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Directed *ortho*-lithiation of unprotected diphenylphosphinic acids

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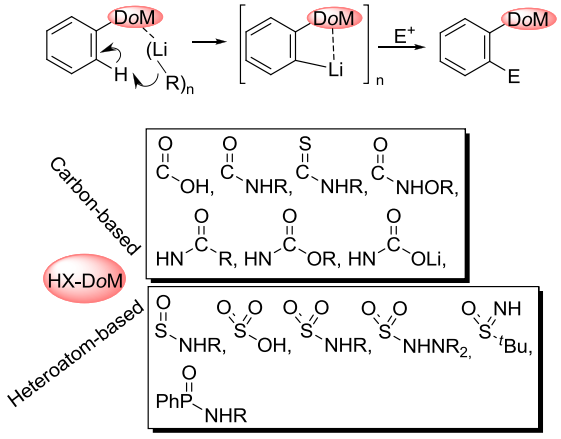
ABSTRACT

Directed ortho lithiation of diphenylphosphinic acid and subsequent electrophilic trapping provides mono *ortho*-functionalized derivatives including enantiopure γ-aminophosphinic acids in moderate yields. Copper catalyzed coupling of the ortho anion leads to biphenyl-2,2′-diylbis(phenylphosphinic acid), a phosphorus analogue of biphenyl-2,2′-dicarboxylic acid. Preliminary studies of the metal-binding abilities of this *O*,*O*-chelating ligand towards a series of metal cations are included.

1. Introduction

Directed *ortho*-lithiation (DoLi) has become a valuable method for the regiospecific construction of polysubstituted aromatic systems in academe[1,2] and industry.[3] The method consists of a one-pot process, in which an aromatic proton ortho to a polar functional group (directing *ortho*-metallation group, DoM) is selectively abstracted by a base and the anion formed is used in carbon–carbon and carbon–heteroatom bond forming reactions through in situ trapping with a variety of electrophiles. The role of the DoM group is threefold: increase the acidity of the ortho protons, facilitates the approach of the lithium base to the deprotonation site and contributes to the stabilization of the ortho lithiated species through intramolecular coordination (Scheme 1).

A variety of functional groups based on phosphonic and phosphinic acid moieties have shown their ability to direct metallation to the ortho position of a *P*-phenyl ring. They include esters, amides and thioamides.[4,5] Since these compounds are derivatives of the corresponding acids, a more straightforward procedure would be the ortho functionalization of the unprotected organophosphorus acids themselves. The process would involve the initial deprotonation of the OH linkage and the $-P(=O)O^-$ group formed may be too weak for promoting a ring *ortho*-metallation that would lead to a dimetallated species. *Ortho*-lithiations directed by X(=O)YH functional groups containing acidic protons, such as $-CO_2H$,[6] −CONHR,[7] −CSNHR,[8] −CONHOR,[9] −NHCOR,[10] −NHCOOR,[11] −NRCOOLi,[12] −SONHR,[13] $-SO_3H$,[14] $-SO_2NHR$,[15] SO_2NHNR_2,[16] (^{t}Bu)S(=O)(=NH),[17] and −PONHR,[5b] have been reported (Scheme 1).



Scheme 1. *Ortho*-lithiation directed by X(=O)YH groups and electrophilic trapping. Carbon/heteroatom-based refers to the atom connecting the functional group to the aromatic ring.

Unsymmetrical diarylphosphinic acids are commonly prepared utilizing stepwise procedures involving mostly nucleophilic displacement of *P*-halogen bonds[18] or palladium-catalyzed cross-coupling reactions of phosphinate[19] and have attracted considerable attention in the last decades due to their applications.[19c]

Phosphinic acids are phosphorus analogues of carboxylic acids showing a broad range of applications in areas as diverse as industrial,[20] agricultural,[21] medicinal,[22] and synthetic organic and

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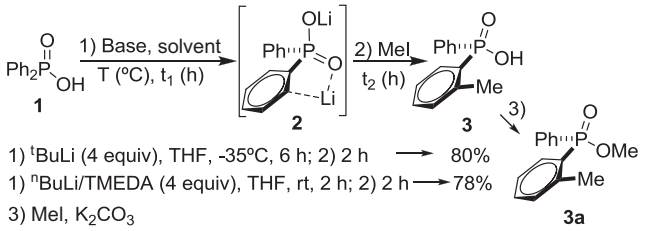
organometallic chemistry.[18b,23] In addition, the tetrahedral phosphinic acid moiety mimics the transition state of enzymatic amide formation or hydrolysis.[19b,24] These features make aminophosphinic acids particularly interesting compounds as useful enzyme inhibitors with potential therapeutic activity.[25]

Here we describe the direct synthesis of unsymmetrical diarylphosphinic acids through *ortho*-lithiation of diphenylphosphinic acid followed by electrophilic trapping reactions. The process provides access to a variety of derivatives containing new ortho C–C and *C*-heteroatom bonds. In addition, oxidative coupling of the ortho anion gives access to a new bis(phosphinic acid) that behaves as an *O*,*O*-chelating ligand.

2. Results and discussion

Firstly, optimized conditions for the ortho deprotonation of diphenylphosphinic acid[26] **1** were evaluated. The degree of *ortho*-lithiation was determined through the reaction of dianion **2** with MeI to give the *ortho*-methyl derivative **3**. After some experimentation, we found that the treatment of **1** with 4 equiv of *t*-BuLi at −35 °C in THF during 6 h and subsequent quench with MeI afforded after 2 h of reaction phenyl(*o*-tolyl)phosphinic acid **3** in a conversion of 80% (Scheme 2). Less than 8% of the di(*ortho*-tolyl) derivative was detected. Similar results were obtained by using *n*-BuLi/TMEDA as a base and performing the reaction at room temperature during 2 h. The use of temperatures relatively high as compared with other DoLi processes involving non metallated functional groups, typically in the range of −90 to −70 °C,[1] indicates that the lithium phosphinate is a rather poor activating group of *P*-phenyl *ortho*-deprotonation. Purification of **3** through column chromatography proved to be cumbersome due to strong interactions between the phosphinic acid moiety and the solid support. Using CH_2Cl_2:methanol (10:1) as eluent the product was isolated in 36% yield. Better results were achieved through pre-column derivatization. The reaction of **3** with iodomethane and potassium carbonate afforded the corresponding methyl phosphinate **3a** that could be isolated in good yield (68%).

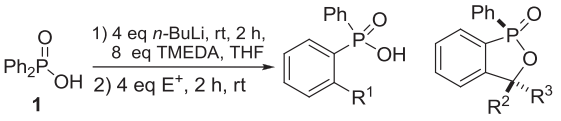


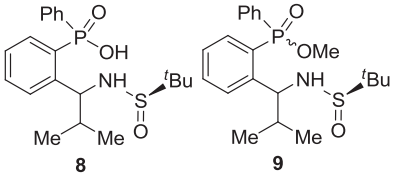
Scheme 2. Optimization of the *ortho*-lithiation/methylation of **1**. Conversions were determined through ^{31}P NMR of the crude reaction mixture.

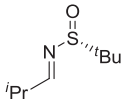
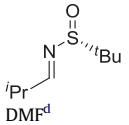
Once suitable reaction conditions for *ortho*-lithiation of **1** were established, the scope of the transformation was investigated by allowing to react anion **2** with a variety of electrophiles. In all cases, ortho deprotonation was achieved with the less hazardous and cheaper base *n*-BuLi in the presence of the chelating diamine TMEDA. The results obtained are shown in Table 1. The new products obtained were isolated through column chromatography using mixtures of ethyl acetate/hexane and methylenedichloride/methanol as eluent (see Supplementary data). Generally, conversions to products above 60% were observed in the ^{31}P NMR spectra of the crude reaction mixtures. The performance of the purification improved by transforming the unproctected phosphinic acid into the corresponding methyl ester.

The reaction with benzyl bromide led to the product of bromine transfer **4** (entry 2). Products of *ortho*-benzylation were not detected through NMR analysis of the crude reaction mixture. This unexpected halogen abstraction by the ortho anion **2** suggests that

Table 1
Ortho functionalization of diphenylphosphinic acid **1** through sequential *ortho*-lithiation/electrophilic quench





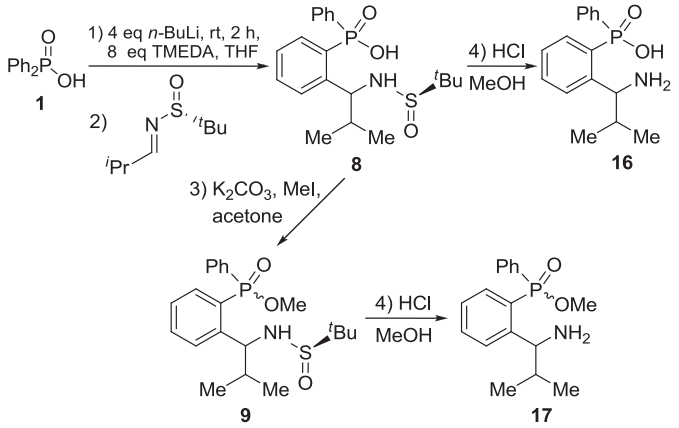
Entry	Comp.	E^+	R^1	R^2	R^3	Yield (%)
1	**3**(**3a**)[a]	MeI	Me			36 (68)
2	**4**	$PhCH_2Br$	Br			36[b]
3	**5**(**5a**)[a]	ICH_2CH_2I	I			38[b] (70)
4	**6**	Me_3SnCl	$SnMe_3$			68
5	**7**	PhCH=NPh	PhCHNHPh			39
6	**8**		^{i}PrCHNHS(O)^{t}Bu			19
7	**9**		^{i}PrCHNHS(O)^{t}Bu			45[c]
8	**10**	DMF[d]	CH_2OH			34[e]
9	**11**	DMF[d]		H	H	26 (55)[e]
10	**12**	Me_2CO		Me	Me	67
11	**13**	CH_3CHO		H	CH_3	50[f]
12	**14**	PhCHO		H	Ph	43[g]
13	**15**	$HO(CH_2O)_nH$		H	$(CH_2)_2OH$	37[h]

[a] Derivatized as the methyl phosphinate.
[b] Isolated as the triethylamonium salt.
[c] Isolated as the methyl ester of the product of electrophilic quench. Mixture 1:1 of *P*-epimers.
[d] 10 equiv of electrophile were used.
[e] Obtained by in situ reduction of the crude mixture with $NaBH_4$. Yield given in brackets corresponds to the reaction processed with 6 N HCl (see text).
[f] Overall yield. Ratio of l:u stereoisomers formed of 1.1:1, isolated in two chromatographic fractions as mixtures of composition 4.1:1 and 1:3.9.
[g] Ratio of l:u stereoisomers formed of 1.6:1, isolated as a mixture 3.6:1.
[h] Small amounts of compounds **10** (8%) and **11** (10%) were also formed.

the reaction might proceed via a radical mechanism.[27] Ortho iodination was achieved by treating anion **2** with ICH_2CH_2I to give **5** (conversion of 70%, entry 3) in acceptable yield (70% for the methyl ester **5a**). Stannylation with Me_3SnCl takes place more efficiently. The *ortho*-trimethylstannyl derivative **6** was isolated in 68% yield (entry 4). Products **5** and **6** are valuable intermediates for further derivatization via transition metal catalyzed cross-coupling reactions.[28] The reaction with benzaldimine furnished γ-aminophosphinic acid **7** in a yield of 39% (conversion of 68%, entry 5). Chirality was introduced by using the chiral sulfinamide (*R*)-^{i}PrCH=NS(O)^{t}Bu[29] as electrophile. Compound **8** was isolated as a single diastereoisomer, albeit in low yield (entry 6). The NMR spectrum of the crude reaction mixture showed very broad signals that prevented the identification of possible stereoisomers.

The degree of asymmetric induction of the process was established indirectly. The γ-aminophosphinic acid **8** was converted into the corresponding methyl ester **9** by refluxing the crude reaction mixture with MeI in acetone in the presence of K_2CO_3 during 3 h (Scheme 3). The methyl phosphinate **9** was obtained as a 1:1 mixture of diastereoisomers epimers in the configuration of the phosphorus atom (entry 7). Since the esterification step is expected

to proceed without stereocontrol, this result indicates that the addition of **2** to the chiral imine takes place with very high diastereroselectivity (dr>95:5). In addition, esterification of **8** favoured the isolation of compound **9** in a yield of 45%. The configuration of the carbon stereocenter remains unknown. Unfortunately, all attempts of obtaining crystals of either **8** or **9** suitable for X-ray diffraction failed.

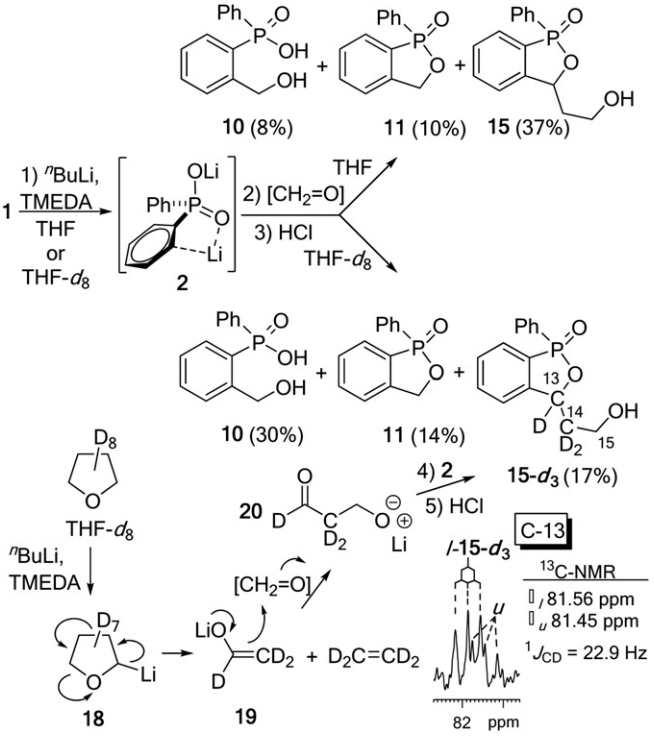


Scheme 3. Synthesis of enantiopure γ-aminophosphinic acid derivatives via DoM methodology.

Compounds **8** and **9** are phosphorus analogues of γ-aminobutyric acid, the major inhibitory neurotransmitter in the mammalian central nervous system. They represent an important class of compounds due to their properties as therapeutic agents.[30] For further applications in synthesis it is interesting to have access to derivatives selectively protected in each functional group. Deprotonation of the OH of **8** with K_2CO_3 and subsequent methylation with MeI gave the amino acid **9** (mixture 1:1 of *P*-epimers) with the phosphinic acid moiety protected as a methyl ester (Scheme 3). Removal of the sulfinyl moiety of **8** and **9** could be accomplished by reaction with 12 M HCl in methanol during 3 days (Scheme 3). In this way were obtained the *N*- and *O*-unprotected γ-aminophenylphosphinic acid **16** (25% yield) and the *N*-unprotected methyl ester **17** (75% yield) (Scheme 3).

DMF reacted with anion **2** to yield a mixture of acyclic and cyclic derivatives with a conversion of 85% that could not be separated. Fortunately, in situ reduction of the adducts with $NaBH_4$ lead to a mixture of the *ortho*-hydroxymethylated phosphinic acid **10** and the corresponding product of cyclocondensation **11** in a ratio of 56:44 that could be separated through column chromatography (entries 8 and 9). Compound **10** was quantitatively converted into **11** by treating the crude reaction mixture with 6 N HCl during workup. The use of acetone, acetaldehyde and benzaldehyde as electrophiles produced alcoholate derivatives that undergo cyclocondensation to give oxaphospholones **12**, **13** and **14**, respectively (entries 10–12). Compounds **13** and **14** consisted of mixtures of *like* and *unlike* isomers. In both cases, the diastereoselectivity was low and improved slightly through chromatographic purification (Table 1). The relative configuration of each isomer was assigned based on 1D gNOESY spectra.

Paraformaldehyde proved to be also a suitable electrophile for functionalizing anion **2**. However, the reaction proceeded in an unexpected manner. The anticipated products **10** and **11** were obtained in a very small conversion (<20%). They were identified in the ^{31}P NMR spectrum of the crude reaction mixture based on their characteristic chemical shift. The major reaction products formed were the diastereomeric γ-phospholactones ***l*-15** and ***u*-15** in a ratio of 1.5:1 (entry 13). The structure of **15** was unequivocally assigned through the analysis of the 1D (^1H, ^{13}C, DEPT135, ^{31}P) and 2D NMR spectra (COSY, HMQC, HMBC) and the stereochemistry deduced from the NOEs observed by selective inversion of the respective benzylic protons. This proton of isomer ***l*-15** produced a strong NOE with the ortho protons of the *P*-phenyl ring (Supplementary data). Since phospholactones **15** apparently involve the unprecedented participation of formaldehyde in the tandem creation of three carbon–carbon bonds driven by an ortho anion,[31] we performed additional experiments to ascertain the origin of the 1,3-propanediol moiety present in **15**. It is well known that organolithiums produce the fragmentation of THF[32] via deprotonation α to oxygen to give a C-2 anion that undergo [3+2] cycloreversion furnishing ethylene and the lithium enolate of acetaldehyde (see Scheme 4).[33a] The latter may function as a source of alkoxy fragments that could participate in the formation of **15**. To validate this hypothesis we carried out the reaction of dianion **2** with paraformaldehyde in THF-d_8 under exactly the same reaction conditions used in the synthesis of **15**. The ^{31}P NMR spectrum of the crude reaction mixture showed two principal differences with respect to the reaction in THF: a lower conversion to products with a chemical shift characteristic of ***l*-15** (δ_P 48.65 ppm) and ***u*-15** (δ_P 48.87 ppm) and a significant increase of the amount of **10** (30%) and **11** (14%) obtained (Scheme 4). Most importantly, the multiplets for the protons of the –CH(O)CH_2– fragment were not present in the ^1H NMR spectrum.

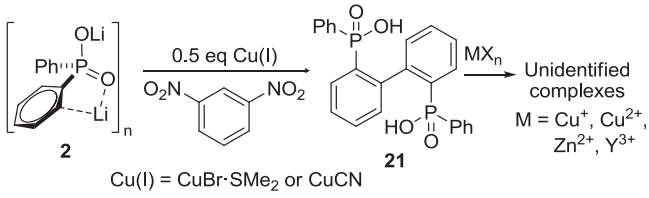


Scheme 4. Mechanism proposed for the formation of **15** in the reaction of **2** with paraformaldehyde.

Purification through column chromatography allowed to isolate **15-*d*$_3$** (mixture of l/u diastereoisomers). The high resolution mass spectrum confirmed the incorporation of 3 deuteriums ($[M+1]^+$ 278.1018) as compared with **15**. The positions deuterated were identified as C-13 and C-14 based on the absence of the signals for H-13 and H-14 in the ^1H NMR spectrum and the multiplicity of these carbons in the ^{13}C NMR spectrum. Scheme 4 shows the two triplets of relative intensity 1:1:1 observed for C-13 (δ_l/δ_u 81.56/81.45 ppm) due to the coupling with one deuterium of spin $I=1$, $^1J_{CD}=22.9$ Hz. The signals of C-14 appear as unresolved multiplets centred at δ_C 39.05 (*u*) and 39.35 (*l*) ppm (Supplementary data).

These results establish that products of decomposition of THF by the base are involved in the pathway leading to compound **15**. In agreement with this conclusion, when the reaction was achieved using toluene as solvent the only products observed were **10** and **11**, albeit in a very low conversion (17%). A reaction mechanism explaining the formation of **15-*d*$_3$**/**15** is shown in Scheme 4.The *per*-deuterated lithium enolate **19** arising from the α lithiation of THF-d_8[33a] reacts with paraformadehyde to give the trideuterated aldol adduct **20**. Addition of the ortho anion **2** to the carbonyl group of **20** followed by cyclocondensation during acidic workup would yield **15-*d*$_3$**. The increase of the conversion of **10** and **11** observed in the reaction in THF-d_8 is assigned to a primary isotope effect.[34] Decomposition of THF-d_8 would proceed at a slower rate than THF, thus increasing the probabilities of reaction of anion **2** with paraformaldehyde. Clearly, decomposition of THF takes place in all reactions shown in Table 1. This explains the need for a large excess of base to achieve the ortho lithiation of **1** in high yield. Compounds analogue to **15** were observed in the reaction of **2** with acetaldehyde in less than 10% of conversion. 1D TOCSY experiments performed on the crude reaction mixture with selective excitation of H-13 revealed the whole spin system arising from the aliphatic protons (O–CH(Ar)–CH_2CH(OH)CH_3). These compounds were not detected in the reaction with benzaldehyde. The high reactivity of paraformaldehyde appears to favour the indiscriminate reaction with the nucleophiles present in the reaction medium, the ortho anion **2** and the acetaldehyde enolate provided by the THF fragmentation.

The utility of *ortho*-lithiation of diphenylphosphinic acid was further extended to the synthesis of the biphenyl-2,2′-diylbis-(phenylphosphinic acid) **21** through Cu(I) catalysed oxidative coupling following the method described by Spring et al. for the preparation of 2,2-biarylcarboxylates.[35] Thus, by allowing to react anion **2** with 0.5 equiv of CuBr·SMe_2 or CuCN in the presence of 2.5 equiv of 1,3-dinitrobenzeno at room temperature during 2 h the biphenylic diacid **21** was obtained in a yield of 45% (Scheme 5).



Scheme 5. Synthesis of biphenyl-2,2′-diylbis(phenylphosphinic acid) **21** by oxidative coupling of **2**.

Diacid **21** is a phosphorus analogue of diphenic acid (2,2′-biphenyldicarboxylic acid), an important chelating ligand that has been extensively used in the preparation of coordination polymers of a large number of metals showing a variety of applications.[36] A preliminary study of the complexation ability of **21**[37] showed the quantitative formation of a precipitate in the presence of salts of Cu(II), Zn(II), Eu(III) and Y(III). The solids obtained proved to be insoluble in all solvents (H_2O, methanol, ethanol, THF, toluene, DMF, DMSO, diethyl ether, hexane, nitrobencene) and temperatures (up to 210 °C, refluxing nitrobencene) assayed. Although this behaviour supports the formation of coordination complexes no structural information could be obtained. The equimolar mixture of **21** and Y(NO_3)·$6H_2O$ in HNO_3 as solvent afforded a homogeneous solution, from which ^{1}H and ^{31}P NMR spectra were measured. However, a solution of **21** in nitric acid devoid of the yttrium salt provided the same spectra, i.e., the nitric acid displaced the metal ion from the coordination sphere of the ligand. Indirect evidence about the complexation ability of **21** was obtained through quantitative ^{1}H NMR analysis of samples containing diacid **21** and Y(NO_3)$_3$·$6H_2O$ in MeOH-d_4 using cyclooctadiene as internal standard. Assuming a coordination number of six for Y^{3+}, a first sample was prepared by mixing the ligand and the yttrium salt in a ratio 1:0.3. After sonication for 15 min, the ^{1}H NMR spectrum of the supernatant showed the presence of a 50% of free ligand **21**. When a 1:1 stoichiometry was used, the ^{1}H NMR spectrum of the solution consisted of the signals of the standard exclusively.

3. Conclusions

In conclusion, we have developed a general method for the synthesis of mono *ortho*-substituted diphenylphosphinic acids through ortho lithiation of unprotected diphenylphosphinic acid followed by electrophilic quench. Carbon- and heteroatom-centred electrophiles can be used for the ortho functionalization of the parent compound. In the particular case of paraformaldehyde and acetaldehyde as electrophiles, the reaction includes a tandem process, in which the ortho anion is quenched by the aldol adduct formed in the reaction of formaldehyde with the acetaldehyde enolate generated in the decomposition of the solvent by the base. Enantiopure γ-aminophosphinic acids were obtained by trapping the ortho anion with a chiral sulfinylimine. The product was further elaborated to synthesize unproctected or selectively *N*- and *O*-protected derivatives. Oxidative coupling of the ortho anion afforded biphenyl-2,2′-diylbis(phenylphosphinic acid) **21**, an *O*,*O*-chelating ligand structurally related with biphenic acid, in which the C=O group has been replaced by a tetrahedral PhP=O moiety. Compound **21** showed promising coordination properties. Even though the unsolubility of the complexes formed prevented their characterization, this behaviour indicates that diacid **21** may be a useful agent for metal decontamination of fluids. Further studies in this field are currently under investigation.

4. Experimental section

4.1. General experimental conditions

The reactions involving organolithium reagents were performed under an inert atmosphere of nitrogen using Schlenk techniques. The solvents were dried prior to use in a Pure Solv 400-4-MD system, according to the procedure described by Pangborn and Grubbs.[38] Commercial reagents *t*-BuLi, *n*-BuLi, IMe, paraformaldehyde were used as obtained from commercial sources without further purification. TMEDA was dried over CaH_2 and distilled under reduce pressure. Benzaldehyde, aniline and chlorodiphenylphosphine were distilled before use. TLC was performed on Merck plates with aluminium backing and silica gel 60 F254. For column chromatography silica gel 60 (230–400 mesh μm) was used. NMR spectra were recorded in $CDCl_3$, CD_3OD or DMSO-d_6 on a Bruker Avance DPX300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz; ^{31}P, 121.47 MHz) equipped with a QNP ^{1}H/^{13}C/^{19}F/^{31}P probe and a Bruker Avance 500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125.7 MHz; ^{31}P, 202.4 MHz) using a TBO ^{1}H/^{31}P/BB probe (only for compound **16**). Chemical shifts are referred to internal tetramethylsilane for ^{1}H and ^{13}C and to external 85% H_3PO_4 for ^{31}P. Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (J) are measured in Hertz (Hz). Mass spectra were determined on an LC-MS apparatus (APCI ionization mode). High resolution mass spectrometry (HRMS) spectra were measured using a LC/MSD-TOF Agilent Technologies instrument. Infrared spectra were obtained in KBr pellets or using ATR techniques. Elemental analyses were registered on Carlo Erba Instruments EA 1108 CHNS-O.

4.2. General procedure for the synthesis of *o*-substituted phosphinic acids 3–10 and phosphinates 11–15

Over a solution of diphenylphosphinic acid **1** (150 mg, 0.69 mmol) and TMEDA (0.88 mL, 8.8 equiv) in THF (5 mL) at room

temperature, was added a solution of *n*-BuLi (1.9 mL of a 1.6 M solution in hexane, 4.4 equiv). The lithiation was allowed to proceed during 2 h and then the corresponding electrophile was added (4.4 except for DMF where 10 equiv were used). After 2 h of additional stirring, the reaction mixture was poured into a 1 N HCl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The organic layers were concentrated in vacuo. ^1H, $^1H\{^{31}P\}$, and $^{31}P\{^1H\}$ NMR spectra of the crude reaction mixture were measured in order to establish the performance of the reaction. For the reaction with DMF as electrophile 8 equiv of $NaBH_4$ (0.21 g) in MeOH (2 mL) were added prior to the quenching step. The reduction was allowed to proceed during 1 h and then processed according to the procedure described above. The products were purified by flash chromatography using mixtures of AcOEt, hexane, CH_2Cl_2 and methanol (Chart 1).

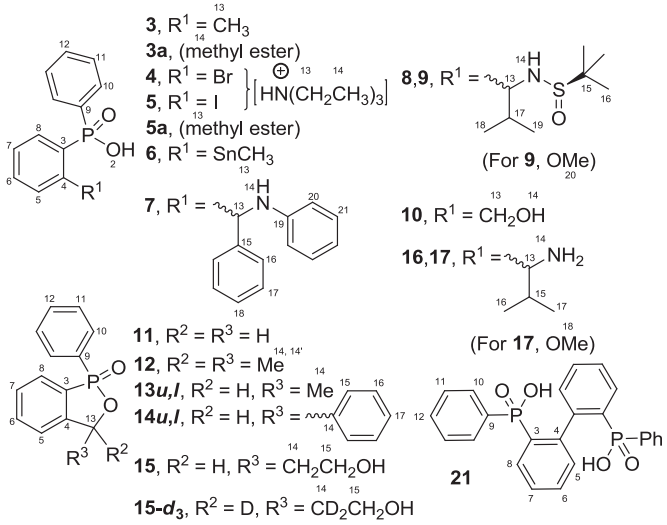


Chart 1. Scheme numbering used for the NMR assignments of the new compounds synthesized.

*4.2.1. (2-Methylphenyl)phenylphosphinic acid (**3**).* Yield after chromatography (CH_2Cl_2:methanol, 10:1) 36% (57 mg); oil; ν (KBr) 3397, 1156, 1138, 1127 cm^{-1}; δ_H (CD_3OD) 2.37 (s, 1H, H13), 7.16 (dd, 1H, $^4J_{PH}$ 4.2, $^3J_{HH}$ 7.5 Hz, H5), 7.23 (bt, 1H, $^3J_{HH}$ 7.5 Hz, H7), 7.39 (m, 4H, H6, H11, H12), 7.71 (ddd, 2H, $^3J_{PH}$ 12.1, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.5 Hz, H10), 7.95 (ddd, 1H, $^3J_{PH}$ 12.5, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.2 Hz, H8); δ_C (CD_3OD) 21.74 (d, $^3J_{PC}$ 4.0 Hz, C13), 126.04 (d, $^3J_{PC}$ 12.0 Hz, C7), 128.94 (d, $^3J_{PC}$ 12.5 Hz, C11), 131.45 (d, $^4J_{PC}$ 2.6 Hz, C12), 131.94 (d, $^3J_{PC}$ 11.7 Hz, C5), 131.89 (d, $^4J_{PC}$ 2.5 Hz, C6), 132.20 (d, $^2J_{PC}$ 10.1 Hz, C10), 133.75 (d, $^2J_{PC}$ 9.0 Hz, C8), 136.39 (d, $^1J_{PC}$ 131.3, Hz, C3), 139.20 (d, $^1J_{PC}$ 132.0, Hz, C9), 142.35 (d, $^2J_{PC}$ 10,4 Hz, C4); δ_P (CD_3OD) 23.71; MS (*m*/*z*): 254.9 (M+Na), 277.0 (M+2Na-1).

*4.2.2. Methyl (2-methylphenyl)phenylphosphinate (**3a**).* Yield after chromatography (AcOEt:hexane, 1:1) 68% (77 mg); oil; ν (ATR), 1224, 1034 cm^{-1}; δ_H ($CDCl_3$) 2.43 (bs, 3H, H13), 3.76 (d, 3H, $^3J_{PH}$ 11.2 Hz, H14), 7.21 (m, 1H, H5), 7.28 (m, 1H, H7), 7.48 (m, 4H, H11, H12, H6), 7.75 (ddd, 2H, $^3J_{PH}$ 12.7, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.4 Hz, H10), 7.89 (ddd, 1H, $^3J_{PH}$ 12.9, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.4 Hz, H8); δ_C ($CDCl_3$) 21.14 (d, $^3J_{PC}$ 4.2 Hz, C13), 51.15 (d, $^2J_{PC}$ 5.4 Hz, C14), 125.45 (d, $^3J_{PC}$ 12.0 Hz, C7), 128.43 (d, $^3J_{PC}$ 13.2 Hz, C11), 128.94 (d, $^1J_{PC}$ 135.2 Hz, C9), 131.42 (d, $^3J_{PC}$ 12.4 Hz, C5), 131.45 (d, $^1J_{PC}$ 134.8 Hz, C3), 131.57 (d, $^2J_{PC}$ 10.8 Hz, C10), 132.01 (d, $^4J_{PC}$ 3.0 Hz, C12), 132.36 (d, $^4J_{PC}$ 2.3 Hz, C6), 133.17 (d, $^2J_{PC}$ 9.0 Hz, C8), 141.92 (d, $^2J_{PC}$ 11,4 Hz, C4); δ_P ($CDCl_3$) 34.72; HRMS (ESI) calcd for $C_{14}H_{15}O_2P$: 247.0888 (MH+), found: 248.0889.

*4.2.3. Triethylammonium 2-bromophenyl(phenyl)phosphinate (**4**).* Yield after chromatography on silica gel impregnated with Et_3N (5%) (CH_2Cl_2:methanol, 20:1) 36% (101 mg); oil; ν (KBr) 3426, 1188, 1129 cm^{-1}; δ_H (CD_3OD) 1.28 (t, 9H, $^3J_{HH}$ 7.4 Hz, H14), 3.16 (q, 6H, $^3J_{HH}$ 7.4 Hz, H13), 7.30 (ddt, 1H, $^5J_{PH}$ 1.0, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.7 Hz, H6), 7.33–7.44 (m, 4H, H7, H11, H12), 7.55 (ddd, 1H, $^4J_{PH}$ 3.7, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.2 Hz, H5), 7.76 (ddd, 2H, $^3J_{PH}$ 12.3, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.7 Hz, H10), 8.12 (ddd, 1H, $^3J_{PH}$ 11.7, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.9 Hz, H8); δ_C (CD_3OD) 7.67 (C14), 46.08 (C13), 125.41 (d, $^2J_{PC}$ 5.7 Hz, C4), 126.22 (d, $^3J_{PC}$ 10.2 Hz, C7), 127.20 (d, $^3J_{PC}$ 12.9 Hz, C11), 129.68 (d, $^4J_{PC}$ 2.9 Hz, C-12), 131.31 (d, $^2J_{PC}$ 9.9 Hz, C-10), 131.49 (d, $^4J_{PC}$ 2.3 Hz, C6), 133.52 (d, $^3J_{PC}$ 8.3 Hz, C5), 134.56 (d, $^2J_{PC}$ 7.2 Hz, C8), 138.10 (d, $^1J_{PC}$ 138.0 Hz, C9), 138.59 (d, $^1J_{PC}$ 129.9 Hz, C3); δ_P (CD_3OD) 18.80; MS (*m*/*z*): 297 (M+1), 102 (M, Et_3NH^+).

*4.2.4. Triethylammonium 2-iodophenyl(phenyl)phosphinate (**5**).* Yield after chromatography on silica gel impregnated with Et_3N (5%) (CH_2Cl_2:methanol, 20:1) 38% (118 mg); oil; ν (KBr) 3395, 1190, 1131, 1098, 1053 cm^{-1}; δ_H (CD_3OD) 1.26 (t, 9H, $^3J_{HH}$ 7.4 Hz, H14), 3.13 (q, 6H, $^3J_{HH}$ 7.4 Hz, H13), 7.08 (ddt, 1H, $^5J_{PH}$ 1.3, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.8 Hz, H6), 7.33–7.40 (m, 3H, H11, H12), 7.44 (ddt, 1H, $^4J_{PH}$ 1.0, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.0 Hz, H7), 7.76 (ddd, 2H, $^3J_{PH}$ 12.2, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.7 Hz, H10), 7.91 (ddd, 1H, $^4J_{PH}$ 3.5, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.1 Hz, H5), 8.12 (ddd, 1H, $^3J_{PH}$ 11.7, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.9 Hz, H8); δ_C (CD_3OD) 7.70 (C14), 45.95 (C13), 98.42 (d, $^2J_{PC}$ 7.4 Hz, C4), 126.88 (d, $^3J_{PC}$ 10.5 Hz, C7), 127.23 (d, $^3J_{PC}$ 13.0 Hz, C11), 129.65 (d, $^4J_{PC}$ 2.7 Hz, C12), 131.20 (d, $^4J_{PC}$ 2.6 Hz, C6), 131.66 (d, $^2J_{PC}$ 9.9 Hz, C10), 134.28 (d, $^2J_{PC}$ 8.1 Hz, C8), 137.64 (d, $^1J_{PC}$ 136.8 Hz, C9), 140.94 (d, $^3J_{PC}$ 9.8 Hz, C5), 141.90 (d, $^1J_{PC}$ 130.8 Hz, C3); δ_P (CD_3OD) 20.24; MS (*m*/*z*): 345 (M+2), 102 (M, Et_3NH^+).

*4.2.5. Methyl 2-iodophenyl(phenyl)phosphinate (**5a**).* Yield after chromatography (AcOEt:hexane, 1:1) 70% (110 mg); oil; ν (ATR) 1225, 1034 cm^{-1}; δ_H ($CDCl_3$) 3.77 (d, 3H, $^3J_{PH}$ 11.4 Hz, H13), 7.30 (ddt, 1H, $^4J_{PH}$ 1.3, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.7 Hz, H7), 7.57 (m, 4H, H11, H12, H6), 7.78 (m, 2H, H10), 8.03 (ddd, 1H, $^4J_{PH}$ 4.3, $^3J_{HH}$ 7.9, $^4J_{HH}$ 1.1 Hz, H5), 8.07 (ddd, 1H, $^3J_{PH}$ 12.3, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6 Hz, H8); δ_C ($CDCl_3$) 51.01 (d, $^2J_{PC}$ 6.0 Hz, C13), 97.32 (d, $^2J_{PC}$ 9.1 Hz, C4), 127.74 (d, $^3J_{PC}$ 11.7 Hz, C7), 128.34 (d, $^3J_{PC}$ 13.5 Hz, C11), 128.91 (d, $^1J_{PC}$ 142.9 Hz, C9), 132.03 (d, $^2J_{PC}$ 10.8 Hz, C10), 132.52 (d, $^4J_{PC}$ 3.0 Hz, C12), 133.77 (d, $^4J_{PC}$ 3.0 Hz, C6) 133.45 (d, $^1J_{PC}$ 142.5 Hz, C3), 135.25 (d, $^2J_{PC}$ 8.4 Hz, C8), 141.86 (d, $^1J_{PC}$ 10.8 Hz, C7); δ_P ($CDCl_3$) 34.87; HRMS (ESI) calcd for $C_{13}H_{13}IO_2P$: 358.9698 (MH+), found: 358.9691.

*4.2.6. Phenyl(2-(trimethylstannyl)phenyl)phosphinic acid (**6**).* Yield after chromatography on silica gel impregnated with Et_3N (5%) (CH_2Cl_2:methanol, 20:1) 68% (180 mg); white solid mp 260–261 °C; ν (KBr) 3395, 3052, 1126, 1104 cm_{-1}; δ_H (CD_3OD) 0.61 (s, 9H, H13), 7.40 (m, 4H, H7, H11, H12), 7.48 (bt, 1H, $^3J_{HH}$ 6.6 Hz, H6), 7.67 (dd, 1H, $^2J_{PH}$ 11.0, $^3J_{HH}$ 6.6 Hz, H8), 7.73 (ddd, 2H, $^3J_{PH}$ 11.2, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6 Hz, H10), 7.97 (bd, 1H, H5); δ_C (CD_3OD) -3.47 (C13), 127.59 (d, $^3J_{PC}$ 12.5 Hz, C11), 128.25 (d, $^3J_{PC}$ 12.3 Hz, C7), 129.48 (d, $^4J_{PC}$ 2.7 Hz, C6), 130.08 (d, $^4J_{PC}$ 2.1 Hz, C11), 130.85 (d, $^2J_{PC}$ 9.9 Hz, C10), 130.95 (d, $^2J_{PC}$ 13.5 Hz, C8), 135.00 (d, $^3J_{PC}$ 14.9 Hz, C5), 138.00 (d, $^1J_{PC}$ 132.5 Hz, C9), 143.52 (d, $^1J_{PC}$ 134.0 Hz, C3), 147.66 (d, $^2J_{PC}$ 15.3 Hz, C4); δ_P (CD_3OD) 26.60; MS (*m*/*z*): 367 (M−15).

*4.2.7. Phenyl(2-(phenyl(phenylamino)methyl)phenyl)phosphinic acid (**7**).* Yield after chromatography (AcOEt→AcOEt:MeOH 10:1) 39% (106.5 mg); oil; ν (KBr) 3397, 3053, 2924, 1665, 1598, 1179, 1131 cm^{-1}; δ_H (CD_3OD) 6.41 (d, 2H, $^3J_{HH}$ 7.8 Hz, H20), 6.52 (t, 1H, $^3J_{HH}$ 7.2 Hz, H22), 6.57 (s, 1H, H13), 6.92 (dd, 2H, $^3J_{HH}$ 7.8 Hz, $^3J_{HH}$ 7.8 Hz, H21), 7.06–7.35 (m, 11H, H5, H6, H7, H11, H12, H16, H17, H18), 7.62 (ddd,, $^3J_{PH}$ 11.9, $^3J_{HH}$ 6.9, $^4J_{HH}$ 1.3 Hz, H10), 8.15 (ddd, $^3J_{PH}$ 11.8, $^3J_{HH}$ 6.6, $^4J_{HH}$ 1.8 Hz, H8); δ_C (CD_3OD) 59.15 (d, $^3J_{PC}$ 3.6 Hz, C13), 115.24 (C20), 117.88 (C22), 127.28 (C18), 127.41 (d, $^3J_{PC}$ 11.1 Hz, C5), 128.59 (d, $^3J_{PC}$ 12.4 Hz, C11), 128.68 (C16), 128.95 (C17), 129.34 (C21), 130.53 (d, $^3J_{PC}$ 10.6 Hz, C7), 130.80 (d, $^4J_{PC}$ 2.5 Hz, C12), 131.81 (d, $^4J_{PC}$ 2.3 Hz, C6), 132.19 (d, $^2J_{PC}$ 10.1 Hz, C10), 134.27 (d, $^2J_{PC}$ 8.4 Hz,

C8), 138.15 (d, $^{1}J_{PC}$ 127.2 Hz, C3), 140.60 (d, $^{1}J_{PC}$ 132.5 Hz, C9), 144.73 (C15), 147.08 (d, $^{2}J_{PC}$ 9.8 Hz, C4), 148.85 (C19); δ_P (CD_3OD) 20.37; MS (*m*/*z*): 444.0 (M+2Na-1).

*4.2.8. 2-(1-(1,1-Dimethylethylsulfinamido)-2-methylpropyl)phenyl (phenyl)phosphinic acid (**8**).* Yield after chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:MeOH, 10:1) 19% (50 mg); oil; δ_H (DMSO-d_6, 130 °C) 0.09 (d, 3H, $^{3}J_{HH}$ 6.1 Hz, H18), 0.80 (d, 3H, $^{3}J_{HH}$ 6.3 Hz, H-19), 1.11 (s, 9H, H16), 1.88 (m, 1H, H17), 7.00–7.13 (m, 3H, ArH), 7.20–7.36 (m, 2H, ArH), 7.47 (m, 1H, ArH), 7.60 (m, 2H, $^{3}J_{PH}$ 11.4 Hz, H10), 8.04 (m, 1H, $^{3}J_{PH}$ 11.6 Hz, H8); δ_P (DMSO-d_6, 130 °C) 12.02; MS (*m*/*z*): 394.2 (M+1).

*4.2.9. 2-(Hydroxymethyl)phenyl(phenyl)phosphinic acid (**10**).* Yield after chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:MeOH, 10:1) 35% (61 mg); oil; ν (KBr) 3403, 3203, 1153, 1019, cm^{-1}; δ_H (DMSO-d_6, 110 °C) 4.47 (s, 2H, H13), 7.14–7.28 (m, 6H, H5, H6, H7, H11, H12), 7.65 (ddd, 2H, $^{3}J_{PH}$ 11.1, $^{3}J_{HH}$ 7.8 Hz, H10), 7.95 (ddd, 1H, $^{3}J_{PH}$ 11.6, $^{3}J_{HH}$ 7.3 Hz, H8); δ_C (DMSO-d_6, rt) 63.21 (d, $^{3}J_{PC}$ 6.9 Hz, C13), 125.96 (d, $^{3}J_{PC}$ 11.6 Hz, C5), 127.15 (d, $^{3}J_{PC}$ 11.6 Hz, C11), 127.85, 128.81, 129.47, 130.88 (d, $^{2}J_{PC}$ 8.5 Hz, C10), 133.82 (d, $^{2}J_{PC}$ 6.7 Hz, C8), 144.44 (d, $^{2}J_{PC}$ 10.5 Hz, C4). δ_P (DMSO-d_6, 110 °C) 13.75; MS (*m*/*z*): 249.1 (M+1).

*4.2.10. 1-Phenyl-1,3-dihydrobenzo[c][1,2]oxaphosphole 1-oxide (**11**).* Yield after chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:MeOH, 10:1) 27% (42 mg); oil; ν (KBr) 3060, 1200, 1122 cm^{-1}; δ_H ($CDCl_3$) 5.44 (dd, 1H, $^{3}J_{PH}$ 11.5, $^{2}J_{HH}$ 13.7, Hz, H13), 5.61 (dd, 1H, $^{3}J_{PH}$ 3.3, $^{2}J_{HH}$ 13.7 Hz, H13), 7.39–7.48 (m, 4H, H5, H7, H11), 7.54 (dtt, 1H, $^{5}J_{PH}$ 1.5, $^{3}J_{HH}$ 7.5, $^{4}J_{HH}$ 1.4 Hz, H12), 7.61 (ddt, 1H, $^{5}J_{PH}$ 1.4, $^{3}J_{HH}$ 7.6, $^{4}J_{HH}$ 1.1 Hz, H6), 7.66–7.76 (m, 3H, H8, H10); δ_C ($CDCl_3$) 72.59 (C13), 122.18 (d, $^{3}J_{PC}$ 11.2 Hz, C5), 127.98 (d, $^{1}J_{PC}$ 126.7 Hz, C3), 128.28 (d, $^{2}J_{PC}$ 13.3, Hz, C8), 128.56 (d, $^{3}J_{PC}$ 14.0 Hz, C11), 128.95 (d, $^{3}J_{PC}$ 12.3 Hz, C7), 130.91 (d, $^{1}J_{PC}$ 141.2 Hz, C9), 131.70 (d, $^{2}J_{PC}$ 11.4 Hz, C10), 132.69 (d, $^{4}J_{PC}$ 3.0 Hz, C12), 132.76 (d, $^{4}J_{PC}$ 2.7 Hz, C6), 143.95 (d, $^{2}J_{PC}$ 20.8 Hz, C4); δ_P ($CDCl_3$) 50.30; MS (*m*/*z*): 231.1 (M+1).

*4.2.11. 3,3-Dimethyl-1-phenyl-1,3-dihydro-2,1-benzoxaphos-phole 1-oxide (**12**).* Yield after chromatography (AcOEt:hexane, 1:1) 67% (100 mg); oil; ν (KBr) 1236, 1225 cm^{-1}; δ_H (CD_3OD) 1.81 (s, 3H, H14), 1.84 (s, 3H, H14′), 7.49–7.66 (m, 6H, H5, H7, H8, H11, H12), 7.70–7.80 (m, 3H, H6, H10); δ_C (CD_3OD) 29.37 (d, $^{3}J_{PC}$ 5.0 Hz, C14), 31.55 (C14′), 91.35 (d, $^{2}J_{PC}$ 1.2 Hz, C13), 122.49 (d, $^{3}J_{PC}$ 12.2 Hz, C5), 127.97 (d, $^{1}J_{PC}$ 126.0 Hz, C3), 128.92 (d, $^{3}J_{PC}$ 12.9 Hz, C8), 129.99 (d, $^{3}J_{PC}$ 14.0 Hz, C11), 130.42 (d, $^{2}J_{PC}$ 12.6 Hz, C7), 131.46 (d, $^{1}J_{PC}$ 142.8 Hz, C9), 132.89 (d, $^{2}J_{PC}$ 11.6 Hz, C10), 134.24 (d, $^{4}J_{PC}$ 3.0 Hz, C12), 134.79 (d, $^{4}J_{PC}$ 2.6 Hz, C6), 154.25 (d, $^{2}J_{PC}$ 18.2 Hz, C4); δ_P (CD_3OD) 46.79; MS (*m*/*z*): 281.0 (M+Na).

*4.2.12. 3-Methyl-1-phenyl-1,3-dihydro-2,1-benzoxaphos-phole 1-oxide (**u**/**l**-**13**).* Yield after chromatography (AcOEt:hexane, 1:1) 41% (56 mg), mixture of l:u isomers (4.1:1 and 1:3.9); isomer ***l*-13**: oil; ν (ATR) 1264, 1232 cm^{-1}; δ_H ($CDCl_3$) 1.81 (d, 3H, $^{3}J_{HH}$ 6.6 Hz, H14) 5.70 (dq, 1H, $^{3}J_{PH}$ 10.0, $^{3}J_{HH}$ 6.6 Hz, H13), 7.35–7.69 (m, 6H), 7.70 (m, 2H, H10), 7.72 (m, 1H, H8); δ_C ($CDCl_3$) 23.59 (C14), 81.11 (C13), 122.27 (d, $^{3}J_{PC}$ 11.8 Hz, C5), 128.06 (d, $^{1}J_{PC}$ 125.6 Hz, C9), 128.26 (d, $^{2}J_{PC}$ 12.6, Hz, C8), 128.51 (d, $^{3}J_{PC}$ 13.9 Hz, C11), 128.99 (d, $^{3}J_{PC}$ 12.0 Hz, C7), 131.21 (d, $^{1}J_{PC}$ 141.2 Hz, C3), 131.54 (d, $^{2}J_{PC}$ 11.4 Hz, C10), 132.51 (d, $^{4}J_{PC}$ 3.0 Hz, C12), 132.81 (d, $^{4}J_{PC}$ 2.4 Hz, C6), 148.71 (d, $^{2}J_{PC}$ 20.0 Hz, C4); δ_P ($CDCl_3$) 47.06; HRMS (ESI) calcd for $C_{14}H_{14}O_2P$: 245.0731 (MH+), found: 245.0726. Isomer ***u*-13**: oil; ν (ATR) 1228, 1204 cm^{-1}; δ_H ($CDCl_3$) 1.74 (d, 3H, $^{3}J_{HH}$ 6.6 Hz, 14), 5.89 (q, 1H, $^{3}J_{HH}$ 6.6 Hz, H13), 7.35–7.69 (7H, ArH), 7.77 (m, 2H, H10); δ_C ($CDCl_3$) 22.12 (d, $^{4}J_{PC}$ 4.8 Hz, C14), 80.40 (C13), 121.94 (d, $^{3}J_{PC}$ 12.1 Hz, C5), 128.18 (d, $^{2}J_{PC}$ 13.2, Hz, C8), 128.29 (d, $^{1}J_{PC}$ 125.6 Hz, C9) 128.51 (d, $^{3}J_{PC}$ 13.7 Hz, C11), 128.96 (d, $^{3}J_{PC}$ 12.6 Hz, C7),130.86 (d, $^{1}J_{PC}$ 141.8 Hz, C3), 132.04 (d, $^{2}J_{PC}$ 11.4 Hz, C10), 132.56 (d, $^{4}J_{PC}$ 3.0 Hz, C12), 132.81 (d, $^{4}J_{PC}$ 3.0 Hz, C6), 148.75 (d, $^{2}J_{PC}$ 18.62 Hz, C4); δ_P ($CDCl_3$) 47.29; HRMS (ESI) calcd for $C_{14}H_{14}O_2P$: 245.0731 (MH+), found: 245.0720.

*4.2.13. 1,3-Diphenyl-1,3-dihydro-2,1-benzoxaphosphole 1-oxide (**u**/**l**-**14**).* 1,3-Diphenyl-1,3-dihydro-2,1-benzoxaphosphole 1-oxide (**u**/**l**-**14**)Yield after chromatography (CH_2Cl_2:MeOH, 10:1) 43% (57 mg), mixture of l:u isomers (3.6:1); oil; ν (KBr) 3059, 1231, 1143, 1122 cm^{-1}; δ_H (CD_3OD) 6.77 (d, 1H, $^{3}J_{PH}$ 10.1, H13, **l**), 6.88 (s, 1H, H13, **u**), 7.26–7.87 (m, 13H, ArH), 8.03 (m, 1H, H8); δ_C (CD_3OD) 87.65 (d, $^{2}J_{PC}$ 0.6 Hz, C13, **u**), 88.10 (d, $^{2}J_{PC}$ 1.4 Hz, C13, **l**), 125.30 (d, $^{3}J_{PC}$ 11.6 Hz, C5, **l**), 125.40 (d, $^{2}J_{PC}$ 11.7 Hz, C5, **u**), 128.40 (d, $^{1}J_{PC}$ 126.3 Hz, C3, **l**), 128.37 (C15, **l**), 128.74 (d, $^{2}J_{PC}$ 13.1 Hz, C7, **l**), 128.96 (d, $^{2}J_{PC}$ 12.7 Hz, C7, **u**), 129.26 (C17, **l**), 129.96 (C16, **l**), 130.04 (d, $^{3}J_{PC}$ 14.0 Hz, C11, **u**), 130.08 (d, $^{3}J_{PC}$ 14.1 Hz, C11, **l**), 130.66 (d, $^{2}J_{PC}$ 12.4 Hz, C8, **l**), 131.45 (d, $^{1}J_{PC}$ 142.79 Hz, C9, **l**), 132.85 (d, $^{2}J_{PC}$ 11.7 Hz, C10, **l**), 133.04 (d, $^{2}J_{PC}$ 11.7 Hz, C10, **u**), 134.44 (d, $^{4}J_{PC}$ 3.0 Hz, C6, **l**), 134.51 (d, $^{4}J_{PC}$ 3.0 Hz, C6, **u**), 134.66 (d, $^{4}J_{PC}$ 2.3 Hz, C12, **u**), 134.69 (d, $^{4}J_{PC}$ 2.7 Hz, C12, **l**), 139.41 (d, $^{3}J_{PC}$ 5.7 Hz, C14, **u**), 140.69 (d, $^{3}J_{PC}$ 1.2 Hz, C14, **l**), 148.51 (d, $^{2}J_{PC}$ 17.7 Hz, C4, **u**), 149.20 (d, $^{2}J_{PC}$ 19.8 Hz, C4, **l**); δ_P (CD_3OD) 50.12 (**u**), 50.28 (**l**); MS (*m*/*z*): 329.0 (M+Na).

*4.2.14. 3-(2-Hydroxyethyl-1-phenyl-1,3-dihydrobenzo-[c][1,2]oxaphosp-hole 1-oxide) (**u**/**l**-**15**).* Yield after chromatography (CH_2Cl_2:MeOH, 30:1) 37% (70 mg), mixture of l:u isomers (1.5:1); oil; ν (KBr) 3376, 1222 cm^{-1}; δ_H ($CDCl_3$) 1.90 (m, 1H, H14, **u**), 2.08 (m, 1H, H14, **l**), 2.35 (m, 1H, H14′), 3.88 (m, 2H, H15), 5.82 (ddd, 1H, $^{3}J_{PH}$ 10.8, $^{3}J_{HH}$ 9.2, $^{3}J_{HH}$ 2.9 Hz, H13, **l**), 5.94 (d, 1H, $^{3}J_{HH}$ 10.2 Hz, H13, **u**), 7.34–7.74 (m, 9H, ArH); δ_C ($CDCl_3$) 39.60 (d, $^{3}J_{PC}$ 4.4 Hz, C14, **u**), 40.52 (C14, **l**), 58.24 (C15, **l**), 58.60 (C15, **u**), 81.86 (d, $^{2}J_{PC}$ 0.8 Hz, C13, **u**), 82.36 (d, $^{2}J_{PC}$ 1.1 Hz, C13, **l**), 122.32 (d, $^{3}J_{PC}$ 11.7 Hz, C5, **u**), 122.61 (d, $^{3}J_{PC}$ 11.6 Hz, C5, **l**), 127.99 (d, $^{1}J_{PC}$ 126.0 Hz, C3, **u**), 128.05 (d, $^{1}J_{PC}$ 126.1 Hz, C3, **l**), 128.22 (d, $^{3}J_{PC}$ 13.1 Hz, C7), 128.63 (d, $^{3}J_{PC}$ 13.8 Hz, C11, **l**), 128.68 (d, $^{3}J_{PC}$ 14.0 Hz, C11, **u**), 129.13 (d, $^{2}J_{PC}$ 12.4 Hz, C8), 130.53 (d, $^{1}J_{PC}$ 142.0 Hz, C9, **u**), 130.72 (d, $^{1}J_{PC}$ 141.6 Hz, C9, **l**), 131.75 (d, $^{2}J_{PC}$ 11.7 Hz, C10, **l**), 132.02 (d, $^{2}J_{PC}$ 11.6 Hz, C10, **u**), 132.76 (d, $^{4}J_{PC}$ 2.9 Hz, C6/12, **l**), 132.79 (d, $^{4}J_{PC}$ 2.9 Hz, C6/12, **u**), 132.96 (d, $^{4}J_{PC}$ 2.8 Hz, C6/12, **l**), 133.00 (d, $^{4}J_{PC}$ 2.7 Hz, C6/12, **u**), 147.77 (d, $^{2}J_{PC}$ 20.1 Hz, C4, **l**), 147.90 (d, $^{2}J_{PC}$ 19.0 Hz, C4, **u**); δ_P ($CDCl_3$) 48.22, 48.23; MS (*m*/*z*): 297.0 (M+Na).

*4.2.15. 3-(1,1-Dideuterium-2-hydroxyethyl-3-deuterium-1-phenyl-1,3-dihydrobenzo-[c][1,2]oxaphosphole 1-oxide) (**u**/**l**-**15**-**d_3**).* Yield after chromatography (AcOEt:hexane, 1:1) 20% (25 mg), mixture of l:u isomers (1.6:1); oil; ν (ATR) 3379, 2880, 1264, 1219 cm^{-1}; δ_H ($CDCl_3$) 3.92 (m, 2H, H15), 7.37–7.79 (m, 9H, ArH); δ_C ($CDCl_3$) 39.05 (m, C14, **u**), 39.35 (C14, **l**), 58.33 (C15, **l**), 58.91 (C15, **u**), 81.45 (d, $^{1}J_{CD}$ 22.9 Hz, C13, **u**), 81.56 (t, $^{1}J_{CD}$ 22.9 Hz, C13, **l**), 122.13 (d, $^{3}J_{PC}$ 11.7 Hz, C5, **u**), 122.44 (d, $^{3}J_{PC}$ 11.6 Hz, C5, **l**), 128.14 (d, $^{1}J_{PC}$ 126.1 Hz, C3, **u**), 128.23 (d, $^{1}J_{PC}$ 126.1 Hz, C3, **l**), 128.27 (d, $^{3}J_{PC}$ 12.9 Hz, C7, **l**), 128.28 (d, $^{3}J_{PC}$ 13.1 Hz, C7, **u**), 128.55 (d, $^{3}J_{PC}$ 14.3 Hz, C11, **l**), 128.61 (d, $^{3}J_{PC}$ 13.9 Hz, C11, **u**), 129.11 (d, $^{2}J_{PC}$ 12.1 Hz, C8), 130.55 (d, $^{1}J_{PC}$ 142.0 Hz, C9, **u**), 130.68 (d, $^{1}J_{PC}$ 141.7 Hz, C9, **l**), 131.73 (d, $^{2}J_{PC}$ 11.4 Hz, C10, **l**), 131.98 (d, $^{2}J_{PC}$ 11.5 Hz, C10, **u**), 132.69 (d, $^{4}J_{PC}$ 2.9 Hz, C6/12, **l**), 132.70 (d, $^{4}J_{PC}$ 2.9 Hz, C6/12, **u**), 132.86 (d, $^{4}J_{PC}$ 2.8 Hz, C6/12, **l**), 132.91 (d, $^{4}J_{PC}$ 2.7 Hz, C6/12, **u**), 147.51 (d, $^{2}J_{PC}$ 19.9 Hz, C4, **l**), 147.63 (d, $^{2}J_{PC}$ 19.1 Hz, C4, **u**); δ_P ($CDCl_3$) 48.22, 48.23; HRMS (ESI) calcd for $C_{15}H_{13}D_3O_3P$: 278.1022 (MH+), found: 278.1018.

4.3. Synthesis of methyl (2-{1-[(*tert*-butylsulfinyl)amino]-2-methylpropyl}phenyl)phenylphosphinate 9

To a solution of the crude reaction mixture of **8** (340 mg) in acetone (10 mL), was added K_2CO_3 (0.95 g, 10 equiv) and MeI (0.48 mL, 5 equiv). The reaction was stirred at reflux for 3 h. The crude reaction was centrifuged at 4500 rpm for 5 min and the

solvent was concentrated in vacuo. The product **9** was purified by flash chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:MeOH, 10:1) 45% (128 mg), mixture 1:1 of *P*-epimers; oil; ν (KBr) 3440, 2960, 2358, 2340, 1214, 1127, 1035 cm^{-1}; δ_H (CD_3OD) 0.45 (d, 3H, $^3J_{HH}$ 6.7 Hz, H18), 0.74 (d, 3H, $^3J_{HH}$ 6.9 Hz, H19), 0.76 (s, 9H, H16), 1.05 (d, 3H, $^3J_{HH}$ 6.7 Hz, H18), 1.11 (d, 3H, $^3J_{HH}$ 6.6 Hz, H19), 1.04 (s, 9H, H16), 2.00 (m, 2H, H17), 3.72 (d, 3H, $^3J_{PH}$ 11.2 Hz, H20), 3.75 (d, 3H, $^3J_{PH}$ 11.4 Hz, H20), 4.95 (m, 2H, H13), 7.31–7.80 (m, 16H, 16ArH), 7.91 (ddd, 1H, $^3J_{PH}$ 12.1, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.2 Hz, H8); δ_C (CD_3OD) 19.89 (C18), 19.92 (C-19), 20.30 (C18), 20.35 (C19), 22.69 (C16), 22.93 (C16), 35.21 (C17), 36.26 (C17), 52.10 (d, $^2J_{PC}$ 6.0 Hz, C20), 52.33 (d, $^2J_{PC}$ 6.0 Hz, C20), 56.74 (C15), 57.22 (C15), 64.67 (d, $^3J_{PC}$ 4.2 Hz, C13), 65.06 (d, $^3J_{PC}$ 4.8 Hz, C13), 127.96 (d, $^3J_{PC}$ 13.3 Hz, C5/7), 127.97 (d, $^3J_{PC}$ 11.5 Hz, C5/7), 129.00 (d, $^1J_{PC}$ 136.3 Hz, C3), 129.45 (d, $^1J_{PC}$ 137.5 Hz, C3), 129.84 (d, $^3J_{PC}$ 12.1 Hz, C7/5), 129.91 (d, $^3J_{PC}$ 12.6 Hz, C7/5), 130.00 (d, $^3J_{PC}$ 13.2 Hz, C11), 130.11 (d, $^3J_{PC}$ 13.2 Hz, C11), 131.96 (d, $^1J_{PC}$ 134.5 Hz, C9), 132.56 (d, $^1J_{PC}$ 134.3 Hz, C9), 133.15 (d, $^2J_{PC}$ 10.3 Hz, C10), 133.21 (d, $^2J_{PC}$ 10.6 Hz, C10), 133.39 (d, $^2J_{PC}$ 8.5 Hz, C8), 133.67 (d, $^2J_{PC}$ 10.7 Hz, C8), 133.81 (d, $^4J_{PC}$ 2.8 Hz, C6/12), 134.04 (d, 2C, $^4J_{PC}$ 2.5 Hz, C6/12), 134.08 (d, $^4J_{PC}$ 2.9 Hz, C6/12), 149.42 (d, $^2J_{PC}$ 10.9 Hz, C4), 150.19 (d, $^2J_{PC}$ 12.6 Hz, C4); δ_P (CD_3OD) 34.43, 36.85; MS (*m*/*z*): 408.2 (M+1).

4.4. Synthesis [2-(1-amino-2-methylpropyl)phenyl] phenylphosphinic acid 16

To a solution of the crude reaction mixture of **8** (340 mg) in 8 mL of MeOH was added 2 mL of 12 M HCl at room temperature and the reaction was stirred for 3 days. Then, the pH was set to neutral by adding 6 M NaOH and the solvent was evaporated in vacuo. To the crude mixture was added water (10 mL) and CH_2Cl_2 (10 mL) and the mixture was centrifuged at 4500 rpm for 5 min showing a white solid interface. The water and the CH_2Cl_2 were eliminated and the solid was dried in vacuo to give the amino acid **16** in 25% yield (50 mg); white solid mp 289–290 °C; ν (KBr) 3440, 3050, 1184, 1125 cm^{-1}; δ_H (500.13 MHz, D_2O+NaOD) 0.12 (d, 3H, $^3J_{HH}$ 6.4 Hz, H16), 0.77 (d, 3H, $^3J_{HH}$ 6.4 Hz, H17), 1.72 (dhp, 1H, $^3J_{HH}$ 9.8, $^3J_{HH}$ 6.4, H15), 3.94 (d, 1H, $^3J_{HH}$ 9.8 Hz, H13), 4.71 (s, 2H, H14), 7.30–7.39 (m, 3H, H5, H7, H11, H12), 7.45 (t, 1H, $^3J_{HH}$ 7.6 Hz, H6), 7.52 (ddd, 2H, $^3J_{PH}$ 12.1, $^3J_{HH}$ 7.8, $^3J_{HH}$ 1.9 Hz, H10), 7.86 (ddd, 1H, $^3J_{PH}$ 12.1, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.9 Hz, H8); δ_C (D_2O+NaOD) 18.60 (C16), 19.03 (C17), 33.25 (C15), 57.36 (d, $^3J_{PC}$ 4.8 Hz, C13), 126.29 (d, $^3J_{PC}$ 11.5 Hz, C5), 126.95 (d, $^3J_{PC}$ 11.0 Hz, C7), 128.26 (d, $^3J_{PC}$ 12.4 Hz, C11), 130.48 (d, $^2J_{PC}$ 10.3 Hz, C10), 130.51 (d, $^4J_{PC}$ 2.7 Hz, C12), 131.53 (d, $^4J_{PC}$ 2.5 Hz, C6), 132.25 (d, $^2J_{PC}$ 9.1 Hz, C8), 135.49 (d, $^1J_{PC}$ 128.4 Hz, C3), 138.76 (d, $^1J_{PC}$ 131.0 Hz, C9), 147.95 (d, $^2J_{PC}$ 10.5 Hz, C4); δ_P (D_2O+NaOD) 22.43; MS (*m*/*z*): 290.2 (M+1).

4.5. Synthesis methyl [2-(1-amino-2-methylpropyl)phenyl] phenylphosphinate 17

To a solution of methyl phosphinate **9** (0.23 mmol, 94 mg) in 8 mL of MeOH was added 2 mL of 12 M HCl at room temperature and the reaction was stirred for 3 days. Then, the reaction was extracted with CH_2Cl_2, the aqueous layers were alkalized with 1 M NaOH and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give methyl phosphinate **17** in 75% yield (53 mg), mixture 1:1 of *P*-epimers; oil; ν (KBr) 3421, 3059, 1214, 1032 cm^{-1}; δ_H (CD_3OD) 0.15 (d, 3H, $^3J_{HH}$ 7.0 Hz, H16), 0.56 (d, 3H, $^3J_{HH}$ 7.0 Hz, H16), 0.97 (d, 3H, $^3J_{HH}$ 6.5 Hz, H17), 1.03 (d, 3H, $^3J_{HH}$ 6.6 Hz, H17), 1.83–2.02 (m, 2H, H15), 3.78 (d, 3H, $^3J_{PH}$ 11.1 Hz, H18), 3.81 (d, 3H, $^3J_{PH}$ 11.2 Hz, H18), 4.12 (dd, 1H, $^4J_{PH}$ 0.9, $^3J_{HH}$ 11.1 Hz, H13), 4.21 (dd, 1H, $^4J_{PH}$ 0.9, $^3J_{HH}$ 8.6 Hz, H13), 7.39–7.48 (m, 2H, H7), 7.53–7.60 (m, 4H, H11), 7.62–7.68 (m, 6H, H5, H6, H12), 7.74–7.82 (m, 4H, H10), 7.88 (dddd, 1H, $^3J_{PH}$ 13.0, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.3, $^5J_{HH}$ 0.8 Hz, H8), 7.93 (dddd, 1H, $^3J_{PH}$ 12.7, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.3, $^5J_{HH}$ 0.8 Hz, H8); δ_C (CD_3OD) 18.02 (C16), 18.42 (C16), 18.73 (C17), 19.05 (C17), 33.49 (C15), 34.58 (C15), 50.74 (d, $^2J_{PC}$ 6.0 Hz, C18), 50.86 (d, $^2J_{PC}$ 6.0 Hz, C18), 57.97 (d, $^3J_{PC}$ 5.0 Hz, C13), 58.43 (d, $^3J_{PC}$ 5.0 Hz, C13), 126.49 (d, $^3J_{PC}$ 12.8 Hz, C7), 126.60 (d, $^3J_{PC}$ 12.2 Hz, C7), 127.51 (d, $^3J_{PC}$ 12.4 Hz, C5), 127.58 (d, $^3J_{PC}$ 12.6 Hz, C5), 128.26 (d, $^1J_{PC}$ 137.3 Hz, C3), 128.64 (d, $^1J_{PC}$ 138.4 Hz, C3), 128.62 (d, $^3J_{PC}$ 13.2 Hz, C11), 128.62 (d, $^3J_{PC}$ 13.2 Hz, C11), 130.99 (d, $^1J_{PC}$ 133.7 Hz, C9), 131.15 (d, $^1J_{PC}$ 134.7 Hz, C9), 131.38 (d, $^2J_{PC}$ 10.6 Hz, C10), 131.56 (d, $^2J_{PC}$ 10.8 Hz, C10), 132.15 (d, $^2J_{PC}$ 8.7 Hz, –8), 132.43 (d, $^2J_{PC}$ 9.7 Hz, C8), 132.46 (d, $^4J_{PC}$ 2.9 Hz, C12), 132.54 (d, $^4J_{PC}$ 2.9 Hz, C12), 133.02 (d, $^4J_{PC}$ 2.7 Hz, C6), 133.09 (d, $^4J_{PC}$ 2.7 Hz, C6), 149.66 (d, $^2J_{PC}$ 12.2 Hz, C4), 149.81 (d, $^2J_{PC}$ 11.9 Hz, C4); δ_P (CD_3OD) 35.83, 36.26; MS (*m*/*z*): 304 (M+1).

4.6. Synthesis of biphenyl-2,2′-diylbis(phenylphosphinic acid) 21

Over a solution of diphenylphosphinic acid **1** (150 mg, 0.69 mmol) and TMEDA (0.88 mL, 8.8 equiv) in dry THF (5 mL) at rt, was added a solution of *n*-BuLi (1.9 mL of a 1.6 M solution in hexane, 4.4 equiv). After 2 h of lithiation at rt it was added $CuBr \cdot SMe_2$ (70 mg, 0.5 equiv) and a solution of 1,3-dinitrobenzene (290 mg, 2.5 equiv) in dry THF (1.7 mL). The reaction was stirred for an additional 1 h and then was filtered through a pad of silica, washed firstly with CH_2Cl_2 to remove the 1,3-dinitrobenzene and subsequently with MeOH to extract the product. The solvent was removed under reduced pressure and the crude mixture obtained was dissolved in CH_2Cl_2, washed with HCl (1 N) and water, dried over Na_2SO_4 and concentrated in vacuo. The product was purified by precipitation from AcOEt to give 24 in 45% yield (74 mg); brown solid mp 220 dec °C; ν (KBr) 3438, 3055, 1139, 962 cm^{-1}; δ_H (CD_3OD) 6.23 (ddd, 1H, $^4J_{PH}$ 4.7, $^3J_{HH}$ 6.7, $^4J_{HH}$ 0.7 Hz, H5), 7.07 (ddt, 1H, $^5J_{PH}$ 1.3, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.2 Hz, H6), 7.22–7.34 (m, 4H, H10, H11), 7.45–7.52 (m, 2H, H7, H12), 8.15 (ddd, $^3J_{PH}$ 12.8, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.1 Hz, H8); δ_C (CD_3OD) 128.69 (d, $^3J_{PC}$ 11.8 Hz, C7), 129.35 (d, $^3J_{PC}$ 13.6 Hz, C11), 132.07 (d, $^1J_{PC}$ 129.6 Hz, Hz, C3), 132.40 (d, $^4J_{PC}$ 2.6 Hz, C6), 132.43 (d, $^2J_{PC}$ 10.7 Hz, C10), 132.85 (dd, $^3J_{PC}$ 11.6, $^4J_{PC}$ 0.6 Hz, C5), 133.05 (d, $^4J_{PC}$ 2.8 Hz, C12), 133.41 (d, $^2J_{PC}$ 8.2 Hz, C8), 134.17 (d, $^1J_{PC}$ 145.9 Hz, C9), 144.38 (dd, $^2J_{PC}$ 11.7, $^3J_{PC}$ 4.1 Hz, C4); δ_P (CD_3OD) 28.25. MS (*m*/*z*): 435.0 (M+1).

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Supplementary data

^1H, ^{13}C and ^{31}P NMR spectra of the new products. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.088.

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