeric ratio reaction was determined thanks the ^{31}P NMR analysis of the obtained crude. Purification was performed by column chromatography on silica gel using a mixture of Cyclohexane / EtOAc (7/3) as eluent.

Methyl 3-O-[(S)-(2-methoxyphenyl)phenylphosphinate]-4,6-O-benzylidene-2-deoxy-2-N-p-toluenesulfonamido-α-D-glucopyranoside *S*$_P$-5. 2 diastereoisomers were detected by ^{31}P NMR indicating a d.r. of reaction of 90%, ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 37.1 (0.95P), 35.9 (0.05P). After purification by column chromatography on silica gel followed by recristallisation using a mixture of Heptane / *i*-Propanol (85 / 15) as solvent, a yellow solid was isolated in 83% yield, m.p.= 232°C. Rf = 0.35 (Cyclohexane / EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$), δ(ppm) = 8.00 (ddd, *J* = 13.7, 7.5, 1.7 Hz, 1H), 7.71 – 7.55 (m, 5H), 7.53 – 7.46 (m, 1H), 7.39 – 7.21 (m, 5H), 7.06 (br d, *J* = 8.0 Hz, 2H), 6.90 (dddd, *J* = 7.5, 7.5, 2.7, 0.7 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.17 (dd, *J* = 8.1, 6.4 Hz, 1H), 5.36 (s, 1H), 4.99 (d, *J* = 3.4 Hz, 1H), 4.61 (ddd, *J* = 9.6, 9.6, 9.6 Hz, 1H), 4.24 – 4.10 (m, 1H), 3.79 – 3.54 (m, 3H), 3.36 (s, 3H), 3.32 (ddd, *J* = 10.1, 3.6, 3.6 Hz, 1H), 2.97 (s, 3H), 2.23 (s, 3H); ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 37.1; ^{13}C NMR (75 MHz, $CDCl_3$), δ(ppm) = 160.7 (d, *J* = 4.4 Hz, C), 142.5 (C), 137.0 (C), 136.8 (C), 135.1 (d, *J* = 7.0 Hz, CH), 134.7 (d, *J* = 1.8 Hz, CH), 131.7 (d, *J* = 3.0 Hz, CH), 131.6 (d, *J* = 10.8 Hz, 2 x CH), 131.4 (d, *J* = 147.7 Hz, C), 129.3 (CH), 129.1 (2 x CH), 128.2 (2 x CH), 127.6 (d, *J* = 14.1 Hz, 2 x CH), 127.2 (2 x CH), 126.7 (2 x CH), 120.0 (d, *J* = 12.7 Hz, CH), 117.8 (d, *J* = 131.8 Hz, C), 111.2 (d, *J* = 7.9 Hz, CH), 102.3 (CH), 100.5 (CH), 80.2 (d, *J* = 4.8 Hz, CH), 71.0 (d, *J* = 5.9 Hz, CH), 69.0 (CH_2), 62.5 (CH), 57.3 (CH), 56.0 (CH_3), 54.2 (CH_3), 21.5 (CH_3). HRMS $[M+Na]^+$ $C_{34}H_{36}NNaO_9PS$ calcd 688.1741 found 688.1734. $[\alpha]^{25}_D$ = -30.8 (c = 0.22, $CHCl_3$).

Methyl 3-O-[(R)-methylphenylphosphinate]-4,6-O-benzylidene-2-deoxy-2-N-p-toluenesulfonamido-α-D-glucopyranoside *R*$_P$-6. 2 diastereoisomers were detected by ^{31}P NMR indicating a d.r. of reaction of 94%, ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 49.1 (0.03P), 48.2 (0.97P). After purification by column chromatography on silica gel followed by recristallisation using a mixture of Heptane / *i*-Propanol (85/15) as solvent, a yellow solid was isolated in 83% yield, m.p. = 109°C. Rf = 0.12 (Cyclohexane / EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$), δ(ppm) = 7.71 - 7.54 (m, 5H), 7.49 – 7.38 (m, 4H), 7.37 – 7.31 (m, 3H), 6.85 (d, J = 8.0 Hz, 2H), 6.52 (br d, J = 5.5 Hz, 1H), 5.53 (s, 1H), 4.84 (d, J = 3.4 Hz, 1H), 4.68 (ddd, J = 9.4, 9.4, 9.4 Hz, 1H), 4.29 (dd, J = 10.0, 4.5 Hz, 1H), 3.93 - 3.82 (m, 1H), 3.75 (dd, J = 10.0, 10.0 Hz, 1H), 3.64 (dd, J = 10.0, 9.3 Hz, 1H), 3.36 (s, 3H), 3.36 - 3.27 (m, 1H), 2.21 (s, 3H), 1.59 (d, J = 14.1 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 48.2; ^{13}C NMR (75 MHz, $CDCl_3$), δ(ppm) = 142.8 (C), 137.0 (C), 136.9 (C), 132.4 (d, J = 2.8 Hz, CH), 131.1 (d, J = 136.9 Hz), 130.7 (d, J = 10.4 Hz, 2 x CH),129.2 (3 x CH), 128.5 (d, J = 13.3 Hz, 2 x CH), 128.3 (2 x CH), 127.1 (2 x CH), 126.0 (2 x CH), 101.8 (CH), 100.2 (CH), 80.1 (d, J = 3.6 Hz, CH), 70.8 (d, J = 5.9 Hz, CH), 68.9 (CH_2), 62.6 (CH), 57.1 (CH), 56.0 (CH_3), 21.4 (CH_3), 15.9 (d, J = 94.5 Hz, CH_3). HRMS $[M+Na]^+$ $C_{28}H_{32}NNaO_8PS$ calcd 596.1478 found 596.1467; HRMS $[M+H]^+$ $C_{28}H_{33}NO_8PS$ calcd 574.1659 found 574.1647. $[\alpha]^{25}_D$ = - 6.1 (c = 0.805, $CHCl_3$).

Methyl 3-O-[(2-methoxyphenyl)phenylphosphinate]-4,6-O-benzylidene-2-deoxy-2-N-p-toluenesulfonamido-β-D-glucopyranoside 7. 2 diastereoisomers were detected by ^{31}P NMR indicating a d.r. of reaction of 14%, ^{31}P NMR (121 MHz, $CDCl_3$), δ (ppm) = 38.0 (0.57P), 36.2 (0.43P).

General procedure for the cleavage of P-N bond with P(III)-strategy from sulfonylated derivative 1. In a dried and inert schlenk, sulfonylated derivative **1** (100 mg, 0.23 mmol) and anhydrous dichloromethane (1 mL) were placed. After the addition of *N*-Methylimidazole (41 mg, 0.50 mmol) and dichlorophenylphosphine (45 µg, 0.25 mmol), the mixture was stirred for 30 minutes at room temperature, before to cooling down to -78°C. *o*-AnMgBr 1M in THF (800 µL, 0.80 mmol) was then slowly added. The reaction was carried out overnight, and then diluted with dichloromethane (5 mL), quenched with saturated ammonium chloride solution (5 mL). The organic phase was washed successively with hydrogen peroxide 12% solution (5 mL), saturated thiosulfate solution (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, and concentrated. The diastereoisomeric ratio reaction was determined thanks to ^{31}P NMR analysis of the obtained crude. Purification was performed by column chromatography on silica gel using a mixture of Cyclohexane / EtOAc (7/3) as eluent.

Methyl 3-O-[(R)-(2-methoxyphenyl)phenylphosphinate]-4,6-O-benzylidene-2-deoxy-2-N-p-toluenesulfonamido-α-D-glucopyranoside *R*$_P$-5. Only 1 diastereoisomer was detected by ^{31}P NMR indicating a d.r. of reaction over 99%. After purification, a yellow solid was isolated in 59% yield, m.p.= 225-227°C. Rf = 0.28 (Cyclohexane / EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$), δ(ppm) = 7.79 – 7.72 (m, 3H), 7.68 (ddd, J = 13.2, 8.2, 1.2 Hz, 2H), 7.54 – 7.46 (m, 2H), 7.41 – 7.22 (m, 6H), 7.00 – 6.90 (m, 5H), 6.82 (dd, *J* = 8.2, 6.4 Hz, 1H), 5.42 (s, 1H), 4.98 (d,

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J = 3.3 Hz, 1H), 4.55 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 1H), 4.21 (dd, *J* = 9.2, 3.4 Hz, 1H), 3.77 – 3.61 (m, 3H), 3.55 (s, 3H), 3.35 – 3.30 (m, 4H), 2.26 (s, 3H); ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 35.9; ^{13}C NMR (75 MHz, $CDCl_3$), δ(ppm) = 161.3 (d, *J* = 4.9 Hz, C), 142.8 (C), 137.1 (C), 137.0 (C), 134.5 (d, *J* = 1.7 Hz, CH), 133.7 (d, *J* = 5.7 Hz, CH), 133.0 (d, *J* = 11.2 Hz, 2 x CH), 132.1 (d, *J* = 2.9 Hz, CH), 130.2 (d, *J* = 136.7 Hz, C), 129.4 (2 x CH), 129.4 (CH), 128.3 (2 x CH), 127.7 (d, *J* = 13.5 Hz, 2 x CH), 127.6 (2 x CH), 126.7 (2 x CH), 120.5 (d, *J* = 12.5 Hz, CH), 119.0 (d, *J* = 143.4 Hz, C), 111.6 (d, *J* = 8.3 Hz, CH), 102.3 (CH), 100.6 (CH), 80.7 (d, *J* = 5.2 Hz, CH), 71.4 (d, *J* = 5.8 Hz, CH), 69.1 (CH_2), 62.6 (CH), 57.7 (CH), 56.1 (CH_3), 55.8 (CH_3), 21.7 (s, CH_3). HRMS $[M+H]^+$ $C_{34}H_{37}NO_9PS$ calcd 666.1921 found 666.1927. $[\alpha]^{25}_D$ = +16.9 (c = 1.05, $CHCl_3$).

General procedure for the cleavage of P-O bond from P(V)- or P(III)-strategy. In a dried and inert schlenk, the appropriate phosphinate (0.14 mmol) was placed. The commercially available organomagnesium (6.0 eq) was then added dropwise. The resulting mixture was stirred for 15 minutes and the temperature was then increased to 40°C. The reaction was carried out overnight. After completion of the reaction, the reaction mixture was diluted with dichloromethane (5 mL), quenched with saturated ammonium chloride (5 mL). After extraction, the organic phase was dried over Na_2SO_4, and concentrated. Purification was performed by column chromatography on silica gel using first dichloromethane / EtOAc (9/1) and then EtOAc / MeOH (95/5) as eluent. D-Glucosamine derivative **1** was recovered without loss of the enantiomeric purity, and could be used again for the synthesis of the phosphinate derivatives with the same diastereoselectivity (based on ^{31}P NMR).

Characterization of enriched (*R*)- and (*S*)-*o*-anisylmethylphenylphosphine oxide *R*$_P$- and *S*$_P$-8. Colorless oil in 75% yield with 90% e.e. from ***S*$_P$-5** [P(V)-strategy], in 84% yield with 98% e.e. from ***R*$_P$-6** [P(V)-strategy], and in 75% yield with 96% e.e. from ***R*$_P$-5** [P(III)-strategy]. Rf = 0.15 (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$), δ(ppm) = 7.96 (ddd, *J* = 13.1, 7.5, 1.5 Hz, 1H), 7.73 (ddd, *J* = 12.4, 7.9, 1.3 Hz, 2H), 7.54 – 7.34 (m, 4H), 7.09 (dddd, *J* = 7.5, 7.5, 1.8, 0.9 Hz, 1H), 6.88 (dd, *J* = 8.2, 5.4 Hz, 1H), 3.72 (s, 3H), 2.07 (d, *J* = 14.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 28.6; ^{13}C NMR (75 MHz, $CDCl_3$), δ(ppm) = 160.0 (d, *J* = 4.2 Hz, C), 135.1 (d, *J* = 103.9 Hz, C), 134.1 (d, *J* = 4.2 Hz, CH), 134.0 (d, *J* = 5.9 Hz, CH), 131.4 (d, *J* = 2.7 Hz, CH), 130.4 (d, *J* = 10.1 Hz, 2 x CH), 128.3 (d, *J* = 12.1 Hz, 2 x CH), 121.6 (d, *J* = 100.0 Hz, C), 121.2 (d, *J* = 11.1 Hz, CH), 111.0 (d, *J* = 6.6 Hz, CH), 55.4 (CH_3), 16.3 (d, *J* = 75.3 Hz, CH_3). Chiral HPLC (Chiralpack AD Heptane/IPA 85/15 1 mL/min): *(R)*-enantiomer, R_t = 13.2 min, *(S)*-enantiomer, R_t = 17.7 min. The NMR and HPLC data are in agreement with the literature.[12,14]

Characterization of enriched (*S*)-*o*-anisylethylphenylphosphine oxide *S*$_P$-9. Colorless oil in 85% yield with 92% e.e. from ***S*$_P$-5** [P(V)-strategy]. Rf = 0.14 (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$), δ(ppm) = 8.00 (ddd, *J* = 12.7, 7.5, 1.8 Hz, 1H), 7.77 (ddd, *J* = 11.7, 7.9, 1.6 Hz, 2H), 7.47 – 7.30 (m, 4H), 7.04 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.82 (dd, *J* = 8.2, 5.1 Hz, 1H), 3.69 (s, 3H), 2.43 – 2.24 (m, 2H), 1.16 (dt, *J* = 18.2, 7.7 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 33.6; ^{13}C NMR (75 MHz, $CDCl_3$), δ(ppm) = 159.8 (d, *J* = 4.4 Hz, C), 134.7 (d, *J* = 5.2 Hz, CH), 134.0 (d, *J* = 99.6 Hz, C), 133.7 (d, *J* = 2.1 Hz, CH), 131.2 (d, *J* = 2.8 Hz, CH), 130.7 (d, *J* = 9.5 Hz, 2 x CH), 128.2 (d, *J* = 11.8 Hz, 2 x CH), 121.2 (d, *J* = 10.6 Hz, CH), 120.3 (d, *J* = 99.9 Hz, C), 110.7 (d, *J* = 6.6 Hz, CH), 55.2 (CH_3), 22.2 (d, *J* = 74.2 Hz, CH_2), 5.6 (d, *J* = 5.4 Hz, CH_3). Chiral HPLC (Chiralpack Heptane/IPA 85/15 1 mL/min): *(R)*-enantiomer, R_t = 12.2 min, *(S)*-enantiomer, R_t = 18.7 min. The NMR data are in agreement with the literature.[31]

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Characterization of enriched (*S*)-ethylmethylphenylphosphine oxide *S*$_P$-10. Colorless oil in 99% yield with 94% e.e. from ***R*$_P$-6** [P(V)-strategy]. Rf = 0.15 (AcOEt/MeOH 95/5). ^{1}H NMR (300 MHz, $CDCl_3$), δ(ppm) = 7.70 (ddd, *J* = 11.2, 7.6, 1.6 Hz, 2H), 7.57 – 7.40 (m, 3H), 2.07 – 1.77 (m, 2H), 1.68 (d, *J* = 12.7 Hz, 3H), 1.11 (dt, *J* = 17.4, 7.7 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 39.0; ^{13}C NMR (75 MHz, $CDCl_3$), δ(ppm) = 133.5 (d, *J* = 95.4 Hz, C), 131.6 (d, *J* = 2.7 Hz, CH), 130.1 (d, *J* = 9.1 Hz, 2 x CH), 128.6 (d, *J* = 11.4 Hz, 2 x CH), 24.7 (d, *J* = 71.3 Hz, CH_2), 15.4 (d, *J* = 69.5 Hz, CH_3), 5.7 (d, *J* = 5.0 Hz, CH_3). Chiral HPLC (Cellulose OD-H Heptane/IPA 95/5 1 mL/min): *(R)*-enantiomer, R_t = 12.6 min, *(S)*-enantiomer, R_t = 13.9 min. The NMR and HPLC data are in agreement with the literature.[12]

Characterization of enriched (*S*)-*i*-propylmethylphenylphosphine oxide *S*$_P$-11. Colorless oil in 34% yield with 90% e.e. from ***R*$_P$-6** [P(V)-strategy]. Rf = 0.17 (AcOEt/MeOH 95/5). ^{1}H NMR (300 MHz, $CDCl_3$), δ(ppm) = 7.75 – 7.63 (m, 2H), 7.57 – 7.42 (m, 3H), 2.10 – 1.90 (m, 1H), 1.69 (d, *J* = 12.4 Hz, 3H), 1.19 (dd, *J* = 16.3, 7.1 Hz, 3H), 1.06 (dd, *J* = 16.4, 7.2 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$), δ(ppm) = 43.3; ^{13}C NMR (75 MHz, $CDCl_3$), δ(ppm) = 132.6 (d, *J* = 92.8 Hz, C), 131.5 (d, *J* = 2.7 Hz, CH), 130.5 (d, *J* = 8.6 Hz, 2 x CH), 128.5 (d, *J* = 11.1 Hz, 2 x CH), 29.6 (d, *J* = 71.5 Hz, CH), 15.5 (d, *J* = 2.5 Hz, CH_3), 15.3 (d, *J* = 2.5 Hz, CH_3), 12.9 (d, *J* = 67.7 Hz, CH_3). Chiral HPLC (Cellulose OD-H Heptane/IPA 95/5 1 mL/min): *(R)*-enantiomer, R_t = 23.6 min, *(S)*-enantiomer, R_t = 28.3 min. The NMR and HPLC data are in agreement with the literature.[32]

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25 The diastereoselectivity of the cyclization step was evaluated by ^{31}P NMR: two signals at 28.7 and 24.0 ppm were observed in a 5:95 ratio respectively.

26 CCDC 1400048 and 1400046 references contain the supplementary crystallographic data for compounds ***R***$\boldsymbol{R_P}$**-3** and $\boldsymbol{S_P}$**-5**, respectively. These data can be obtained free of charge form the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

27 Some cleaved products possess the same configuration descriptor as the starting compounds but the spatial arrangement around the phosphorous atom differs.

28 In the course of the synthesis of phosphine oxide $\boldsymbol{S_P}$**-8**, glucopyranoside **1** could be recovered in 95 % yield during the purification by column chromatography on silica gel, without any significant modification of its optical properties (observed $[\alpha]^{25}_D$ = +36,0 (c = 0,97, $CHCl_3$), litt. $[\alpha]^{25}_D$ = +34,4 (c = 0,77, $CHCl_3$) – see Supp. Inf.).

29 The synthesis of $\boldsymbol{S_P}$**-5** using the recovered chiral auxiliary was performed in 82% yield with an excellent diastereoselectivity (>99%).

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