Harvesting New Chiral Phosphotriesters by Phosphorylation of BINOL and Parent Bis-phenols

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The phosphorylation of BINOL and other bis-phenols operated by chlorophosphates led to the synthesis of new chiral mono- and bisphosphates.

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Abstract The systematic study on the phosphorylation of BINOL and other bis-phenols operated by chlorophosphates is described. An intriguing reactivity has been observed, which is attributable to the hydroxyl group acidity and the leaving group nucleofuge character within the phosphorylating agent used. By playing on these two parameters new chiral monophosphotriesters, symmetrical homo-BINOL bisphosphates and unsymmetrical non-homo-BINOL ones, incorporating a non-chiral side unit, were synthesized selectively and in good yields.

Key words chiral phosphotriesters, chiral phosphates, BINOL, bis-phenols, phosphorylation

Asymmetric catalysis represents one of the most efficient way to prepare enantiopure building blocks to be exploited in modern industry for the synthesis of pharmaceuticals, agrochemicals, polymers, and even new materials with different properties.[1] To achieve this goal big efforts have been done in the synthesis of libraries of chiral catalysts and ligands for metal coordination. Among the plethora of chiral backbones 1,1'-bi-2-naphthol (BINOL) and the partially hydrogenated H_8-BINOL are widely used in the development of chiral catalysts and ligands for a huge number of catalytic asymmetric transformations.[2] In this field, chiral phosphorus compounds have proved to be an ubiquitous class of catalysts, as evidenced by many reviews,[3] and phosphorus-based BINOL architectures such as phosphanes,[4] phosphites,[4b] phosphoric acids or phosphate metal salts,[5] and phosphoramidites[6] have undoubtedly a place of honor in asymmetric catalysis.

On the other hand, pure phosphotriesters (phosphates) are surprisingly much less used in transition metal catalysis, as only three examples were reported to date.[7] Miura's group investigated the Pd/phosphate-catalyzed oxidative coupling between arylboronic acids and alkynes,[7a] while the Zn/triphenylphosphate (TPP)-catalyzed hydrosilylation of ketones together with the Ti/bisphosphate-promoted diethylzinc addition to aldehydes were reported by us.[7b] Moreover only two examples of chiral phosphates appeared as organocatalysts.[8] Ishihara's group exploited chiral BINOL-derived triaryl phosphates as nucleophilic catalysts for the *N*-iodolactonisation of 4-arylmethyl-4-pentenoic acids.[8a] Luo and co-workers reported a latent concept for asymmetric carbocation catalysis with chiral BINOL-derived trityl phosphate, and its application to Friedel-Crafts, inverse electron-demanding hetero-Diels-Alder, and carbonyl-ene reactions.[8b]

In continuation with our interest in organocatalytic enantioselective transformations[9] and in transition metal catalysis,[10] we took in consideration the possibility to further exploit the Lewis base P=O coordination site of P(V) compounds by designing novel chiral (*S*)-BINOL-derived mono- and bis-phosphotriester architectures such as **A** and **B**, respectively (Figure 1).

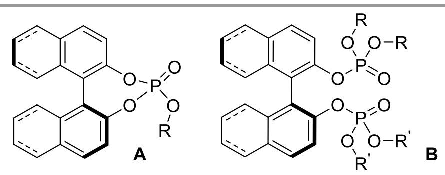


Figure 1 New chiral BINOL-derived phosphotriester general structures.

In the literature, beyond the phosphorylation of biological molecules,[11] there are several available methods to synthesize phosphate esters starting from phosphoric acids derivatives,[12] which are summarized in Figure 2. The access to the target compounds can be direct through either esterification in the presence of different additives (eq. 1, Figure 2),[12a-d] or alkylation with alkyl halides (eq. 2, Figure 2).[12e] Alternatively the phosphotriesters can be synthesized *via* a stepwise procedure involving the formation of the corresponding P(O)Cl followed by its nucleophilic substitution in the presence of alcohols (eq. 3, Figure 2).[12f-h]

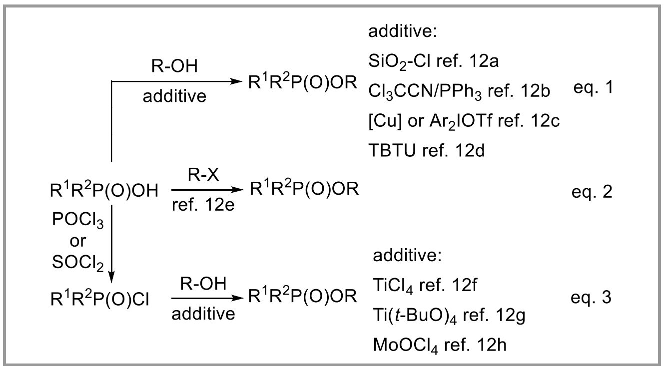
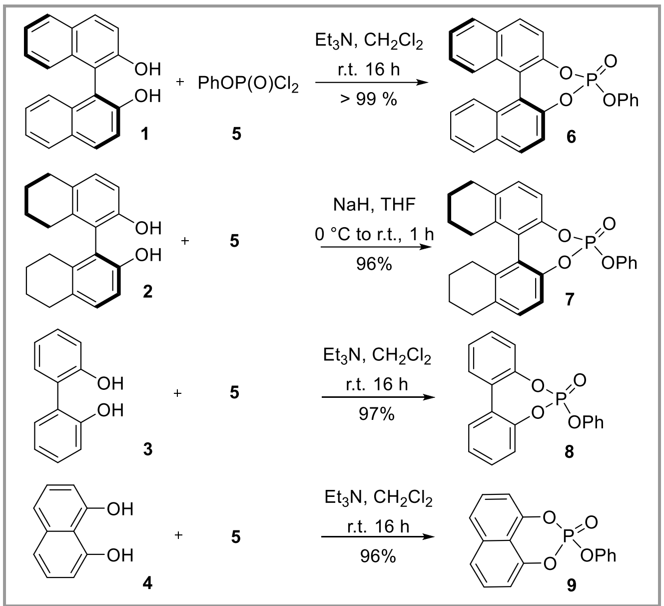


Figure 2 Typical procedures for the synthesis of phosphates.

In line with our preliminary report,[7b] we started to investigate the reactivity of (*S*)-BINOL (**1**) and (*S*)-H_8-BINOL (**2**) with different chlorophosphates in the presence of a base and without additives. It has to be pointed out that, compared to what has been previously described in the literature, this represents the first study dedicated to the systematic study on the phosphorylation of BINOL and analogous bis-phenol-based structures that showed an unexpected reactivity ascribable to the combination of two different parameters: the hydroxyl group acidity on one hand, and the leaving group nature within the phosphorylating agent of general formula $R^1R^2P(O)Cl$ on the other hand.

First of all we wondered how to selectively obtain monophosphates of general formula **A** (Figure 1). Without any surprise they were readily obtained by reaction between precursors **1-4** and dichlorophosphates. Thus phosphotriesters **6**,[13] **7**, **8**[14] and **9**[15] were isolated in very good yields, from 96% to > 99%, by reacting (*S*)-BINOL (**1**), (*S*)-H_8-BINOL (**2**),[16] 2,2'-biphenol (**3**) and 1,8-dihydroxynaphthalene (**4**) respectively with the commercially available phenyl dichlorophosphate (**5**) in basic conditions (Scheme 1). The structures of compounds **8** and **9** have been unambiguously confirmed by single crystal X-ray analysis (Figure 3).[17]



Scheme 1 Synthesis of monophosphates **6**-**9** from phenyl dichlorophosphate (**5**).

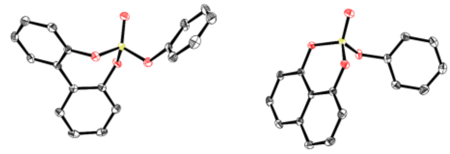
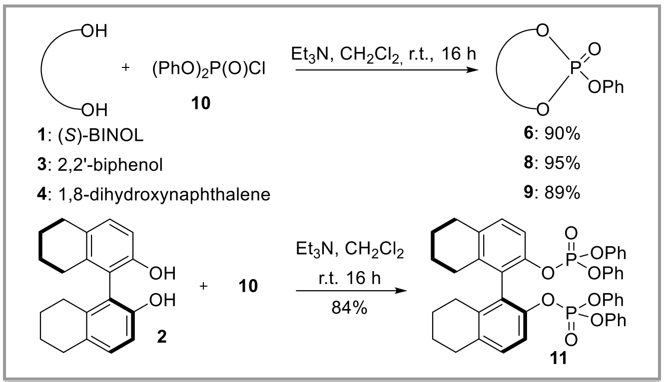


Figure 3 ORTEP representations of compounds **8** (left) and **9** (right) at 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

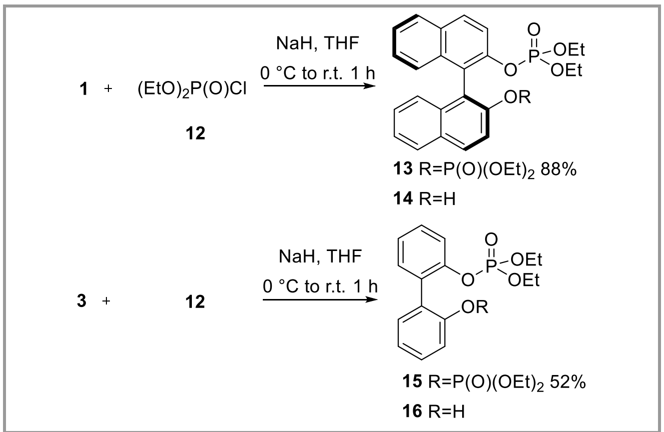
We next attempted the esterification of the commercially available diphenyl phosphoryl chloride (**10**) with **1**-**4** in order to synthesize bisphosphates of general formula **B** (Figure 1). To this end we let (*S*)-BINOL (**1**) react with an excess of **10** in the presence of Et_3N as proton scavenger (Scheme 2). Surprisingly the desired compound was not recovered from the reaction mixture but monophosphate **6** was again isolated in 90% yield, together with a reasonable amount of triphenyl phosphate (TPP), arising from the trapping of the excess of **10** by the phenol released in the course of the reaction. From **3** and **4** we similarly obtained the corresponding monophosphates **8** and **9**, in 95% and 89% yields respectively, along with TPP. In parallel we investigated the reaction between (*S*)-H_8-BINOL (**2**) and **10** under the same reaction conditions and we were surprised to find out that this time the expected bisphosphate **11** could be isolated in 84% yield.



Scheme 2 Synthesis of phosphates **6**, **8**, **9** and **11** in the presence of diphenyl phosphoryl chloride (**10**).

Which reaction pathways leading to cyclic monophosphates **6**, **8** or **9** from **1**, **3** or **4** and to the bisphosphate **11** from (*S*)-H$_8$-BINOL (**2**) are involved? To answer this in a more detailed way and to gain insights into the different behaviors of the bis-phenols, we decided to bring light on their phosphorylation reactions operated by chlorophosphates of general formula $R^1R^2P(O)Cl$.

To this point we went back to the literature and we found out that it was possible to obtain the bisphosphate **13** in 88% yield by phosphorylation of **1** with the commercially available diethyl chlorophosphate (**12**) in the presence of NaH (Scheme 3).[18] When we tried to change NaH for Et_3N a complex mixture was obtained, from which the starting materials, the desired bisphosphate **13** and compound **14** as the major product were isolated. The structure of **14** has been confirmed by single crystal X-ray analysis (Figure 4).[17] Additionally **3** was phosphorylated with **12** to give 52% of bisphosphate **15**[19] as the major product, together with the opened monophosphate form **16**, following again a trend close to that of BINOL.



Scheme 3 Synthesis of phosphates **13** and **15** in the presence of diethyl chlorophosphate (**12**).

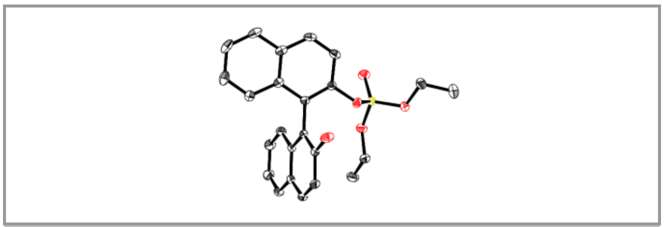


Figure 4 ORTEP representation of compound **14** at 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

The analysis of these sets of experiments indicated that the acidity of the protons on the phenolic counter-parts, together with the nucleofuge character of the OR groups installed on the chlorophosphates, have an influence on the reaction outcome leading to a competitive mono- *vs* bisphosphate formation.

If we try to compare the estimated pK_a values of the four compounds we used, we can deduce a scale of decreasing acidity going from 2,2'-biphenol[20] and 1,8-dihydroxynaphthalene, through BINOL,[21] to H$_8$-BINOL, **3**≈**4**<**1**<**2**, as depicted in Figure 5.

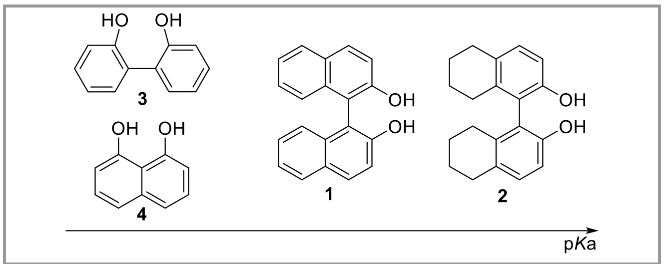
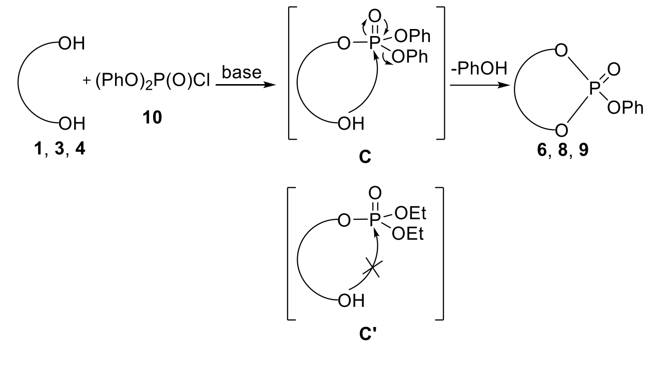


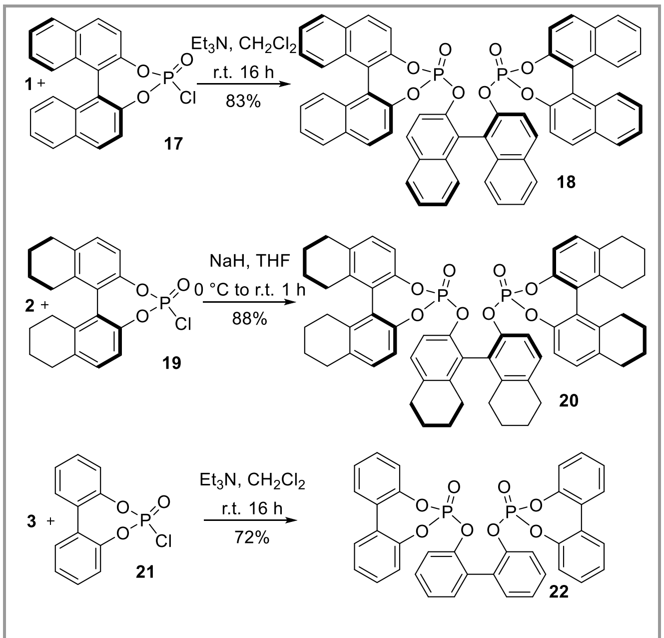
Figure 5 Estimated scale of acidity of the different substrates.

By virtue of this, we suppose that the reaction pathway goes through intermediate **C** and that in the case of **1**, **3** and **4**, even with an excess of diphenyl phosphoryl chloride (**10**), the intramolecular cyclisation to deliver the monophosphate of type **A**, with the release of a molecule of PhOH, is faster than the coupling with a second molecule of **10**, i.e. the displacement of the chloride on a second chlorophosphate (Scheme 4). This principle is not valid for (*S*)-H$_8$-BINOL (**2**) which possesses much less acidic phenolic protons, therefore the limit in the acidity scale is reached and in this case only the substitution of chlorides onto the P(V) can take place leading to a bisphosphate of type **B** (compound **11** on Scheme 2). The formation of the bisphosphates of type **B** (together with the opened monophosphates **14** and **16**) is favored in the case of diethyl chlorophosphate (**12**) because the phosphorous atom in **C'** is less electrophilic with respect to **12** and also the nucleofuge character is lowered for the ethoxy group. In other words, by establishing the acidity threshold of the substrates and the nucleofugality scale[22] $Cl^->PhO^->EtO^-$, the reactivity of different diols with chlorophosphates can be modulated in order to guide the reaction towards the preferential formation of mono- or bis phosphotriesters.



Scheme 4 Reaction pathway for the strongest acidic substrates in the presence of diphenyl chlorophosphate (**10**).

With these results in hand we decided to further explore the scope and limitations of such esterification reactions and in particular the access to new chiral bisphosphates. In the phosphorylation reactions below, the idea was to use phosphoryl chlorides whose structures couldn't preclude the reaction to evolve toward the formation of bisphosphates, contrary to diphenyl phosphoryl chloride (**10**). We started with the synthesis of symmetric architectures; the reaction of (*S*)-BINOL (**1**) with an excess of its phosphorochloridate **17**[23] in the presence of Et_3N smoothly led to the formation of the tris-BINOL bisphosphate **18** (BINOPHAT) in 83% yield (Scheme 5). The structure of the new BINOPHAT **18** has been confirmed by single crystal X-ray analysis (Figure 6).[17] Similarly when (*S*)-H_8-BINOL (**2**) was reacted with the corresponding phosphorochloridate **19**[24] in the presence of a stronger base such as NaH to offset the lower acidity of **2**, the tris-H_8-BINOL bisphosphate **20** (H_8-BINOPHAT) was obtained in 88% yield. Finally the same strategy was successfully applied to the synthesis of the previously reported bisphosphate **22**,[7b] which was obtained in 72% yield starting from **3** and its corresponding chlorophosphate **21**.



Scheme 5 Improved phosphorylations leading to single motif bisphosphates.

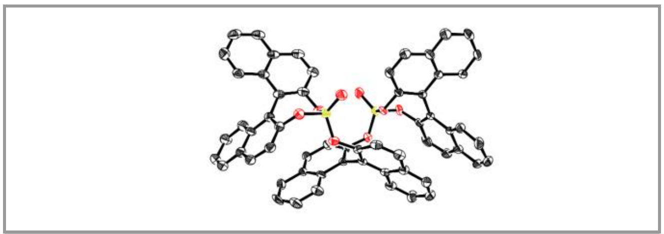
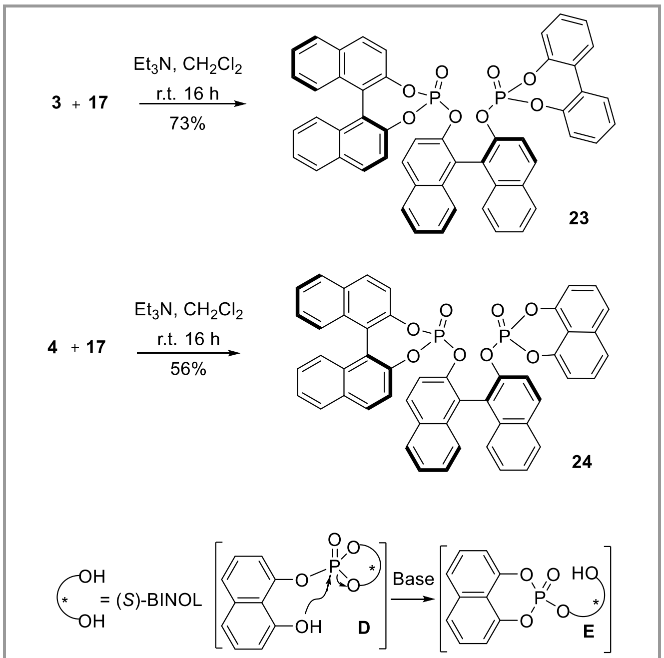


Figure 6 ORTEP representation of compound **18** at 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

We wondered next if it was possible to obtain symmetrical non-homo-BINOL bisphosphates, incorporating a non-chiral central unit such as 2,2'-biphenol (**3**) or 1,8-dihydroxynaphthalene (**4**). Thus we carried out the reaction between **3** or **4** and an excess of **17** and we were surprised to find out that these combinations readily led to the formation of the unsymmetrical bisphosphates **23** (73%) and **24** (56%) respectively, bearing one BINOL motif in the side position and the other as the central core of the molecules (Scheme 6), as confirmed by single crystal X-ray analysis of **24** (Figure 7).[17] These results corroborate the above hypothesis of a two-step reaction mechanism (Scheme 4) involving a transient species of type **D** which, owing to the strong acidity of **4** in conjunction with the nucleophilicity of the BINOL naphtholate, rearranges into an intermediate of type **E**. The latter then reacts with the excess of **17** to generate the final product.



Scheme 6 Synthesis of unsymmetrical chiral bisphosphates **23** and **24** and plausible reaction pathway.

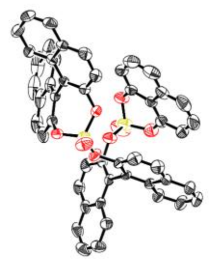
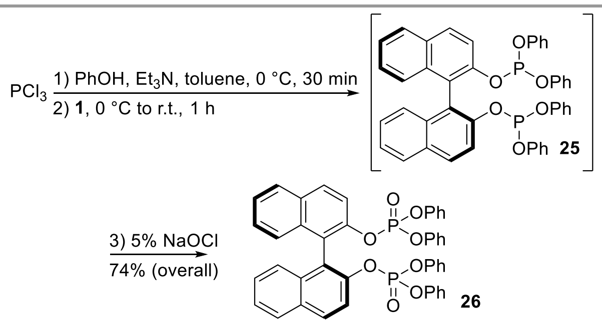


Figure 7 ORTEP representation of compound **24** at 50% thermal ellipsoids. Hydrogen atoms and one molecule of pentane are omitted for clarity.

As seen above, replacement of **10** by phosphoryl chlorides **17** and **19** in their reactions with BINOL and other closely related structures allowed us to prepare original bisphosphate architectures. Nonetheless, the question remains of whether the bisphosphate that was expected in place of **6** by the reaction between (*S*)-BINOL (**1**) and diphenyl phosphoryl chloride (**10**) is accessible. To answer this, we turned our attention towards the synthesis and oxidation of the corresponding phosphite (Scheme 7). According to this method, pre-mixing in basic conditions PCl_3 with PhOH delivers the corresponding diphenyl phosphorochloridite $(PhO)_2PCl$, that in turn reacts with (*S*)-BINOL (**1**) to give the desired bisphosphite **25**.[25] In this case the intramolecular cyclisation can't take place due to the much less electrophilic character of P(III), therefore **25** is formed exclusively and undergoes *in situ* oxidation, in mild conditions with a 5% NaOCl aqueous solution, to afford the corresponding phosphotriester **26** in 74% yield. The structure of the new bisphosphate **26** has been confirmed by single crystal X-ray analysis (Figure 8).[17]



Scheme 7 . Straightforward preparation of chiral bisphosphate **26** *via in situ* oxidation of bisphosphite **25**.

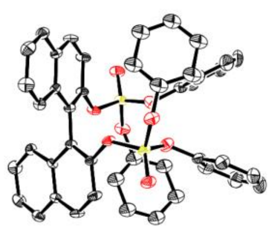


Figure 8 ORTEP representation of compound **26** at 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

In conclusion we have reported the phosphorylation of BINOL and other bis-phenols with chlorophosphates and observed an unexpected reactivity due to the pK_a of hydroxyl group of four different bis-phenols associated with the leaving group nucleofugal behavior of six different chlorophosphates. Monophosphotriesters can be selectively obtained by reaction of the four bis-phenols **1-4** with phenyl dichlorophosphate (**5**), and diphenyl phosphoryl chloride (**10**) with only one exception for (*S*)-H_8-BINOL (**2**) which delivers a new bisphosphate **11**. This represents thus the threshold in the acidity scale to switch from mono- to bis-phosphotriesters. Bisphosphates **13** and **15** were instead selectively obtained by reaction of **1** and **3** respectively with diethyl chlorophosphate (**12**), this time under control of the EtO^- nucleofuge behavior. New symmetrical homo-BINOL bisphosphates have been obtained in very good yields by reaction of (*S*)-BINOL (**1**) or (*S*)-H_8-BINOL (**2**) with their chlorophosphates, while unsymmetrical non-homo-BINOL ones, incorporating a non-chiral side unit, were synthesized from 2,2'-biphenol (**3**) or 1,8-dihydroxynaphthalene (**4**) in the presence of **17**. A plausible reaction pathway has been proposed based on acidity and nucleofugality scales. Finally a different route to bisphosphate **26** through *in situ* oxidation of its bisphosphite has been evaluated to overcome the previous methodology limits. Further researches on the substrate scope and investigations of those new chiral Lewis bases as ligands in enantioselective metal-based catalytic transformations, in line with our research interests are underway and will be reported in due course.

All the reactions were performed in dried glassware, under argon atmosphere, and sealed with a rubber septum. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. TLC analyses were performed using precoated Merck TLC Silica Gel 60 F254 plates. Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (0,040-0,063 nm). Petroleum ether (PE) used for purifications was the low boiling point fraction (40-60 °C). ^1H and ^{13}C spectra were recorded on a Bruker Avance 300 instruments using TMS and $CDCl_3$ respectively as internal standard. ^{31}P NMR spectra were recorded on a Bruker DMX 500. Chemical shifts (δ) are reported in parts per million (ppm) relatively to TMS and residual solvent as internal standards. The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; td, triplet of doublets; m, multiplet. Coupling constants (*J*) are reported in Hertz (Hz). HRMS analyses were obtained using a Waters Q-TOF 2 or a Micromass ZABSpec TOF or a Bruker Micro-TOF Q II or a LTQ Orbitrap XL instrument for ESI. X-ray crystallographic data were collected on a D8 Venture or a APEXII Bruker AXS diffractometers at 150 K. Optical rotations were recorded on a Perkin Elmer Model 341 polarimeter. Melting points were obtained on a hot bench. IR spectra were recorded on a Perkin Elmer FT-IR Spectrometer UATR Spectrum Two.

General procedure for the synthesis of monophosphates 6, 8, and 9 from phenyl dichlorophosphate (5): Under an argon atmosphere, to a solution of **1**, **3**, or **4** (1 eq) and Et_3N (3 eq) in dry CH_2Cl_2 (0.15 M), **5** (1.2 eq) was added drop by drop at 0 °C. The mixture was stirred at room temperature overnight, then hydrolyzed with H_2O and extracted with CH_2Cl_2. The organic phase was washed with an aqueous 1N HCl solution and with H_2O, then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as eluent. X-ray single quality crystals of compounds **8** and **9** were grown by slow diffusion of pentane in CH_2Cl_2 solution.

Synthesis of monophosphate 7 with phenyl dichlorophosphate (5): Under an argon atmosphere, to a solution of **2** (250 mg, 1 eq) in dry THF (0.3 M), NaH (2.5 eq) was added at 0 °C and the mixture was stirred at this temperature for 30 min before the addition of **5** (1.2 eq) drop by drop at 0 °C. The mixture was stirred at room temperature for an additional 30 min, then hydrolyzed with H_2O and extracted with CH_2Cl_2. The organic phase was washed with an aqueous 1N HCl solution and with H_2O, then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 7/3 as eluent, to give a white solid, 369 mg, 96% yield. M.p. 89-91 °C; $[\alpha]^{20}_D$ +75 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 2923, 2854, 1589, 1488, 1300, 1190, 1159, 1008, 947, 812, 751; ESI-HRMS calculated for $C_{26}H_{26}O_4P$ $[M+H]^+$ 433.1563, found 433.1564; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.36-7.31 (m, 2H), 7.26 (d, *J* = 7.2 Hz, 2H), 7.20-7.16 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 2.83-2.79 (m, 4H), 2.71-2.64 (m, 2H), 2.31-2.25 (m, 2H), 1.80-1.78 (m, 6H), 1.61-1.51 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.6 (d, J_{CP} = 6.2 Hz), 147.0 (d, J_{CP} = 11.0 Hz), 145.4 (d, J_{CP} = 7.7 Hz), 138.8 (d, J_{CP} = 1.5 Hz), 138.7 (d, J_{CP} = 1.5 Hz), 136.4 (d, J_{CP} = 2.2 Hz), 135.9 (d, J_{CP} = 2.1 Hz), 130.6 (d, J_{CP} = 1.4 Hz), 130.1 (d, J_{CP} = 1.3 Hz), 129.9, 126.0 (d, J_{CP} = 1.7 Hz), 125.9 (d, J_{CP} = 1.9 Hz), 125.5, 120.1 (d, J_{CP} = 5.0 Hz), 118.7 (d, J_{CP} = 3.5 Hz), 117.9 (d, J_{CP} = 3.9 Hz), 29.3, 29.2, 28.1, 28.0, 22.6, 22.5, 22.4, 22.3 ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -5.24 ppm.

General procedure for the synthesis of monophosphates 6, 8, 9, and 11 with diphenyl phosphoryl chloride (10): Under an argon atmosphere, to a solution of **1**-**4** (1 eq) and Et_3N (3 eq) in dry CH_2Cl_2 (0.15 M), **10** (3 eq) was added drop by drop at 0 °C. The mixture was stirred at room temperature overnight, then hydrolyzed with H_2O and extracted with CH_2Cl_2. The organic phase was washed with an aqueous 1N HCl solution and with H_2O, then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as eluent.

Compound 11: from **2** (590 mg, 1 eq), purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 7/3 as eluent, to give a colorless oil, 1.28 g, 84% yield. $[\alpha]^{20}_D$ -25 (c = 1.2, $CHCl_3$); IR (neat, cm^{-1}) 2925, 1588, 1484, 1297, 1184, 1159, 1008, 938, 752, 686; ESI-HRMS calculated for $C_{44}H_{40}O_8P_2Na$ $[M+Na]^+$ 781.2090, found 781.2088; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 8.4 Hz, 2H), 7.21-7.19 (m, 8H), 7.14-7.04 (m, 6H), 7.02-6.97 (m, 4H), 6.84-6.81 (m, 4H), 2.78-2.57 (m, 4H), 2.30 (td, *J* = 17.1, 6.0 Hz, 2H), 2.05 (dt, *J* = 17.1, 5.7 Hz, 2H), 1.63-1.50 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.5 (d, J_{CP} = 4.1 Hz), 150.4 (d, J_{CP} = 4.1 Hz), 146.0 (d, J_{CP} = 6.5 Hz), 137.9, 134.6, 129.9 (d, J_{CP} = 0.6 Hz), 129.8, 129.7, 126.8 (d, J_{CP} = 8.6 Hz), 125.4 (d, J_{CP} = 0.9 Hz), 125.2 (d, J_{CP} = 0.9 Hz), 120.1 (d, J_{CP} = 4.9 Hz), 120.0 (d, J_{CP} = 4.9 Hz), 116.4 (d, J_{CP} = 1.9 Hz), 29.5, 27.3, 22.8, 22.6 ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -18.40 ppm.

General procedure for the synthesis of bisphosphates 13 and 15 with diethyl chlorophosphate (12): Under an argon atmosphere, to a solution of **1** or **3** (1 eq) in dry THF (0.3 M), NaH (2.5 eq) was added at 0 °C and the mixture was stirred at this temperature for 30 min before the addition of **12** (2.1 eq). The mixture was stirred at room temperature for an additional 30 min, then hydrolyzed with H_2O and extracted with CH_2Cl_2. The organic phase was washed with an aqueous 1N HCl solution and with H_2O, then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as eluent.

Compound 13: $[\alpha]^{20}_D$ -2.2 (c = 1.2, $CHCl_3$) vs -5.1 (c = 0.85, $CHCl_3$) described.

Compound 15: from **3** (500 mg, 1 eq), purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 2/3 as eluent, to give a colorless oil, 640 mg, 52% yield. IR (neat, cm^{-1}) 3495, 2984, 1477, 1440, 1270, 1208, 1021, 926, 761; ESI-HRMS calculated for $C_{20}H_{28}O_8NaP_2$ $[M+Na]^+$ 481.1151, found 481.1154; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.46-7.43 (m, 2H), 7.37-7.33 (m, 4H), 7.24-7.19 (m, 2H), 3.95-3.84 (m, 8H), 1.17 (t, *J* = 7.2 Hz, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.3 (d, J_{CP} = 6.7 Hz), 131.8, 129.3, 129.2, 124.6, 119.6 (d, J_{CP} = 1.5 Hz), 64.4 (d, J_{CP} = 6.7 Hz), 16.0 (d, J_{CP} = 6.7 Hz) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -7.16 ppm.

General procedure for the synthesis of bisphosphates 18, 23, and 24: Under an argon atmosphere, to a solution of **1**, **3**, or **4** (1 eq), and (*S*)-1,1'-Binaphthyl-2,2'-diyl phosphorochloridate **17** (3 eq) in dry CH_2Cl_2 (0.15 M), Et_3N (3 eq) was added drop by drop. The mixture was stirred at room temperature overnight, then hydrolyzed with H_2O and extracted with CH_2Cl_2. The organic phase was washed with an aqueous 1N HCl solution and with H_2O, then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as eluent.

Compound 18: from **1** (200 mg, 1 eq), purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 7/3 to 1/1 as eluent, to give a white solid, 568 mg, 83% yield. M.p. > 280 °C; $[\alpha]^{20}_D$ +354 (c = 1; $CHCl_3$); IR (neat, cm^{-1}) 3056, 1505, 1305, 1202, 1187, 965, 950; ESI-HRMS calculated for $C_{60}H_{36}O_8P_2Na$ $[M+Na]^+$ 969,1777, found 969,1780; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.60-7.42 (m, 12H), 7.39-7.25 (m, 8H), 7.20-7.11 (m, 6H), 6.51 (dd, *J* = 8.7, 0.9 Hz, 2H), 5.94 (dd, *J* = 8.7, 0.9 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.9 (d, J_{CP} = 11.6 Hz), 146.0 (d, J_{CP} = 5.9 Hz), 145.9 (d, J_{CP} = 8.6 Hz), 133.2, 132.1 (d, J_{CP} = 0.9 Hz), 131.9 (d, J_{CP} = 0.9 Hz), 131.7 (d, J_{CP} = 1.0 Hz), 131.6 (d, J_{CP} = 1.0 Hz), 131.1, 130.9, 130.8, 130.0, 128.8, 128.3, 128.2, 127.4, 127.2, 126.9, 126.6, 126.5, 126.0, 125.9, 125.8, 125.7, 121.6 (d, J_{CP} = 8.1 Hz), 121.1 (d, J_{CP} = 2.2 Hz), 120.4 (d, J_{CP} = 2.2 Hz), 120.2 (d, J_{CP} = 2.8 Hz), 119.3 (d, J_{CP} = 3.2 Hz), 119.2 ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -3.58 ppm. Crystals suitable for X-ray diffraction study were grown by slow diffusion of a CH_2Cl_2 solution layered with pentane.

Compound 23: from **3** (85 mg, 1 eq), purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 7/3 as eluent, to give a white solid, 160 mg, 73% yield. M.p. 165-167 °C; $[\alpha]^{20}_D$ +141 (c = 1.1, $CHCl_3$); IR (neat, cm^{-1}) 3059, 1589, 1505, 1475, 1433, 1304, 1212, 1187, 1000, 965, 951, 886, 747; ESI-HRMS calculated for $C_{52}H_{32}O_8P_2Na$ $[M+Na]^+$ 869.1464, found 869.1464; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 9.3 Hz, 1H), 7.87-7.77 (m, 6H), 7.54-7.39 (m, 7H), 7.35-7.30 (m, 3H), 7.23-7.06 (m, 11H), 7.01 (td, *J* = 8.1, 0.9 Hz, 1H), 6.55 (dt, *J* = 8.1, 1.2 Hz, 1H), 6.18 (d, *J* = 9.0 Hz, 1H), 6.12 (d, *J* = 8.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.3 (d, J_{CP} = 9.0 Hz), 147.2 (d, J_{CP} = 9.0 Hz), 146.9 (d, J_{CP} = 11.2 Hz), 146.2 (d, J_{CP} = 6.0 Hz), 146.2, 146.0 (d, J_{CP} = 6.0 Hz), 145.9, 133.3 (d, J_{CP} = 9.8 Hz), 132.2 (d, J_{CP} = 0.9 Hz), 131.9 (d, J_{CP} = 0.9 Hz), 131.8, 131.5 (d, J_{CP} = 1.0 Hz), 131.2, 131.1, 130.9, 130.8, 130.4, 130.0, 129.9 (d, J_{CP} = 5.8 Hz), 129.4 (d, J_{CP} = 2.5 Hz), 128.7, 128.5, 128.2, 128.0, 127.7 (d, J_{CP} = 1.2 Hz), 127.6 (d, J_{CP} = 1.2 Hz), 127.3 (d, J_{CP} = 5.3 Hz), 127.2, 127.0, 126.7, 126.5, 126.2, 126.1, 125.8, 125.7 (d, J_{CP} = 6.0 Hz), 125.7, 121.9 (d, J_{CP} = 7.9 Hz), 121.3 (d, J_{CP} = 2.3 Hz), 121.0 (d, J_{CP} = 4.4 Hz), 120.8, 120.7, 120.5 (d, J_{CP} = 2.9 Hz), 120.4 (d, J_{CP} = 2.3 Hz), 119.5, 119.2 (d, J_{CP} = 3.2 Hz), 118.4 ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -3.46, -5.28 ppm.

Compound 24: from **4** (80 mg, 1 eq), purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 7/3 as eluent, to give a white solid, 230 mg, 56% yield. M.p. 171-173 °C; $[\alpha]^{20}_D$ +112 (c = 1.2, $CHCl_3$); IR (neat, cm^{-1}) 3059, 1614, 1590, 1506, 1463, 1321, 1296, 1260, 1208, 1188, 966, 950, 899, 884, 811, 747; ESI-HRMS calculated for $C_{50}H_{31}O_8P_2$ $[M+H]^+$ 821.1488, found 821.1496; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.00-7.89 (m, 3H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.65-7.53 (m, 6H), 7.48-7.40 (m, 3H), 7.36-7.22 (m, 9H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.05-6.89 (m, 4H), 6.19-6.15 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.0 (d, J_{CP} = 11.5 Hz), 146.3 (d, J_{CP} = 8.7 Hz), 145.9, 145.8, 145.7, 145.6 (d, J_{CP} = 6.5 Hz), 134.5, 133.1, 132.7, 132.2, 132.0, 131.9 (d, J_{CP} = 1.0 Hz), 131.6 (d, J_{CP} = 1.0 Hz), 131.4, 131.0, 130.7, 130.2 (d, J_{CP} = 4.0 Hz), 128.8, 128.6, 128.2, 127.8, 127.3, 127.2, 127.0, 127.0, 126.9, 126.8 (d, J_{CP} = 2.6 Hz), 126.1, 125.9, 125.8, 125.6, 125.4, 123.3 (d, J_{CP} = 3.4 Hz), 121.4 (d, J_{CP} = 2.2 Hz), 120.9 (d, J_{CP} = 4.4 Hz), 120.8, 120.7 (d, J_{CP} = 3.1 Hz), 120.6 (d, J_{CP} = 2.2 Hz), 119.5 (d, J_{CP} = 3.3 Hz), 118.8, 118.6, 112.7, 112.5, 112.4, 112.0 (d, J_{CP} = 9.3 Hz) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -3.55, -

24.47 ppm. X-ray single quality crystals were grown by slow diffusion of Et_2O in $CDCl_3$ solution.

Synthesis of bisphosphate 20: Under an argon atmosphere, to a solution of **2** (150 mg, 1 eq) in dry THF (0.3 M), NaH (2.5 eq) was added at 0 °C and the mixture was stirred at this temperature for 30 min before the addition of (*S*)-H_8-BINOL phosphorochloridate **19** (2.1 eq). The mixture was stirred at room temperature for an additional 30 min, then hydrolyzed with H_2O and extracted with CH_2Cl_2. The organic phase was washed with an aqueous 1N HCl solution and with H_2O, then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 7/3 to 1/1 as eluent, to give a white solid, 438 mg, 88% yield. M.p. 207-209 °C; $[\alpha]^{20}_D$ +121 (c = 1.2, $CHCl_3$); IR (neat, cm^{-1}) 2927, 2857, 1589, 1464, 1307, 1210, 992, 956, 884, 811; ESI-HRMS calculated for $C_{60}H_{60}O_8P_2Na$ $[M+Na]^+$ 993.3655, found 993.3657; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.79 (dd, *J* = 8.1, 1.2 Hz, 2H), 5.98 (d, *J* = 8.1 Hz, 2H), 2.78-2.73 (m, 12H), 2.60-2.42 (m, 6H), 2.19-2.03 (m, 6H), 1.74-1.72 (m, 18H), 1.51-1.45 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.8 (d, J_{CP} = 11.0 Hz), 146.0 (d, J_{CP} = 6.5 Hz), 145.6 (d, J_{CP} = 8.4 Hz), 138.4 (d, J_{CP} = 1.4 Hz), 137.9, 137.7, 135.8 (d, J_{CP} = 2.2 Hz), 135.0 (d, J_{CP} = 2.2 Hz), 134.6, 130.2, 130.1, 129.5, 127.1 (d, J_{CP} = 7.4 Hz), 126.2 (d, J_{CP} = 6.9 Hz), 125.3 (d, J_{CP} = 6.9 Hz), 118.6 (d, J_{CP} = 3.4 Hz), 117.6 (d, J_{CP} = 3.7 Hz), 117.3, 29.7, 29.3, 29.2, 27.9, 27.8, 27.4, 23.0, 22.9, 22.6, 22.5, 22.4 ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -4.63 ppm.

Synthesis of bisphosphates 26: Under an argon atmosphere, to a solution of PCl_3 (1 eq) in toluene (0.1 M), phenol (1,07 g, 2 eq) and Et_3N (5 eq) were added at 0 °C. The mixture was stirred at 0 °C for 30 min before the addition of **1** (820 mg, 0.5 eq). The reaction was stirred at room temperature for 1 h, then the mixture was filtered over a pad of celite and the solvent was removed under vacuum. The crude was dissolved in EtOAc, washed with H_2O, an aqueous 5% NaOCl solution and brine, then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate 3/1 as eluent to give a white solid, 1.6 g, 74% yield. M.p. 142-144 °C; $[\alpha]^{20}_D$ +1.2 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3061, 1589, 1481, 1298, 1188, 1159, 995, 967, 944, 753; ESI-HRMS calculated for $C_{44}H_{32}O_8P_2$ $[M]^+$ 750.1567, found 750.1576; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 9.0 Hz, 2H), 7.43-7.37 (m, 2H), 7.25-7.06 (m, 10H), 7.00-6.98 (m, 6H), 6.88-6.85 (m, 4H), 6.57-6.54 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.3 (d, J_{CP} = 8.2 Hz), 150.1 (d, J_{CP} = 7.5 Hz), 146.7 (d, J_{CP} = 6.7 Hz), 133.6, 131.2, 130.5, 129.7, 129.5, 128.1, 127.3, 126.2, 125.8, 125.4 (d, J_{CP} = 1.5 Hz), 125.2 (d, J_{CP} = 1.5 Hz), 121.7 (d, J_{CP} = 9.0 Hz), 120.0 (d, J_{CP} = 5.2 Hz), 119.6 (d, J_{CP} = 5.2 Hz), 119.2 (d, J_{CP} = 1.5 Hz) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -18.60 ppm. Crystals suitable for X-ray diffraction study were grown by slow diffusion of a CH_2Cl_2 solution layered with heptane.

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Supporting Information

YES

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