Phosphoramidite ligands based on simple 1,2-diols: Synthesis, use in Cu-catalyzed asymmetric additions, and achirotopic stereogenic phosphorus centers

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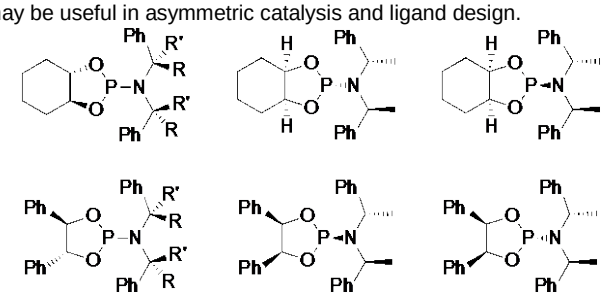
Abstract: Phosphoramidite ligands are widely used in catalysis and normally constructed from large C_2-symmetric diols such as BINOL or TADDOL. We report new ligands based on a set of simple diols that had been previously overlooked. Ligands based on (*S,S*)-*trans*-cyclohexanediol and (*R,R*)-(+)-1,2-diphenyl-1,2-ethanediol, in combination with both chiral and achiral amines, were tested in 3 different copper catalyzed asymmetric reactions and up to 89% ee was observed. A different ligand gave the best results in each reaction examined. Using *meso*-*cis*-cyclohexanediol and *meso*-*cis*-diphenyl-1,2-ethanediol with a chiral non-racemic amine gave diastereomeric ligands bearing achirotopic stereogenic phosphorus atoms which were characterized with the assistance of X-ray crystallography and VT NMR studies. This work provides a new set of ligands that may be useful in some asymmetric reactions when phosphoramidites based on BINOL and TADDOL are ineffective. We also identify a novel stereochemical feature of phosphoramidites that may be useful in asymmetric catalysis and ligand design.



Keywords: Phosphoramidite, ligands, copper catalysis, asymmetric catalysis, achirotopic stereogenic, phosphorus stereochemistry

Introduction

Phosphoramidite ligands are commonly used as the source of asymmetry in enantioselective catalysis. They have proven effective in combination with a broad range of metals including Ir, Rh, Pd, Ag, Au, Ni and Cu,[1] and are particularly popular in asymmetric conjugate addition,[2] allylic substitution[3–6] and hydrogenation reactions.[7,8] The modular nature of phosphoramidites, which are constructed from a diol-backbone and an amine, allows libraries that may be finely tuned for enantioselectivity in specific reactions, and has contributed to the extensive use of these ligands in modern chemistry.

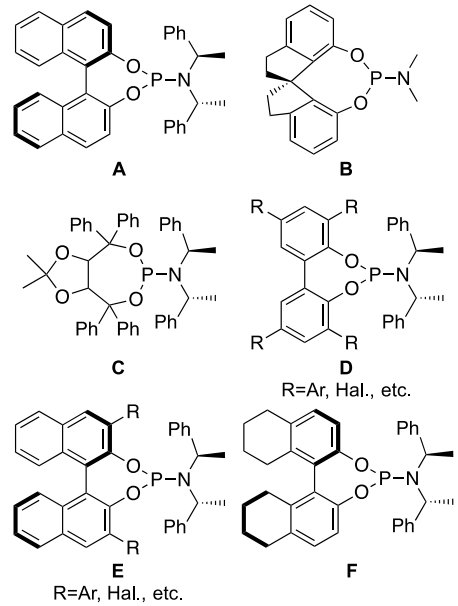


Figure 1. Commonly used phosphoramidite ligands: based on BINOL (A), 'spiro' (B), TADDOL (C), 'flexible' (D) and modified BINOL (E and F) backbones

In terms of the diol-backbone, most phosphoramidites use BINOL[9] (**A**) or a 'spiro' (**B**) or TADDOL[10] (**C**) diol which are powerful sources of asymmetry.[1] More flexible diols, such as the bis-phenol moiety seen in ligand **D**, where backbone asymmetry is induced by the amido-unit, are also effective in certain reactions.[11,12] Generally, BINOL-based phosphoramidites are the most widely used and many modified BINOLs, such as 3,3-disubstituted **E**[13] and hydrogenated **F**,[14] have been reported.

We note that phosphoramidite ligands based on simple diol backbones are almost unreported. To the best of our knowledge, the only relevant use of simple diols was by Gavrilov and co-workers who described combining chiral 1,2-diols with achiral amines to give ligands such as **G**, **H**, and **I** (Figure 2).[15,16]

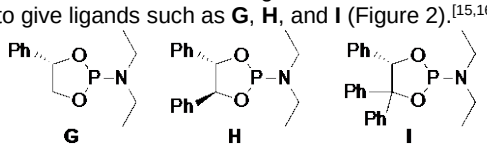


Figure 2. Previously reported phosphoramidites based on simple 1,2-diols.

Here, we describe a set of phosphoramidite ligands based on simple 1,2-diols and test these ligands in copper catalyzed asymmetric addition reactions. We first examined chiral (*S,S*)-*trans*-cyclohexanediol and (*R,R*)-(+)-1,2-diphenyl-1,2-ethanediol in combination with *bis*-(1-phenylethyl)amines to give **J**-**M**, where **J** + **K** (and **L** + **M**) are diastereomers. To obtain **N** and **O**, we used (*S,S*)-*trans*-cyclohexanediol and (*R,R*)-(+)-1,2-diphenyl-1,2-ethanediol in combination with an achiral amine.[17] Finally, using *meso cis*-cyclohexanediol and *meso cis*-diphenyl-1,2-ethanediol with a chiral non-racemic amine gave diastereomeric ligands **P** + **Q** and **R** + **S**, respectively, which bear achirotopic[18] stereogenic phosphorus atoms (*vida infra*).

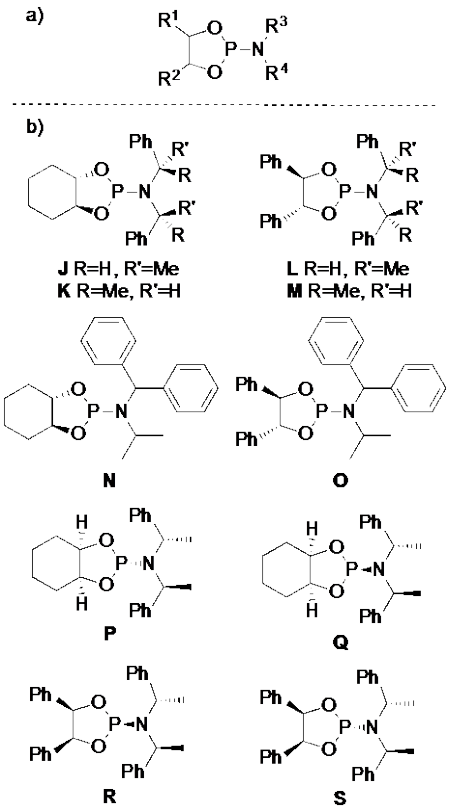
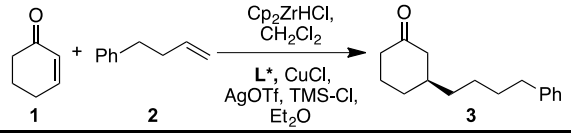


Figure 3. a) Generic phosphoramidite ligand made from a simple diol. b) New ligands reported here.

Results and Discussion

We decided to test the new ligands in copper catalyzed asymmetric addition reactions and first examined a hydrometallation – conjugate addition reaction.[19] Compound **3** was obtained in 91% ee using prototypical phosphoramidite **A** (Table 1, entry 1), which is far superior to all of the results obtained with ligands shown in Figure 3, where **J** gave the best result (56% ee, entry 2).

Table 1. 1,4-Conjugate addition of alkylzirconium reagents.

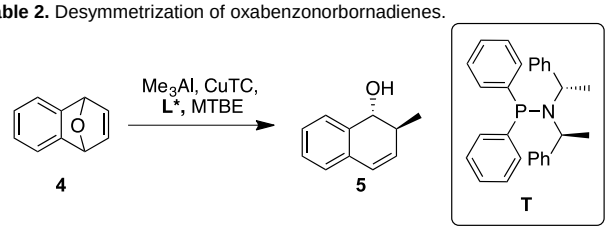


Entry	Ligand	Yield (%)[a]	e.e. (%)[b]
1	**A**	47	91
2	**J**	57	–56
3	**K**	65	–3
4	**L**	40	–37
5	**M**	18	9
6	**N**	39	–20
7	**O**	36	–27
8	**P+Q**	64	–19
9	**Q**	30	–14
10	**P**	36	–12
11	**R+S**	27	–15

[a] Isolated yield [b] Determined by HPLC on a chiral non-racemic stationary phase. Negative sign indicates opposite absolute stereochemistry shown in **3**.

The copper-catalyzed desymmetrization of bicyclic **4** with Me_3Al, was then examined (Table 2).[20] SimplePhos ligands (such as **T**) first described in 2007, are not phosphoramidites, but have obvious similarities – phosphinamines have aryl groups directly attached to the P-atom.[21] Using **T**, compound **5** can be obtained in 91% ee, but we were only able to achieve 83% ee (Table 2, entry 1) using **T** prepared in our laboratory. Pleasingly, all of new ligands examined showed high conversion and excellent *anti*:*syn* ratios. Using ligands **L** and **M**, (entries 4 and 5) which bear a diphenyl backbone, we obtained comparable enantioselectivity to using SimplePhos, with 86% ee and 79% ee observed. Ligand **O**, also bearing the diphenyl backbone, but with an achiral amine, gave the highest observed enantioselectivity (89% ee, entry 7).

Table 2. Desymmetrization of oxabenzonorbornadienes.



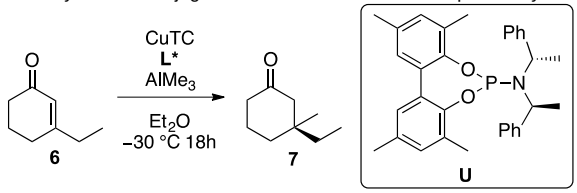
Entry	Ligand	Yield[a] (%)	*anti*:*syn*[b]	e.e. (%)[c]
1	**T**	96	97:3	83
2	**J**	79	99:1	17
3	**K**	93	98:2	–7
4	**L**	93	99:1	86
5	**M**	(84)	97:3	79
6	**N**	(98)	97:3	–8
7	**O**	75	97:3	89
8	**P+Q**	93	99:1	–19
9	**Q**	98	99:1	–18
10	**P**	66	97:3	7
11	**R+S**	99	98:2	Racemic
12	**S**	58	90:10	45

[a] Isolated yield of anti alcohols, Conversion (in parentheses) determined by ^{1}H NMR spectroscopy. [b] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c] Determined by HPLC on a chiral non-racemic stationary phase. Negative sign indicates opposite absolute stereochemistry to that shown in **5**.

The final reaction investigated was a 1,4-additon with Me_3Al to form quaternary centers. The synthesis of enantioenriched all carbon quaternary centers is still considered a synthetic challenge[22] and asymmetric conjugate addition can be highly effective in forming these motifs.[23]

Alexakis and co-workers developed the asymmetric addition of $AlMe_3$ to **6**.[24,25] Ligand **U** (94% ee) gave the best-reported results, and similar enantioselectivity was observed in our hands (92% ee, Table 3, entry 1). Isolated yields here are generally low because the product is highly volatile. The use of the phosphoramidites in Figure 3 was generally detrimental to enantioselectivity, with the notable exception of **M** (Table 3, entry 5, 81% ee). *Matched* / *mismatched* amine and diol stereochemistry is important here. While **M** gave 81% ee, diastereomeric **L** gave –40% ee (in favor of the opposite enantiomer), so that the amine portion of the ligand appears to determine the absolute stereochemistry. The idea that the amine controls the absolute configuration is supported by comparing diastereomeric phosphoramidites **J** and **K** (Table 3, entries 2 and 3), and the lack of fixed stereochemistry in the backbone of **U**.

Table 3. Asymmetric conjugate addition to form all carbon quaternary centers.



Entry	Ligand	Yield[a] (%)	e.e. (%)[b]
1	**U**	41	92
2	**J**	9	–52
3	**K**	29	48
4	**L**	27	–40
5	**M**	21	81
6	**O**	27	33

7	**P+Q**[c]	85	73
8	**Q**	23	–74
9	**R+S**	32	–48
10	**S**	83	–64

[a] Isolated yield, the product is highly volatile. [b] Determined by GC on a chiral non-racemic stationary phase. [c] The opposite enantiomer of the ligand mixture, derived from the *R*,*R*-amine, was used in this example.

Forming all-carbon quaternary centers via asymmetric catalysis is important because of their presence in natural products.[22,23,26] A prominent example is asymmetric addition of Me_3Al to enone **8** which sets the absolute stereochemistry in the synthesis of taxadiene by Baran and co-workers.[27,28] We examined addition to **8** without variation of Alexakis's conditions, but using ligand **M**. We observed 46% yield and a respectable 72% ee and note this would likely improve if reaction optimization took place.

Figure 4. Quaternary center formation from Baran's trisubstituted enone **8**.

Phosphoramidites based on *meso cis*-1,2-cyclohexanediol (**P** and **Q**) and *meso* 1,2-diphenyl-1,2-ethanediol (**R** and **S**) deserve detailed discussion. The vast majority of phosphoramidite ligands do not posses stereochemistry about the phosphorus atom, although P-chiral phosphoramidites with tetrahedral asymmetry have been synthesized from non-C_2-symmetrical diols.[15,29,30] To the best of our knowledge, there are no reports of phosphoramidites with achirotopic stereogenic P-atoms.

Ligand synthesis from *meso-cis*-cyclohexanediol and a chiral non-racemic amine gave a mixture of two diastereomeric ligands as readily observed by ^{31}P NMR spectroscopy on material purified by flash column chromatography. The diastereoisomers can be separated by HPLC using a chiral non-racemic stationary phase (Figure 6a). Semi-preparative conditions (Chiralpak® IC; hexane:^{i}PrOH 99:1; 1 ml.min^{-1}, λ= 210 nm, t_R = 4.29 min (**P**, minor), t_R = 5.96 min (**Q**, major)) allowed us to isolate 104 mg of **Q** and 46 mg of **P** over about 9 hours. Heating either **P** or **Q** at >70 ºC, or any other conditions we examined, does not interconvert **P** and **Q**.

X-ray crystallographic structure analysis revealed that **P** and **Q** differ in their phosphorus stereochemistry, where the amine group is either in a position that could be described as 'equatorial' or 'exo' in **P**, or more 'axial' or 'endo' as in **Q** (Figure 5b). In minor isomer **P**, which has an 'equatorial' amine, the phosphorous lone pair is in an axial-like position, and *vice-versa*.

In each of the X-ray crystallographic structures obtained, only a single cyclohexane conformer was observed, so that the phosphorus has 4 unique substituents and the P-atoms appear to be tetrahedral asymmetric. Presumably, these 3D structures correspond to the lowest energy conformation for each ligand, but packing forces may favor different conformations in the solid state than in solution.[31]

In solution, as observed by ^1H NMR spectroscopy, in both the 'axial' (**Q**) and 'equatorial' (**P**) compounds, two additional isomers are present. Based on the VT NMR studies described below (Figure 6), we attribute these isomers to two chair conformations (Figure 7a) that rapidly interconvert in solution at room temperature. The isomers are present in roughly equal ratios, so that one conformer does not appear favored over the other.

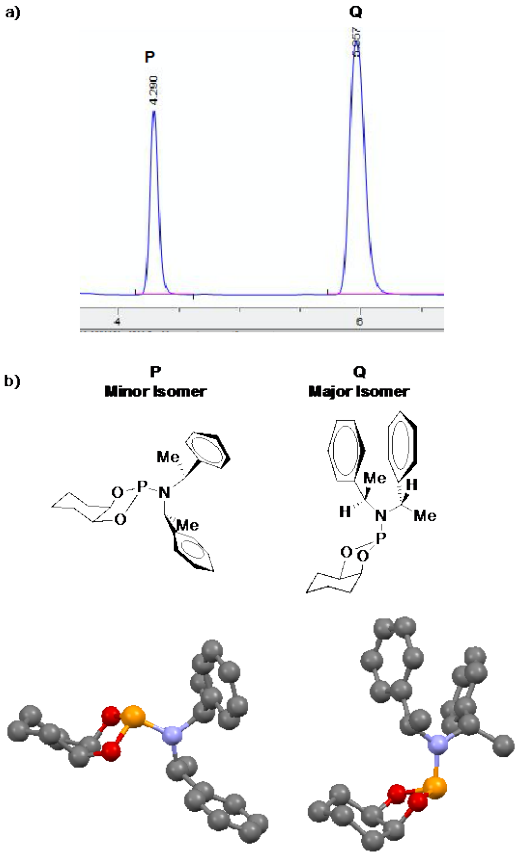


Figure 5. a) HPLC [Chiralpak® IC; hexane:^{i}PrOH 99:1; 1 ml.min^{-1}, λ= 210 nm, t_R = 4.29 min (minor), t_R = 5.96 min (major)] trace showing separation of **P** and **Q** .b) X-ray crystallographic structures of **P** and **Q.** CCDC-1472705-1472707 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Upon cooling 'axial' **Q**, extensive broadening of ^1H NMR spectroscopy signals for the 2 protons at ~3.4 ppm (Figure 6a) is observed. Variable temperature NMR experiments allowed us to quantify the energy associated with the isomerization of **Q**, and it is roughly consistent with a cyclohexane ring flip.

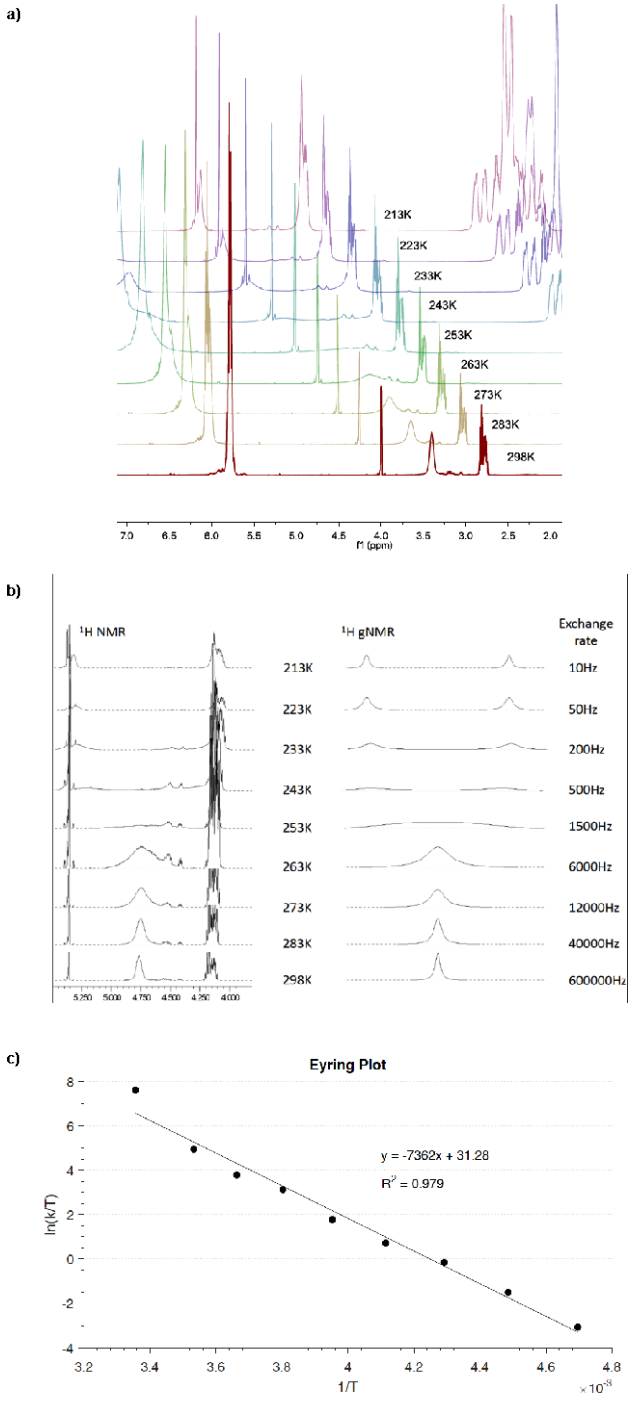


Figure 6. a) Variable temperature NMR experiments on ligand Q. Upon cooling to 213K, the ^{1}H NMR spectroscopy signals associated with Ha and H_e are well resolved b) Simulated spectra using gNMR. c) Eyring plot to determine $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$.

Spectra were recorded on a Bruker AVIII HD 500 MHz spectrometer equipped with a VT probe, with a temperature range of –60 °C to 25 °C, using d_2-dichloromethane as solvent. Using the gNMR modelling package to simulate the spectra (see Figure 6b) allowed us to estimate rate constants (k) for exchange at each temperature. k values obtained by the gNMR package have been previously estimated to have a 10% error.[32] These rate constants, k, were used to construct an Eyring plot (Figure 6c), from which $\Delta H^{\neq}$ (61.2 KJ mol^{-1}) and $\Delta S^{\neq}$ (62.5 J K^{-1} mol^{-1}) were obtained. We note that this $\Delta S^{\neq}$ value is relatively high for a conformational process;[33] the discrepancy may be due to our VT NMR which has an error of ±2 ºC. Nevertheless, these values support chair isomerization, and inserting the values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ into the Gibbs free energy equation ($\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$) enabled the barrier to isomerization ($\Delta G^{\neq}$ = 42.6 KJ mol^{-1}) to be calculated at room temperature (298 K), consistent with the modeled isomerization rate of ~600,000 s^{-1}.

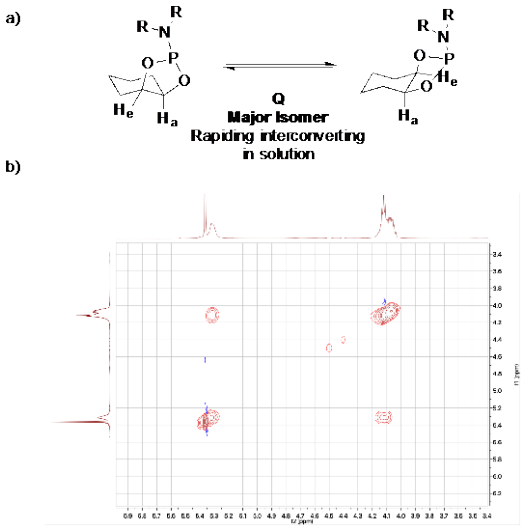


Figure 7. a) The two chair conformations of Q rapidly interconvert in solution at room temperature. b) NOSEY NMR experiments carried out at 213K show that H_a and H_e still interconvert on the NMR timescale at this temperature.

The P-stereochemistry of **Q** is fixed in the solid state so that the P-atom has tetrahedral asymmetry and a single isomer is observed. In solution, at room temperature, the two oxygen substituents appear to rapidly interconvert by a cyclohexane ring flip (see Figure 7a) at ~6x10^5 S^{-1}. EXSY NMR shows rapid exchange on the NMR timescale even at 213 K (Figure 7b). A consequence of these solution dynamics is that the P-atoms stereochemistry rapidly inverts from *r-* to *s-*. Atropisomers are often defined as conformers that have a half life of >1000 seconds at room temperature[34,35] providing guidance as to how to deal with rapidly equilibrating isomers, and suggesting these phosphorus atoms should not be considered chirotopic.

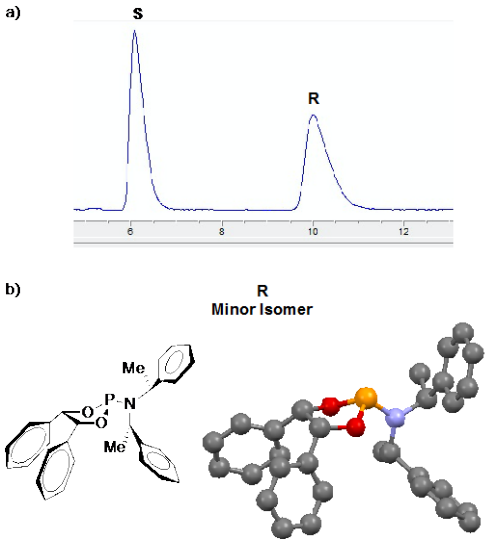


Figure 8. a) HPLC [Chiralpak® IA; hexane:^{i}PrOH 99:1; 1 ml.min^{-1}, λ= 210 nm, t_R = 6.07 min (major), t_R = 9.99 min (minor)] showing separation of **S** and **R.** b) X-ray crystallographic structure of **R.**

The *relative* stereochemistry of **P** and **Q** needs to be addressed. The **P** and **Q** isomeric pair differ according to P-stereochemistry, similar to the stereochemical features of double bonds (cis-trans), cyclohexane ring substituents (axial-equatorial) or bridged systems (endo-exo). As the P-atoms differ in stereochemistry but are not (in solution) chirotopic, the centers are best described as achirotopic stereogenic.[36] As the best

descriptors for the isomeric pairs seen here has not yet been established, we suggest (arbitrarily), 'axial' and 'equatorial'.

Conclusion

We have described a set of phosphoramidite ligands based on simple diols and tested them in catalytic asymmetric C-C bond forming reactions. In the case of *meso*-diols we obtained mixtures of P-isomeric ligands. In a 1,4-conjugate addition reaction, best accomplished using BINOL based phosphoramidites, the new ligands were ineffective. However, good results were obtained in two different reactions that require less sterically demanding monodentate P-ligands. Comparable ee's with those previously reported (up to 89%) for the addition of Me_3Al in ring opening desymmetrization were achieved. We anticipate that the ligands reported here might be useful in asymmetric reactions where BINOL and TADDOL based phosphoramidites are unable to provide high levels of asymmetry.

Experimental Procedures

*General procedure for the synthesis of ligands **J** – **S**:* Freshly distilled PCl_3 (1.0 eq.) was added dropwise over about 1 min to a stirred and cooled (0 °C) solution of Et_3N (8.0 eq.) in CH_2Cl_2 under an argon atmosphere. (*S*)-*Bis*((*S*)-1-phenylethyl)amine (or (*R*)-*Bis*((*R*)-1-phenylethyl)amine, according to Figure 3.) (1.0 eq.) in CH_2Cl_2 was added to the cooled reaction mixture before stirring was continued for 2 hours at room temperature. The reaction mixture was then cooled to 0 °C and the diol (1.0 eq.) was added and stirring was then continued at room temperature overnight. The reaction mixture was concentrated in vacuo. The crude product was taken up in toluene and filtered over a short pad of alumina, washing with more toluene. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (Alumina, 100% toluene) to give the pure ligand.

(3aS,7aS)−N,N−bis((S)−1−phenylethyl)hexahydrobenzo[d][1,3,2]dioxaphosphol−2−amine (J): White solid (17% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.15 – 7.04 (m, 10H), 4.55 – 4.46 (m, 2H), 3.64 (ddd, J = 12.0, 9.0, 3.8, 1H), 3.45 (ddd, J = 12.0, 9.0, 3.8, 1H), 2.24 (ddt, J = 12.3, 9.0, 3.4, 2H), 1.86 – 1.76 (m, 2H), 1.67 (d, J = 7.1, 6H), 1.62 – 1.53 (m, 1H), 1.44 – 1.23 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.4, 143.4, 128.0, 128.0, 127.9, 126.6, 80.7, 78.9, 53.8, 53.7, 30.9 (d, J=6.2), 30.2 (d, J = 5.0), 24.2 (d, J=16.6), 22.7 (d, J = 10.0). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 144.70. $[\alpha]^{25}_{589}$ = –193.6 (c=1.0 in $CHCl_3$). HRMS (CI with ammonia as the reagent gas) m/z calcd. for $C_{22}H_{29}NO_2P$ $[M+H]^+$: 370.1930, found: 370.1950. IR (ATR) ν (cm^{-1}, $CHCl_3$): 696, 766, 1029, 1097, 2943, 3025.

(3aS,7aS)−N,N−bis((R)−1−phenylethyl)hexahydrobenzo[d][1,3,2]dioxaphosphol−2−amine (K): White crystalline solid (17% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 – 7.03 (m, 10H), 4.65 – 4.54 (m, 2H), 3.54 – 3.37 (m, 2H), 2.31 – 2.19 (m, 2H), 1.87 – 1.78 (m, 2H), 1.71 (d, *J* = 7.2, 6H), 1.68 – 1.59 (m, 1H), 1.49 – 1.27 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.3, 127.9, 127.9, 127.9, 126.6, 81.1, 78.5, 78.4, 52.8, 52.7, 30.9 (d, *J* = 5.5), 30.1 (d, *J* = 4.7), 24.3, 24.1, 22.5 (d, *J* = 11.3). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 142.66. $[\alpha]^{25}_{589}$ = +220.0 (c=1.0 in $CHCl_3$). HRMS (CI with methane as the reagent gas) *m/z* calcd. for $C_{22}H_{29}NO_2P$ $[M+H]^+$: 370.1930, found: 370.1934. IR (ATR) ν (cm^{-1}, $CHCl_3$): 696, 765, 1030, 1449, 2938, 3028.

(4R,5R)−4,5−Diphenyl−N,N−bis((S)−1−phenylethyl)−1,3,2−dioxaphospholan−2−amine (L): Foamy white solid (62% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.3 (s, 1H), 7.2 – 7.1 (m, 11H), 7.1 – 7.0 (m, 13H), 4.8 (s, 2H), 4.7 (t, *J* = 8.3, 2H), 1.7 (d, *J* = 7.1, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.0, 137.8 (d, *J* = 8.0), 136.1 (d, *J* = 8.0), 128.5 (d, *J* = 6.1), 127.8, 127.2, 126.7 (d, *J* = 16.0), 84.9, 82.6 (d, *J* = 5.8), 52.6, 52.5, 22.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 148.4. $[\alpha]^{25}_{589}$ = –188.6 (c=1.0 in $CHCl_3$) HRMS (ESI) *m/z* calcd for $C_{30}H_{31}NO_2P$ $[M+H]^+$: 468.2087, found: 468.2088. IR (ATR) ν (cm^{-1}, $CHCl_3$): 697, 782, 996, 1124, 1204, 1451, 1495, 2971, 3030.

(4*R*,5*R*)−4,5−diphenyl−*N*,*N*−bis((*R*)−1−phenylethyl)−1,3,2−dioxaphospholan−2−amine (M): Foamy white solid (36% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.4 – 7.3 (m, 6H), 7.2 (ddt, *J* = 7.3, 5.3, 2.6, 4H), 7.2 – 7.1 (m, 10H), 5.0 (d, *J* = 8.7, 1H), 4.9 (d, *J* = 8.7, 1H), 4.8 – 4.7 (m, 2H), 1.8 (d, *J* = 7.1, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.0, 138.1 (d, *J* = 8.0), 136.5 (d, *J* = 5.0), 128.5 (d, *J* = 7.3), 128.4, 128.0 – 127.7 (m), 127.4, 126.6, 126.4, 84.6 (d, *J* = 4.1), 82.9 (d, *J* = 6.3), 53.1, 53.0, 22.7. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 149.4. $[\alpha]^{25}_{589}$ = +191.1 (c=1.0 in $CHCl_3$) HRMS (CI with methane as the reagent gas) *m/z* calcd. for $C_{30}H_{31}NO_2P$ $[M+H]^+$: 468.2087, found: 468.2093. IR (ATR) ν (cm^{-1}, $CHCl_3$): 697, 1008, 1205, 1305, 2841, 3030.

(3a*S*,7a*S*)−*N*−benzhydryl−*N*−isopropylhexahydrobenzo[*d*][1,3,2]dioxaphosphol−2−amine (N): White crystalline solid (14% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.4 – 7.3 (m, 8H), 7.3 – 7.2 (m, 2H), 5.8 (d, J = 12.2, 1H), 3.8 (hept, J = 6.7, 1H), 3.5 – 3.4 (m, 1H), 3.4 – 3.3 (m, 1H), 2.3 – 2.2 (m, 1H), 2.2 – 2.1 (m, 1H), 1.9 – 1.7 (m, 2H), 1.7 – 1.5 (m, 1H), 1.4 – 1.3 (m, 3H), 1.2 (d, J = 6.8, 3H), 1.0 (d, J = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 129.3, 129.2, 129.0, 129.0, 128.3, 126.9, 126.9, 81.0 (d, *J*=2.5), 78.5 (d, *J*=6.3), 61.0 (d, *J* = 16.2), 47.1 (d, *J* = 5 .4), 30.8, 30.8, 30.1, 30.1, 24.2, 24.1, 24.1, 24.1, 24.0, 24.0. ^{31}P NMR (162 MHz, $CDCl_3$) δ 145.05. $[\alpha]^{25}_{589}$ = +13.3 (c=1.0 in $CHCl_3$) HRMS (CI with methane as the reagent gas) *m/z* calcd. for $C_{22}H_{29}NO_2P$ $[M+H]^+$: 370.1930, found: 370.1939. IR (ATR) ν (cm^{-1}, $CHCl_3$): 698, 775, 1018, 1200, 1307, 2937, 3027.

(4*R*,5*R*)−*N*−benzhydryl−*N*−isopropyl−4,5−diphenyl−1,3,2−dioxaphospholan−2−amine (O): White crystalline solid (54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.4 – 7.3 (m, 12H), 7.3 – 7.2 (m, 5H), 7.2 – 7.2 (m, 3H), 7.1 – 7.0 (m, 2H), 5.9 (d, *J* = 13.3, 1H), 4.9 – 4.8 (m, 2H), 4.1 (h, *J* = 6.6, 1H), 1.4 (d, *J* = 6.7, 3H), 1.2 (d, *J* = 6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.4 (d, *J* = 4.3), 143.2 (d, *J* = 3.6), 138.1 (d, *J* = 8.0), 136.7 (d, *J* = 4.5), 129.1 (d, *J* = 3.1), 128.8 (d, *J* = 3.4), 128.4 (d, *J* = 4.8), 128.4, 128.3 (d, *J* = 4.8), 128.2, 127.4, 126.9 (d, *J* = 8.7), 126.3, 84.6 (d, *J* = 4.6), 83.1 (d, *J* = 6.3), 60.6 (d, *J* = 17.5), 46.8 (d, *J* = 3.5), 23.8. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 151.5. $[\alpha]^{25}_{589}$ = –5.0 (c=1.0 in $CHCl_3$). HRMS (ESI) *m/z* calcd for $C_{30}H_{31}NO_2P$ $[M+H]^+$: 468.2087, found: 468.2085. IR (ATR) ν (cm^{-1}, $CHCl_3$): 698, 790, 1001, 1159, 1453, 2969, 3030.

(3a*R*,7a*S*)*N*,*N*−bis((*S*)−1−phenylethyl)hexahydrobenzo[*d*][1,3,2]dioxaphosphol−2−amine (P + Q): The two isomers were separated by chiral preparative HPLC [Chiralpak® IC; hexane:^{i}PrOH 99:1; 1 ml.min^{-1}, λ= 210 nm, t_R = 4.29 min (minor), t_R = 5.96 min (major)]. **Minor Isomer (P):** White solid (6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.01 (m, 10H), 4.56 – 4.43 (m, 3H), 4.37 (dt, *J* = 4.8, 2.4 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.93 – 1.70 (m, 3H), 1.67 (d, *J* = 7.2 Hz, 6H), 1.63 – 1.56 (m, 1H), 1.55 – 1.47 (m, 1H), 1.35 (ddt, *J* = 10.7, 7.1, 3.7 Hz, 1H), 1.28 – 1.17 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 127.9, 127.9, 127.9, 126.5, 74.7 (d, *J* = 6.9), 73.6 (d, *J* = 7.1), 52.9, 52.8, 29.7 (d, *J* = 3.7), 29.4 (d, *J* = 5.3), 22.6, 22.5, 21.6, 20.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ 143.82. $[\alpha]^{25}_{589}$ = –139.0 (c=1.0 in $CHCl_3$). HRMS (GCMS with ammonia as the reagent gas) *m/z* calcd. for $C_{22}H_{28}NO_2P$ $[M+H]^+$: 370.1930, found: 370.1934. IR (ATR) ν (cm^{-1}, $CHCl_3$): 698, 755, 986, 1125, 1449, 2935

Major Isomer (Q): White solid (104 mg, 13% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.03 (m, 10H), 4.72 (s, 2H), 4.20 – 4.07 (m, 2H), 1.95 (dt, *J* = 21.2, 5.1 Hz, 2H), 1.86 (dq, *J* = 11.8, 4.3 Hz, 2H), 1.70 (d, *J* = 7.2 Hz, 6H), 1.63 – 1.51 (m, 2H), 1.42 – 1.29 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.4, 128.0, 128.0, 127.9, 126.6, 71.9, 71.8, 52.1, 52.0, 30.1 (d, *J* = 2.2), 30.1 (d, *J* = 3.1), 22.5, 21.8, 21.4. ^{31}P NMR (162 MHz, Chloroform-*d*) δ 150.25. $[\alpha]^{25}_{589}$ = –234.5 (c=1.0 in $CHCl_3$). HRMS (CI with methane as the reagent gas) *m/z* calcd. for $C_{22}H_{28}NO_2P$ $[M+H]^+$: 370.1930, found: 370.1940. IR (ATR) ν (cm^{-1}, $CHCl_3$): 698, 770, 989, 1126, 1450, 2935.

(4*S*,5*R*)−4,5−diphenyl−*N*,*N*−bis((*S*)−1−phenylethyl)−1,3,2−dioxaphospholan−2−amine (R + S): The two isomers were separated by chiral preparative HPLC [Chiralpak® IA; hexane:^{i}PrOH 99:1; 1 ml.min^{-1}, λ= 210 nm, t_R = 6.07 min (major), t_R = 9.99 min (minor)]. **Minor Isomer (R):** White solid (2% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.07 (m, 12H), 7.09 – 7.00 (m, 8H), 5.57 – 5.48 (m, 2H), 4.85 (s, 2H), 1.77 (d, *J* = 7.1 Hz,

6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 138.6, 138.1, 138.1, 128.0, 128.0, 127.9, 127.7, 127.5, 127.5, 127.3, 127.2, 126.7, 77.7 (d, *J* = 5.3), 77.4, 52.0, 51.9, 22.8, 22.7. ^{31}P NMR (162 MHz, $CDCl_3$) δ 149.02. $[\alpha]^{25}_{589}$ = –292.8(c=1.0 in $CHCl_3$). HRMS (CI with ammonia as the reagent gas) *m/z* calcd. for $C_{30}H_{30}NO_2P$ $[M+H]^+$: 468.2087, found: 468.2091. IR (ATR) ν (cm^{-1}, $CHCl_3$): 697, 783, 1010, 1451, 2971, 3029.

Major Isomer (S): White solid (8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.09 (m, 10H), 7.09 – 7.03 (m, 6H), 6.99 – 6.90 (m, 4H), 5.83 (dd, *J* = 6.5, 4.0 Hz, 1H), 5.63 (dd, *J* = 6.5, 1.8 Hz, 1H), 4.66 (dq, *J* = 9.5, 7.2 Hz, 2H), 1.78 (d, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 – 143.1 (m), 128.0, 128.0, 127.8, 127.8, 127.5 – 127.5 (m), 127.1, 127.0, 127.0 – 126.9 (m), 126.7, 82.8 (d, *J* = 8.7), 81.8 (d, *J* = 8.3), 53.4, 53.3, 22.7, 22.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ 145.81. $[\alpha]^{25}_{589}$ = –152.1 (c=1.0 in $CHCl_3$). HRMS (CI with ammonia as the reagent gas) *m/z* calcd. for $C_{30}H_{30}NO_2P$ $[M+H]^+$: 468.2087, found: 468.2078. IR (ATR) ν (cm^{-1}, $CHCl_3$): 698, 778, 1008, 1452, 2971, 3030.

Full experimental procedures and spectra can be found in the supporting information.

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