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o-Hydroxyarylphosphanes: Strategies for Syntheses of Configurationally Stable, Electronically and Sterically Tunable Ambiphiles with Multiple Applications

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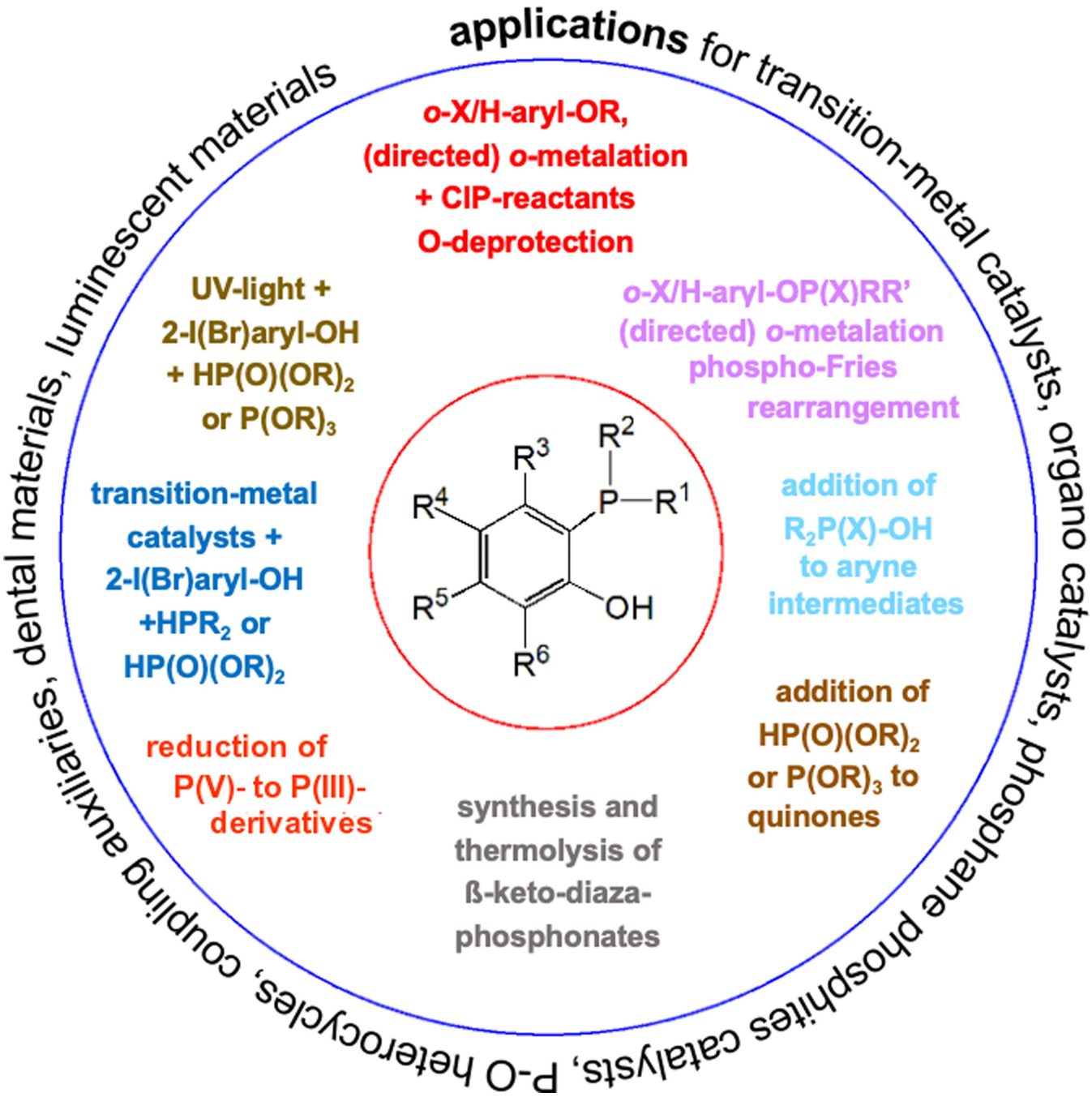
Dedicated to Hansjörg Grützmacher, Dietrich Gudat, Evamarie Hey-Hawkins, Manfred Scheer, Rainer Streubel, and Werner Uhl, recognizing their outstanding contributions to various aspects of p-block chemistry.



o-Hydroxyarylphosphanes are fascinating compounds by their multiple-reactivity features, attributed to the ambident hard and soft Lewis- and also Brønstedt acid-base properties, wide tuning opportunities via backbone substituents with ±mesomeric and inductive, at P and in *o*-position to P and O also steric effects, and in addition, the configurational stability at trivalent phosphorus. Air sensitivity may be overcome by reversible protection with BH_3, but the easy oxidation to P(V)-compounds may also be used. Since the first reports on the title compounds ca. 50 years ago the multiple reactivity has led to versatile applications. This includes various P–E–O and P=C–O heterocycles, a multitude of O-substituted derivatives including acyl derivatives for traceless Staudinger couplings of biomolecules with labels or functional substituents, phosphane-phosphite ligands, which like the *o*-phosphanylphenols itself form a range of transition metal complexes and catalysts. Also main group metal complexes and (bi)arylphosphonium-organocatalysts are derived. Within this review the various strategies for the access of the starting materials are illuminated, including few hints to selected applications.

1. Introduction

Organophosphorus compounds have emerged as essential chemicals in synthetic chemistry and catalysis including also medicinal, pharmaceutical and material research and applications.[1] A special class with tremendous potential for multifunctional and steric variations and versatile applications are *o*-hydroxyarylphosphanes (Figure 1). The most frequently used compound of type **1** is probably still 2-diphenylphosphanylphenol $\mathbf{1}_{Ph}$,[2] but a multitude of new representatives and types of the title compounds, reported in the last ca. 40 years, allows tuning of steric and electronic properties by variation of substituents. In this way the trivalent phosphorus may act as a more or less strong Lewis base or soft nucleophile, P–H functional derivatives also as Brønstedt acids. In addition, P(III) may behave as reducing agent and undergo oxidative addition or cycloaddition reactions. The acid/base properties of OH/O^- can be adjusted via mesomeric and inductive electronic effects of the aryl-substituents.

For the reactivity, illustrated by few examples in Figure 2, also the rigidity of the aromatic ring is of importance. It causes strong steric effects of bulky substituents adjacent to the O- and P-functional groups on preferred or possible conformations with consequences for properties and reaction behavior, for example sensitivity to unusual acid-mediated C-PH_2 bond fission.[3] This may restrict the synthetic feasibility, for example of 1-PHR-substituted 2-naphthols,[4] or cause dependence on special routes, but also end up with particular effects of extremely bulky ligands in catalytic applications. Whereas initial polymerizations with nickel-phosphanylphenolate catalysts using $\mathbf{1}_{Ph}$,[5–8] mixed 2-alkylphenyl- and 2-dialkylphosphanylphenols, also partly substituted in 4 and 6 position, were limited to ethylene polymerizations[6,7] or copolymerizations with low content of α-olefins without or only remote polar groups,[8] the extremely bulky substituents at the P-atom and in position 6 and/or 3, exemplified by the Ni-precatalyst **I**, extend the applicability considerably. Thus, copolymerizations of ethylene with norbornene,[9] polar vinyl monomers[10] or acrylates[11] could be achieved. Another highlight are copolymerizations with CO to novel light-degradable polymers[12] that might help in the endeavors to avoid long-living plastic waste. Other application fields, using the configurational stability of asymmetrically substituted trivalent phosphorus[13] and/or ($R^1 = R^2$) axial-chiral substituents at the *o*-O-atom (e.g. **II**),[14] are enantioselective organic transformations, with chiral phosphane-phosphite transition metal catalysts studied for example for Pd-catalyzed asymmetric allylic substitution reactions[14] and Ir- or Rh-catalyzed hydrogenations of olefins.[15,16] The multitude of chiral phosphane-organocatalysts[17] include also *o*-hydroxyaryl-substituted compounds. A particular example, the chiral electrostatically-enhanced phosphoric diester acid **III**, is useful in asymmetric Friedel–Crafts reactions.[18] O-Acyl-derivatives **IV** of *o*-phosphanylphenols belong to the preferred reagents applied in the traceless Staudinger coupling to label or modify a wide range of biomolecules.[19] Primary *o*-hydroxyarylphosphanes, initially synthesized from *o*-bromophenol via organometallic coupling procedures and reduction of P(III)[20] or more conveniently accessible *o*-hydroxyarylphosphonate precursors,[21] allowed access to first aromatically stabilized 1,3-benzoxaphospholes, for example **V**.[20,22] Extended recent studies on various types of annulated 1,3-oxaphospholes, for example air-stable 2-aryl-substituted 4,6-di-*tert*-butyl-benzoxaphospholes or the biphenyl-type heterocycles **VI**, proved promising for gaining luminescent materials, in part with quantum yields > 60 %.[3,23,24] These compounds might also become of interest for use in

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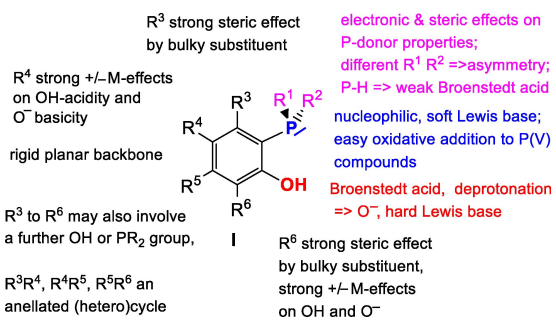


Figure 1. Tunability and reactive sites of *o*-hydroxyarylphosphanes.

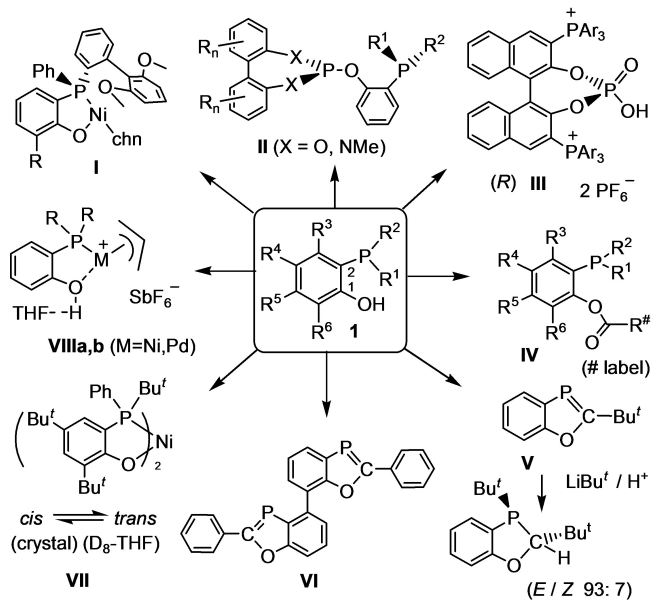


Figure 2. Examples demonstrating the versatile reactivity and potential applications of *o*-hydroxyarylphosphanes.

addition or cycloaddition reactions to mono- or bicyclic 1,3-benzoxaphospholines, so far studied only with **V**.[25] In contrast to the well-known biaryl-type benzoxaphospholine catalyst ligands of the Tang group,[26] the aforementioned addition products have not yet been studied with respect to catalytic applications.

To close the circle to the currently studied extremely bulky *o*-phosphanylphenolate Ni-copolymerization catalyst in Figure 2 still some remarks to nickel and related palladium (*P*,*O*)-chelate complexes. The neutral $(P,O)_2$Ni chelate complexes are thermodynamically favored, except extremely bulky ligands formed from various Ni precursors, particularly in alcohols, and may there deactivate the catalysts. Bulky substituents enforce *trans*-bis(chelates), otherwise *cis*-isomers are favored. For borderline compounds the configuration may be reversible solvent- (benzene *cis*, $CDCl_3$ *trans*) or, as shown for VII, condition-dependent (crystalline *cis* or dissolved *trans*),[27] indicating hemilabile behavior.[28] Cationic *o*-phosphanylphenol Ni or Pd complexes **VIIIa,b** with SbF_6^- anion, active but unselective catalysts for conversion of ethylene to dimers and lower oligomers, might form M^{II} chelates with (*P*,*OH*) ligands, as shown for single crystals with hydrogen-bonded THF of the Pd-precursor **VIIIb** (Pd–O 2.161(2), H…O_{THF} 1.662 Å, < DHA 176.72). In the solid state these compounds decompose slowly (with BF_4^- anions rapidly) to so far sparingly investigated cationic complexes with *O*,*O*′-coordinated *cis*-$(P,O)_2$M chelate ligands, for example $\{Ni[Ni(Cy_2PC_6H_4O)_2]_3\}(SbF_6)_2$.[29]

In current research, using *o*-hydroxyarylphosphanes as necessary reagents, the latter are usually not the focus of the research and often to find only in the Supporting Information, sometimes in patents. The aim of this review is to give an overview on the various known synthetic strategies for the preparation of these compounds with hints also on limits and mechanistic ideas. This may help to select suitable routes, to find references of known compounds and stimulate ideas for syntheses of new variants or structure types of *o*-hydroxyarylphosphanes, research to extent the current scope of the methods or to develop new routes. Occasionally, analogous syntheses of related main-group compounds (As, Si), *o*-aminoaryl-P, *p*-OH or –M-substituted P-compounds were included for comparison. *o*-Hydroxyarylphosphine oxides, known since long and so far very rarely reduced to synthesize the respective OH-functional phosphanes,[30–32] were only occasionally involved. Literature on *o*-hydroxyarylphosphonates and -phosphinates was included by its easy reduction and rather essential use for the preparation of PH-functional *o*-hydroxyarylphosphanes. The literature collection is based on several structure-type Scifinder searches (until end of March 2023) and checks within the reference lists.

Joachim W. Heinicke studied chemistry in Halle. After diploma (1970), PhD (1975) under supervision of Prof. Dr. A. Tzschach and work on a monograph on As-heterocycles (1978) independent research on aromatically stabilized heterocycles with dicoordinated main group elements was started, the first years in the same group. For heterocycles with E=C-O function, o-element-substituted phenols were required, the reason to start research also on o-hydroxyarylphosphanes, later extended to tertiary representatives, transition metal complexes and, in cooperation with W. Keim, to applications in Ni-catalyzed oligo- and polymerizations with ethylene and co-polymerizations with α-olefins. Change of education in Greifswald from chemistry to biochemistry finished these studies in favour of novel α-phosphanyl amino acids. The author hopes with this review to stimulate further research on the very versatile and fascinating multifunctional title compounds and their applications.

2. Routes to 2-Hydroxyarylphosphanes

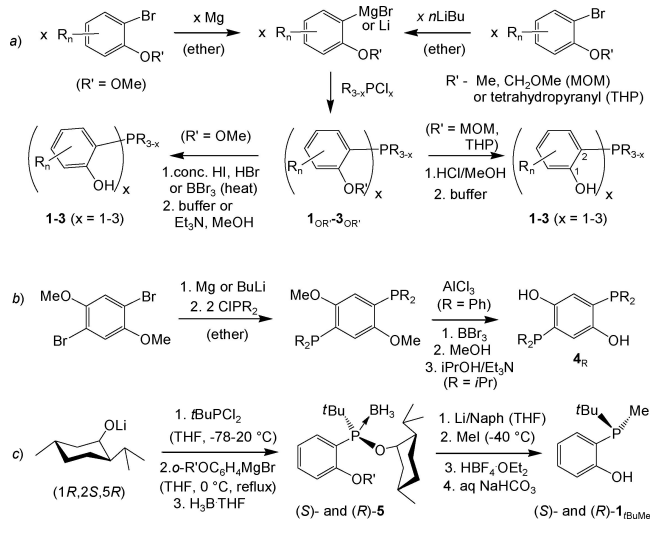
The syntheses of *P*-tertiary mono-, bis- and tris-2-hydroxyarylphosphanes (**1**–**3**) comprise several steps, the crucial being the formation of the (aryl)C–P bond. This is accomplished mainly by various organometallic strategies involving coupling of chlorophosphanes with stable O-protected or intermediate *o*-metalated aryl-OR reagents, by light-initiated or by transition-metal mediated or catalyzed P–C cross-coupling reactions. Alternatives are the addition of PH- or PH(O)-functional compounds to *p*-quinones, yielding 1,4-dihydroxy-substituted phenyl- or -naphthylphosphanes or P(O)derivatives thereof, furthermore the rarely used additions to intermediate benzynes or to intermediate carbenes, generated by N_2-elimination of diazo-precursors. PH-functional *o*-hydroxyarylphosphanes are accessible by reduction of *o*-hydroxarylphosphonites, -phosphinites or, preferably, the more stable *o*-hydroxyarylphosphonates or -phosphinates.

2.1. o-Hydroxyarylphosphanes via metalation of bromaryl ethers and coupling with chlorophosphanes

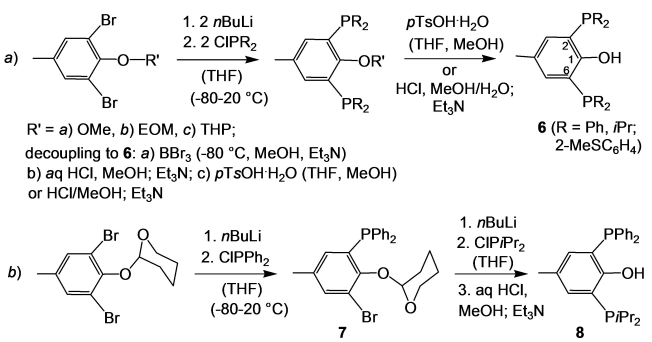
The first *o*-phosphanylphenol was obviously $P(C_6H_4OH)_3$ hydrate (**3**, $R_n = H$), like its *p*-isomer obtained in 1961 by Neunhoefer and Lamza[33] by reaction of anisyl-MgBr and PCl_3, subsequent demethylation of the respective tris(anisyl)phosphane by heating (2-3 h/100 °C) with aqueous HI (57%) in the presence of H_3PO_2 and neutralization of the hydroiodide ($NaOH/CO_2$) Scheme 1a. 2-Diphenylphosphanylphenol and 2-di-(adamantyl)phosphanylphenol **1** (R=Ph, 1-Ada, $R_n = H$),[34,35] were prepared similarly by reaction of *o*-anisyl-MgBr with $ClPPh_2$ and $ClPAda_2$ (2 mol% CuCl), followed by subsequent deprotection with HI/H_3PO_2[34] and $BBr_3/Et_3N/MeOH$,[35] respectively. The method is also applicable to 2,5-diphosphanylhydroquinones, demonstrated for **4** (R=Ph) by conversion of $ClPPh_2$ with the Grignard solution formed from 2,5-dibromo-1,4-dimethoxybenzene or with 2,5-$Li_2C_6H_2(OMe)_2$ and final demethylation with $AlCl_3$[36] (Scheme 1b). Racemic (±)-*o*-$HOC_6H_4P(Me)Ph$ was generated by demethylation of *o*-$MeOC_6H_4P(Me)Ph$ with 48% aqueous HBr and neutralization with NaOH. It was then O-acetylated and used to study the enantiomer separation via enzymatic kinetic resolution. Moderate enantioselectivity was achieved with cholesterol esterase (CE), enantiomeric ratio $E = 4.0$, yielding enriched optically active *o*-$HOC_6H_4P(Me)Ph$ (40% conversion, 49% *ee* by NMR, 33% *ee* after oxidation with H_2O_2) and remaining *o*-$AcOC_6H_4P(Me)Ph$. A similar moderately enantioselective ($E = 3.8$) CE-catalyzed hydrolysis was observed for 1-methylphenylphosphanyl-naphth-2-yl acetate, delivering enriched optically active 1-methylphenyl-naphth-2-ol and unconverted acetate. High *E*-values, with CE $E = 32$, with CRL (Candida rugosa lipase) $E = 81$, were achieved only with 1-MePhP(O)naphth-2-yl acetate.[37] A multistep synthesis of optically active (*R*)- and (*S*)-*o*-phosphanylphenol derivatives using a chiral auxiliary and diastereoisomer separation is depicted in Scheme 1c. There, a Grignard reagent, prepared from *O*-methyl- or *O*-methoxymethyl-protected *o*-bromophenol, was converted with the chlorophosphonite, synthesized from the lithium salt of (1*R*, 2*S*, 5*R*)-menthol with *t*$BuPCl_2$. Borane-protection of the resulting product with BH_3·THF and separation of the two air-stable diastereoisomers (*S*)-**5** and (*R*)-**5** by column chromatography, followed by reductive cleavage of the menthoxy group with Li-naphthalenide (Li/Naph) in THF and *P*-alkylation with MeI afforded the optically active *o*-R′OC_6H_4P*t*BuMe-boranes. Final deprotection with HBF_4·OEt_2 and buffering with aqueous $NaHCO_3$ delivered the *o*-phosphanylphenols (*S*)-$\mathbf{1}_{t\text{BuMe}}$ and (*R*)-$\mathbf{1}_{t\text{BuMe}}$.[38]

For the majority of the *o*-phosphanylphenols **1**, prepared via *o*-bromoaryl methyl ethers, *n*BuLi was used for the metalation step. Examples are a number of bulky dialkyl- (R=Cy, *t*Bu[39]) and diarylphosphanylphenols (e.g. R = 1-naphthyl,[40] OMe precursor[41]) or *P*-asymmetric *o*-(alkylphenylphosphanyl)phenols (**1**, R^1 = ada, np, tetramethylpropyl, R^2 = Ph)[42a,b] as well as 2,5-bis(diisopropylphosphanyl)hydroquinone (**4**, R = *i*Pr)[43] (Scheme 1a,b). The preparations include *i*) synthesis of the required chlorophosphane, *ii*) synthesis and metalation of the *o*-bromoaryl ether with BuLi, *iii*) coupling of the latter with the chlorophosphane, *iv*) dealkylation with BBr_3 and subsequent borate destruction with methanol and neutralization with Et_3N. This optimized deprotection route was used also for the synthesis of further *o*-hydroxyphenylphosphanes ($PR^1R^2 = PPh_2$, PMe_2, $PiPr_2$) and PMePh-(*S*)[41a,44] from the respective methoxy-precursors and, after coupling with asymmetric chloro-2,2′-biaryl phosphites, for studies of enantioselective Rh-catalyzed hydrogenations of dimethyl itaconate.[44]

Use of ethoxymethyl ethers (EOM) in the Br–Li exchange with *n*BuLi, for example 2,6-Br_2-4-MeC_6H_2O-EOM, followed by reaction with two equivalents of $ClPPh_2$, allows deprotection of the coupling product 2,6-$(Ph_2P)_2$-4-MeC_6H_2O-EOM to compound **6** (R=Ph) under mild conditions[45] (Scheme 2). With the somewhat more bulky *O*-tetrahydropyranyl (THP) group dilithiation as well as selective monolithiation of 4-R-2,6-$Br_2C_6H_2OTHP$ with BuLi is possible. Coupling after monolithiation with $ClPPh_2$ to **7**, followed by metal halogen exchange of the second Br atom with BuLi, reaction with $ClPiPr_2$ and subsequent deprotection presents **8** as an example of a sequential lithiation/phosphanylation strategy for incorporation of two different phosphanyl



Scheme 1. a–c. Syntheses of *o*-hydroxyarylphosphanes via metalation of O-protected *o*-bromophenols with magnesium or BuLi, coupling with chlorophosphanes and O-deprotection.



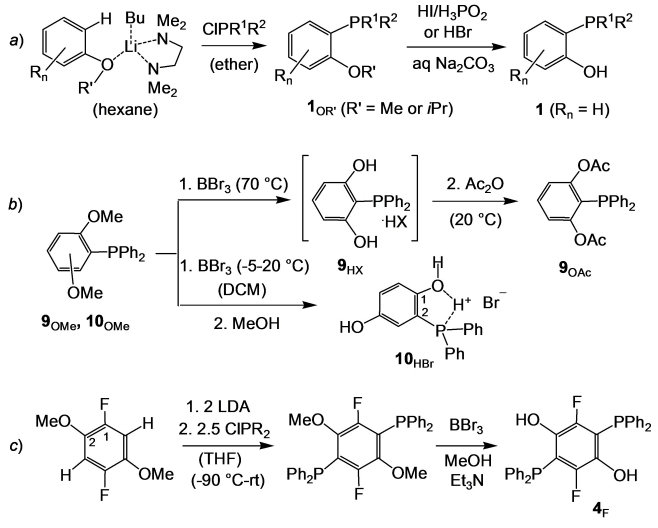
Scheme 2. Symmetric and unsymmetric 2,6-bis(phosphanyl)phenols via concomitant and sequential lithiation of 2,6-dibromophenol ethers.

groups.[46] Another advantage are the mild conditions for cleavage of the acetalic THP protection group (*p*TsOH in THF, 12 h), which are compatible with substituents that would be cleaved or converted by heating with conc. HI, HBr or BBr_3. The usefulness of this protocol was demonstrated by the synthesis of **6** (R = *o*-$MeSC_6H_4$).[47]

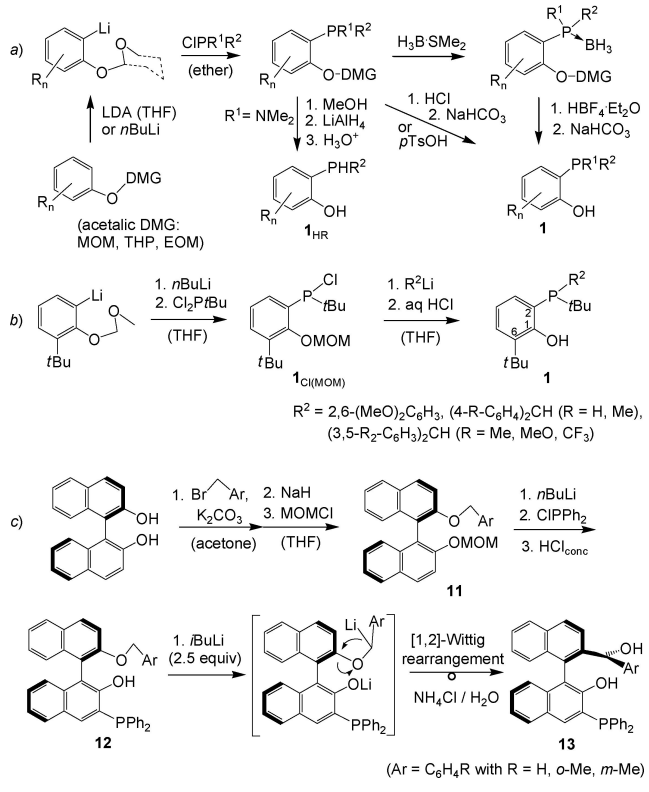
2.2. o-Hydroxyarylphosphanes via directed ortholithiation of aryl ethers and P-C coupling

The ability of alkoxy groups to support lithiation of aryl groups in *ortho*-position[48,49] was used in the organophosphorus chemistry at first by the group of B. L. Shaw for syntheses of *o*-phosphanylphenols, applied in the preparation of transition metal complexes. Phenyl methyl and isopropyl ethers were *o*-lithiated with BuLi/TMEDA (tetramethylethylenediamine) and coupled with chlorophosphanes $ClPR_2$ (R = *t*Bu, Ph) to *o*-phosphanylphenyl ethers $\mathbf{1}_{OR'}$ ($R^{1=2}$ = *t*Bu, R′ = Me, R_n = H; $R^{1=2}$ = Ph, R′ = *i*Pr, R_n = H). Final ether cleavage with conc. aqueous HI/H_3PO_2 or HBr furnished $tBu_2PC_6H_4OH$[50a] and $Ph_2PC_6H_4OH$[50b] (Scheme 3a). This strategy works likewise for $PhP(o\text{-}C_6H_4OH)_2$ (**2**, R_n = H), prepared by reaction of Cl_2PPh with two equivalents of *o*-lithioanisol, deprotection by refluxing with 48% aqueous HBr and neutralization of **2**·HBr by Na_2CO_3.[51] Lithiation of 1,2-dimethoxybenzene with *n*BuLi (1 equiv) and of 1,3-dimethoxybenzene with *n*BuLi/TMEDA (1/1 equiv) in ether, followed by addition of equimolar amounts of chlorophosphanes, furnished the respective 2,3- and 2,6-dimethoxyphenylphosphanes $\mathbf{9}_{OMe}$ (PR_2 = Ph, *t*Bu) in good yields (64–77%). However, refluxing 2,6-$(MeO)C_6H_3PPh_2$ with 45% aqueous HBr caused incomplete demethylation and refluxing in HI resulted in decomposition. Demethylation with BBr_3 at −70 °C worked, as shown by formation of 2,6-di(acetoxy)phenyl-diphenylphosphane $\mathbf{9}_{OAc}$ by subsequent addition of acetic acid anhydride at 20 °C, whereas attempts to isolate the corresponding phosphanylresorcinol 2-$Ph_2PC_6H_3$-1,3-$(OH)_2$ failed.[52] The same happened for 2-$Ph_2PC_6H_3$-1,4-$(OH)_2$. However, its hydrobromide $\mathbf{10}_{HBr}$ was accessed by the reaction sequence *i*) *o*-lithiation of 1,4-dimethoxybenzene (*n*BuLi/TMEDA in hexane), *ii*) reaction with $ClPPh_2$, *iii*) deprotection with BBr_3 in dichloromethane (DCM) (−5 °C, 16 h rt) and final borate destruction with MeOH[53] (Scheme 3b). *o*,*o*′-Dilithiation of 1,4-difluoro-2,5-dimethoxybenzene in THF with lithium diisopropylamide (LDA, 2 equiv, −90 °C), followed by reaction with $ClPR_2$ (2.5 equiv), demethylation with BBr_3 (−80 °C) and treatment with MeOH and Et_3N furnished the difluoro-bis(diorganophosphanyl)hydroquinones $\mathbf{4}_F$ (R=Ph, *i*Pr) in good yields (68 and 60%) (Scheme 3c).[54]

More efficient *ortho*-directing metalation groups (DMG) like methoxymethyl (MOM) or tetrahydropyranyl in phenyl ethers improve the *o*-lithiation strategy unless hindered by bulky neighbor or competing DMG-groups. A further advantage are the above mentioned much milder conditions for cleavage of these acetalic protection groups. The first *o*-phosphanylphenol synthesized via *o*-lithiation of $PhOCH_2OMe$ with *n*BuLi/TMEDA in petroleum ether, coupling with Ph_2PCl and acidic deprotection, was *o*-$Ph_2PC_6H_4OH$ ($\mathbf{1}_{Ph}$), reported by Rauchfuss.[55] The convenient procedure inspired other groups to apply this route, usually with slight modifications of the lithiation, performed with lithium diisopropylamide (LDA) in THF, *n*BuLi/TMEDA, *s*BuLi or *t*BuLi in THF, THF/Et_2O, Et_2O or with *n*BuLi/TMEDA in hydrocarbons,[49] and deprotection steps. Examples for the synthesis of variously substituted *P*-tertiary *o*-phosphanylphenols using this route are **1** ($R^{1=2}$ = *o*Tol, R_n = H),[56] ($R^{1=2}$ = *i*Pr, R_n = 4,6-tBu_2, 4-F),[57] ($R^{1=2}$ = Et, *i*Pr, Cy, R_n = H; R^1 = *t*Bu, R^2 = Ph, R_n = H; $R^{1=2}$ = Ph, R_n = 4-OMe, 4-F; $R^{1=2}$ = *i*Pr, R_n = F; $R^{1=2}$ = Cy, R_n = 4-MeO, 4,6-tBu_2),[58] ($R^{1=2}$ = Ph, R_n = H, 6-Ph, 6-*t*Bu; $R^{1=2}$ = *i*Pr, R_n = 6-*t*Bu),[59a,b] ($R^{1=2}$ = 2,6-$(MeO)C_6H_3$, R_n = 6-*t*Bu, 4,6-tBu_2, 6-C_6F_5, 6-(9-anthryl), 6-$SiMe_3$).[60] THP-protection allows analogous procedures, directed *o*-lithiation with *n*BuLi in THF or *n*BuLi/TMEDA in hexanes, followed by conversion with chlorophosphane and deprotection under mild conditions. It is applied for the synthesis of a variety of phosphanylphenols with bulky substituents at C-6, adjacent to the O atom, for example **1** ($R^{1=2}$ = Ph, R_n = 6-*t*Bu),[46] and additionally at phosphorus, for example **1** ($R^{1=2}$ = Ph, R_n = H, 6-*t*Bu, 4,6-tBu_2, 4,6-$(CMe_2Ph)_2$, 6-(9-anthracenyl); R^1 = *t*Bu, R^2 = Ph, R_n = 6-*t*Bu),[9] (R^1 = Ph, R^2 = 2-[2′,6′-$(OMe)_2$biphenyl, R_n = 6-*t*Bu; R^1 = Ph, R^2 = 2-biphenyl, R_n = 6-*t*Bu; ($R^{1=2}$ = 2-biphenyl, R_n = 6-*t*Bu),[10] ($R^{1=2}$ = Cy, R_n = 6-*t*Bu; R^1 = Ph, R^2 = 2-[2′,6′-$(OMe)_2$biphenyl, R_n = 6-C_6F_5, 6-C_6H_3-3,5-$(C_6F_{13})_2$, 5,6-C_4H_4; R^1 = Ph, R^2 = 1-[8-(3,5-$Me_2C_6H_2$)-naphthyl], 6-C_6F_5).[12] For very air-sensitive *o*-dialkylphosphanylphenols intermediate borane protection is useful. An example is the synthesis of *o*-$tBu_2PC_6H_4OH$ by directed *o*-lithiation of PhO-THP with *n*BuLi in THF, substitution with $ClPtBu_2$, subsequent addition of BH_3·SMe_2 and final P- and O-deprotection of the air-stable *o*-$tBu_2P(BH_3)$-C_6H_4O-THP by reaction with HBF_4·OEt_2 and neutralization with aqueous $NaHCO_3$ (Scheme 4a).[40] As the acetalic protection groups are stable under basic conditions, further transformations can be performed before deprotection. This was used for alcoholysis and subsequent reduction of MOM-protected *o*-hydroxyaryl-P(III) compounds with NMe_2 at phosphorus to PH-functional compounds before acidic deprotection (*cf.* chapter



Scheme 3. a–c. *o*-R_2P-substituted phenols and hydroquinones via directed *o*-lithiation of anisol or dimethoxybenzenes and acidic deprotection.



Scheme 4. a–c. Examples of *o*-phosphanylphenols prepared via directed *o*-lithiation of acetal-protected phenols, including air-protection by BH_3 (if necessary) and few transformations of *O*-protected phosphanylphenols leading to $\mathbf{1_{HR}}$, some *C*-6 and *P* bulky substituted derivatives of **1** and [1,2]-Wittig-rearrangement products **13**.

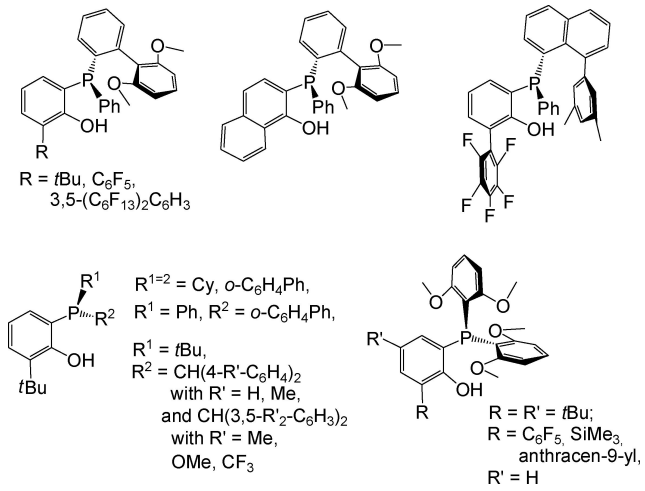


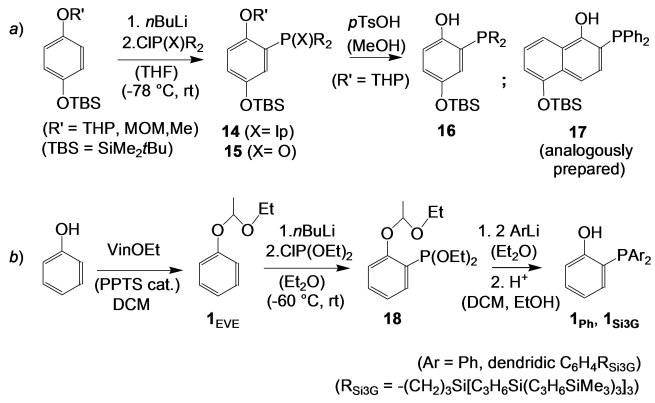
Figure 3. Examples of *o*-hydroxyarylphosphanes (type $\mathbf{1_{6+Pbulk}}$) with very bulky substituents at C-6 and the P-atom to inhibit deactivation of (*P*,*O*)-transition metal catalysts.[12]

2.11, Scheme 39a). Other examples are reactions of bulky aryl- or diarylmethyl-lithium reagents (R^2Li) with *o*-*t*BuPCl-arylO-MOM, applied for the synthesis of bulky P- and C-6 substituted *o*-phosphanylphenols **1** ($R^1 = t$Bu, $R^2 = 2,6\text{-}(MeO)C_6H_3$, Ph_2CH, $(4\text{-}MeC_6H_4)_2CH$, $(3,5\text{-}Me_2C_6H_3)_2CH$, $[3,5\text{-}(MeO)_2C_6H_3]_2CH$, $[3,5\text{-}(CF_3)_2C_6H_3]_2CH$, $R_n = 6$-*t*Bu).[11] For purification of $\mathbf{1_{MOM}}$ ($R^2 = Ph_2CH$) (Scheme 4b) by flash chromatography air protection by addition of BH_3-SMe_2 was necessary. During the final O-deprotection, in this case with MeOH/aqueous HCl, also BH_3 was removed from the P-atom. These and other recently studied phosphanylphenols with bulky substituents at C-6 and the P-atom (Figure 3) were found to form Ni-catalysts for non-alternative copolymerizations of ethylene with CO to polyketones with high content of isolated CO groups, as mentioned in the introduction required for light-induced oxidative waste-degradation of plastics with similar mechanic properties as HDPE.[12] In addition, with such bulky derivatives of **1** a breakthrough was achieved for copolymerization of ethylene with polar vinyl monomers[10] or acrylates,[11] whereas the less bulky phosphanylphenols 2-$Cy_2PC_6H_4OH$ and 2-*i*Pr_2P-4,6-*t*$Bu_2C_6H_2OH$ allowed copolymerizations only with various non- and remote (ethyl undecenoate) functionally substituted α-olefins.[8]

2-Diphenylphosphanylnaphth-1-ol and 1-diphenylphosphanylnaphth-2-ol[60] were prepared in the same or a similar way as the phosphanylphenols, likewise 2′-OCH_2-aryl substituted 3-diphenylphosphanyl-BINOL derivatives **12**. The latter were obtained from (*R*)-BINOL by consecutive treatment with $ArCH_2Br$ (K_2CO_3), NaH and MOMCl to give **11** and subsequent *o*-lithiation and phosphanylation (Scheme 4c). Further lithiation of the OCH_2Ar group with *i*BuLi resulted in a diastereoselective [1,2]-Wittig-rearrangement. Quenching with aqueous NH_4Cl gave 2′-CH(OH)Ar derivatives **13** (Ar-BINMOL-Phos), used for Zn-mediated asymmetric additions of aryl alkynes to aldehydes.[61]

If a second OH-group shall be used for further modification or for anchoring an *o*-hydroxyarylphosphane-based ligand on a matrix for hetereogenized catalytic applications it is suitable to stepwise introduce two different protection groups to the dihydroxyarene. One should be cleavable under basic, for example *t*$BuMe_2Si$ (TBS) or benzyl (Bn), the other under mild acidic conditions (THP, MOM).[62] Examples are reactions of hydroquinone, protected firstly with TBSCl (or BnBr), then directly or after *o*-bromination with $CH_2(OMe)_2/H^+$/molecular sieve or THP/H^+. Subsequent *o*-lithiation of the mixed MOM/TBSO- or THP/TBSO-protected hydroquinone derivative 4-R′$OC_6H_4OSiMe_2t$Bu with *n*BuLi in THF occurs in *o*-position of the OTHP or OMOM group, shown by coupling with $ClPR_2$ to **14** (R=Ph, Cy; R′=THP[60,62] or MOM[62]) or, in the case of a OMe group, with $ClP(NMe_2)_2$ and $ClP(O)Ph_2$ to **14** (R=NMe_2; R′=Me) and **15** (R=Ph; R′=Me).[63] The easy cleavage of the THP-group by *p*TsOH in MeOH allowed selective O-deprotection to **16** and reactions at the OH group with asymmetric chlorophosphites to a library of chiral *o*-phosphanylaryl phosphite ligands, evaluated in the Rh-catalyzed hydroboration of styrene. The study includes also the analogously prepared 5-OTBS-substituted 2-diphenylphosphanylnaphth-1-ol **17** (Scheme 5a).[60]

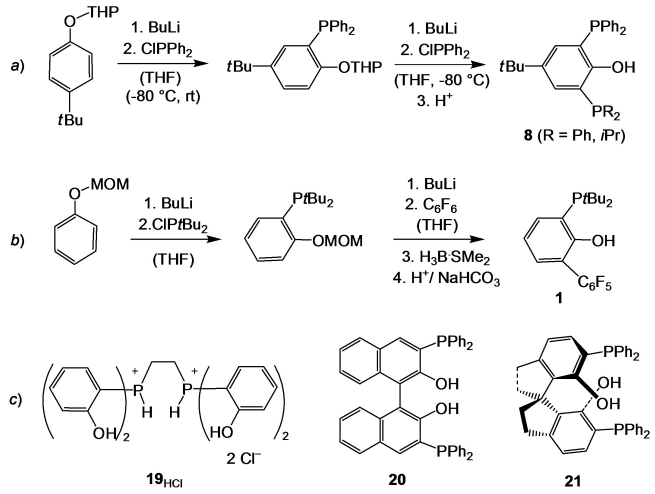
Müller et al. introduced a related *O*-protection group by acid-mediated addition of ethyl vinyl ether (EVE) to the phenolic OH group. This enables *o*-lithiation with *n*BuLi in Et_2O (−60 °C to rt) and coupling with $ClP(OEt)_2$ in good yield (72%). Subsequent *P*-arylation of **18** with a slight excess of PhLi (2.1 equiv) in ether (−80 °C to rt, 99% yield) and PPTS-catalyzed



Scheme 5. a,b. Syntheses *a*) of silyloxy-functional **16** and **17** via THP/TBS-protected hydroquinones and *b*) of *o*-phosphanylphenols $\mathbf{1_{Ph}}$ and $\mathbf{1_{Si3G}}$ via $\mathbf{1_{EVE}}$ and **18**, a rare example of *P*-arylation of an interims phosphonite, circumventing steric problems.

(pyridinium-*p*-toluenesulfonate) deprotection in DCM/EtOH demonstrates an alternative access to $\mathbf{1_{Ph}}$ ($R^{1=2}$ = Ph, R_n = H). This strategy proved applicable also for an analogous synthesis of a backside voluminous substituted dendritic derivative $\mathbf{1_{Si3G}}$ ($R^{1=2}$ = *p*-R_{Si3G}-C_6H_4, R_n = H; R_{Si3G} = $-(CH_2)_3Si[C_3H_6Si(C_3H_6SiMe_3)_3]_3$ (Scheme 5b). Screening in Ni-catalyzed ethylene oligomerizations showed doubled activity compared to $\mathbf{1_{Ph}}$, that may be attributed to steric hinderance of catalyst deactivation.[64]

The acetal-protection strategy allows also sequential *o*-lithiation-coupling reactions. Examples are the directed *o*-lithiation of phenyl THP or MOM ethers (by steric reasons without *o*- and *m*-substituents) with *n*BuLi in THF at low temperature, followed by coupling with $ClPR_2$ and repeated lithiation in the *o*'-position of the DMG group. The lithium can then be replaced by the same or a different phosphanyl group to give **8** (R=Ph or *i*Pr) (Scheme 6a),[46] alternatively by another electrophile. The latter case was used for example to introduce

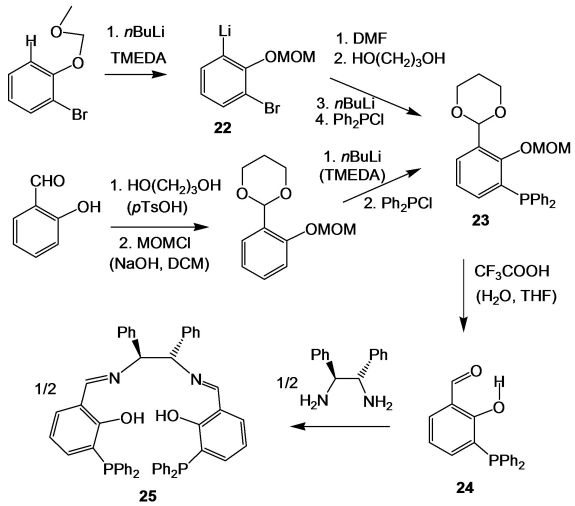


Scheme 6. a–c. Sequential directed *o*-lithiation/phosphanylation synthesis of *o*,*o*'-bis(phosphanyl)phenols **8**, synthesis of *o*-P*t*Bu_2 and *o*'-C_6F_5-substituted **1** and examples of bis-(*o*-phosphanylaryl-OH) compounds, prepared by concomitant lithiation/phosphanylation.

an electron-withdrawing C_6F_5 substituent in *o*'-position to the phosphanyl group of **1**[65] (Scheme 6b). For multiple-coupling reactions with PCl_3,[66] $PhPCl_2$[67,68] or bridged bis(chlorophosphanes) like $Cl_2PC_2H_4PCl_2$[69] the appropriate amounts of *o*-lithio-arylO-MOM reagents are applied. Deprotection with gaseous HCl in MeOH furnished the hydrochloride of phosphanylbis(phenol) $\mathbf{2_{HCl}}$ (R=Ph, R_n = H)[67,68] (*cf.* Scheme 1a) and the dihydrochloride of $(2\text{-}HOC_6H_4)_2P\text{-}C_2H_4\text{-}P(C_6H_4\text{-}2\text{-}OH)_2 \cdot 2HCl$ ($\mathbf{19_{HCl}}$).[69] Twice *o*-lithiation of bis-MOM-protected (*R*)-2,2'-dihydroxybinaphthyl (BINOL) and (*S*)-SPINOL with *n*BuLi in Et_2O and/or THF, followed by conversion with $ClPPh_2$, *O*-deprotection with aqueous or methanolic HCl and neutralization provides (*R*)-BINOL-PHOS) **20**[70,71] and the *o*-SPINOL-PHOS ligand **21**[72] (Scheme 6c), both used for multinuclear Cu/Zn complex catalysts for asymmetric conjugate additions of oranozinc reagents to enones. Cyclocondensation of **20** with PCl_3 and replacement of the remaining Cl-atom by dialkylamino groups to a chelating triphoshorus ligand served for Rh-catalyzed enantioselective hydrogenations of unsaturated amino acid esters.[73] *o*-Hydroxyarylphosphine oxides or -phosphonates are accessible by the same strategy using $R_2P(O)Cl$ or $(RO)_2P(O)Cl$ in the coupling step (e.g.).[66,74,75]

Strong polarization of the R–Li bond by coordination of *n*BuLi at TMEDA and two O-atoms of the *o*-directing MOM-group of 2-bromophenyl-MOM ether facilitates capture of the *o*'-H atom by $n\text{Bu}^{\delta-}$, leading to preferred replacement of the *o*'-H instead of the *o*-Br atom by lithium. The bromo-functional *o*'-lithiumphenyl ether **22** was used to introduce first an aldehyde group (low yield) and after ketal protection to replace bromine by a diphenylphosphanyl group (via lithiation and reaction with Ph_2PCl). The yield of the resulting **23** was improved by an alternative strategy, starting with CHO-acetal- and O-MOM-protection of salicylaldehyde, subsequent *o*-lithiation with *n*BuLi/TMEDA in ether (−60 °C) and reaction with Ph_2PCl (−70 °C to rt). Deprotection and coupling of the resulting CH=O-functional 2-phosphanylphenol **24** with (*R*,*R*)-1,2-diphenylethane-1,2-diamine (2:1 equiv) furnished the enantiopure multidentate phospha-salentype ligand **25**. This offers possibilities for mononuclear bis(chelate) coordination of hard (imino/O) or soft (P/O) metals as well as formation of heterobimetallic bis(chelate) complexes (Scheme 7).[76a,b]

Finally, some hints at possible problems arising during deprotection shall be mentioned. Thus, a minor acid-promoted hydroxymethylation of the *o*-Ph_2P group was observed as a side reaction of the acid-mediated cleavage of the MOM-group from 2-Ph_2P-6-*t*BuC_6H_3OMOM.[59b] A more general problem is that PH-functionalized *o*-phosphanylphenyl ethers are more or less sensitive to acid-mediated P–C bond cleavage. Even splitting of the MOM-group under mild conditions requires removal of acid impurities before distillative workup to avoid decomposition.[77] Major P–C bond cleavage was observed for the sterically unhindered *P*-primary 4-methyl-2-phosphanylphenyl-OMOM by using H^+-charged Amberlyst ion exchanger in MeOH whereas the 2 N HCl-mediated deprotection of *P*-secondary 2-phosphanylphenyl MOM ethers and workup under neutral conditions was less or not significantly influenced.[78] Steric stress, for example by 3,5- or 4,6-*t*Bu_2-substituents in the phenyl ring,

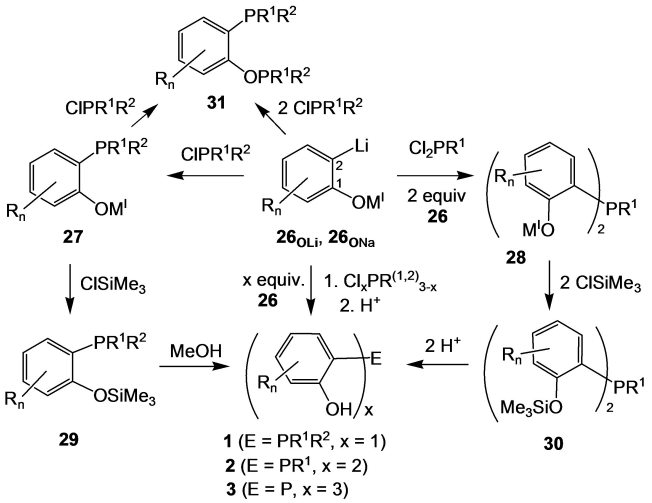


Scheme 7. Synthesis of enantiopure **25** via an unusual combination of directed *o*-lithiation, substitution and Br–Li exchange steps or a modified, single *o*-lithiation route for the access of the precursor **23**.

favors partial decomposition.[3,79] Complete P–C bond cleavage took place in attempts to synthesize 1-PHR-naphth-2-ols (R=Ph, H) by reduction of the respective diethyl phosphinate or phosphonate precursors with $LiAlH_4$ or subsequent workup.[4] For comparison it shall be noted that the higher-row relative 2-$H_2AsC_6H_4OH$ suffers already at room temperature from slow H^+-autocatalytic As–C bond cleavage[80] and that *o*-silylphenols are likewise sensitive to H^+-mediated Si–C-bond scission (see for example[81]).

2.3. o-Hydroxyarylphosphanes via C–P bond formation with o-O,C-dimetalated reagents

A related strategy to prepare *o*-hydroxyarylphosphanes involves *o*-C,OLi_2 reagents **26**$_{OLi}$, formed by primary dilithiation of *o*-bromophenols with BuLi in ether, initially used by Gilman and Arntzen for carboxylation reactions.[82] Direct *o*-C,O-dimetalation of phenol with *t*BuLi(pentane) in tetrahydropyrane solution,[83] recently applied in the synthesis of 10-(2-hydroxyphenyl)phenoxarsine,[84] or with the BuLi/*t*BuOK/2 TMEDA complex[85] is also known but was obviously not yet used in coupling reactions with chlorophosphanes. Initial conversions of the dilithium reagent **26**$_{OLi}$ (R_n = H) with excess $P(OEt)_3$ and even with 2-chloro-1,3,2-dioxaphospholane or $ClP(OEt)_2$, which smoothly react with monolithium organyls, for example *o*-MOM-OC_6H_4Li[78] or *o*-EVE-OC_6H_4Li,[64] displayed unselective attack. The reason is probably *o*-LiC,OLi…O–P bond activation of more than one P–O bond, causing preferred double and triple P-substition (by ^{31}P NMR) and low yield of monoaryl-substituted P-species. Thus, reduction of the crude product mixture with excess $LiAlH_4$ delivered only low yields of *o*-$H_2PC_6H_4OH$ (**1**$_{H2}$) (16–20% referred to **26**$_{OLi}$), used for cyclo-condensation with *t*BuC(=N-*p*Tol)Cl to a first aromatically stabilized P=C–O-heterocycle.[20] Reactions of **26**$_{OLi}$ with PCl_3 or organochlorophosphanes $RPCl_2$ (R=Me, *t*Bu, Ph), molar ratio 3:1 or 2:1, gave good to reasonable yields of the respective *o*-hydroxyphenylphosphanes **3**·H_2O and **2** (R=Me, *t*Bu, Ph)[86] and proved the usefulness of the dilithium reagent (Scheme 8). This strategy or a slight modification, OH-metalation by NaH followed by Br–Li exchange with *n*BuLi,[87] was then used by various groups to couple a variety of *o*-hydroxyarylbromides via *o*-lithiophenolates **26**$_{OLi}$ or **26**$_{ONa}$ with aryl-, alkyl-, R_2N- or mixed substituted chlorophosphanes R^1R^2PCl to *o*-phosphanyl-phenolates **27** or -bis(phenolates) **28**. Single crystal structure analyses of the latter, **28** (M^I=Li, R^1=Ph, *i*Pr, R_n=4,6-*t*Bu_2), directly isolated from the crude product, displayed LiO tetragons, arranged in step-form or face-sharing half-cubane fashion. In addition, cocrystallization with unconverted ArOLi was detected.[88] The crude phosphanylphenolates with one to three phenolate groups were worked up by direct treatment with aqueous acids under pH or buffer control to **1**–**3**, the mono- and diphenoxy compounds **27** and **28** alternatively by trimethysilylation to silylethers **29** and **30** or **26**$_{OLi}$ (via **27**) by use of two equivalents of $ClPR_2$ to *o*-phosphanylarylphosphinites **31**.[89] In the case of steric hindrance at **26**$_{OLi}$ (R_n=4,6-*t*Bu_2) and the chlorophosphane, even use of an equimolar ratio of **26**$_{OLi}$ and chlorophosphane may lead to C,O-diphosphanylated compounds **31** along with the C-monosubstituted products **27** and unconverted **26**$_{OLi}$.[79] Examples of *o*-phosphanylphenols prepared via **26**$_{OLi}$ or **26**$_{ONa}$ are **1** ($R^{1=2}$=Ph, *p*-Tol, R_n=6-*t*Bu),[87] ($R^{1=2}$=Ph, *i*Pr, R_n=4-Me),[90] ($R^{1=2}$=Ph, R_n=6-O*t*Bu)[91] and bis-phosphanylphenols **2** (R=Ph, R_n=4,6-*t*Bu_2),[92,93] (R=*t*Bu, R_n=4,6-*t*Bu_2).[94] The alternative workup with $ClSiMe_3$ allows convenient salt separation (in ether/hexanes) and, for moderately high boiling compounds, purification by vacuum distillation, for example **29** (R^1=Ph, R^2=NMe_2, $R^{1=2}$=NMe_2, R_n=4-Me),[77] (R^1=Ph, NMe_2, R^2=NMe_2, R_n=4,6-*t*Bu_2),[79] (R^1=Ph; R^2=Me, *i*Pr, *t*Bu, Ph, NMe_2, $R_{4/6}$=Me/H; R^2=*i*Pr, R_n=H; R^2=*i*Pr, *t*Bu, Ph, $R_{4/6}$=*t*Bu_2),[89] ($R^{1=2}$=Et, NEt_2, R_n=H),[95] ($R^{1=2}$=NMe_2, R_n=H, 4-Me, 4-Ph, 4-Cl, 6-Me, 6-*t*Bu, 4,6-*t*Bu_2),[96] and **30** (R^1=Me, R_n=H; R^1=Ph, R_n=4-Me).[89] 1-Phosphanylnaphth-2-yl silyl ethers **29** (R_n=3,4-C_4H_4; R^1=Ph, R^2=Ph, *i*Pr, *t*Bu, NMe_2, $R^{1=2}$=NMe_2)[4] are acces-



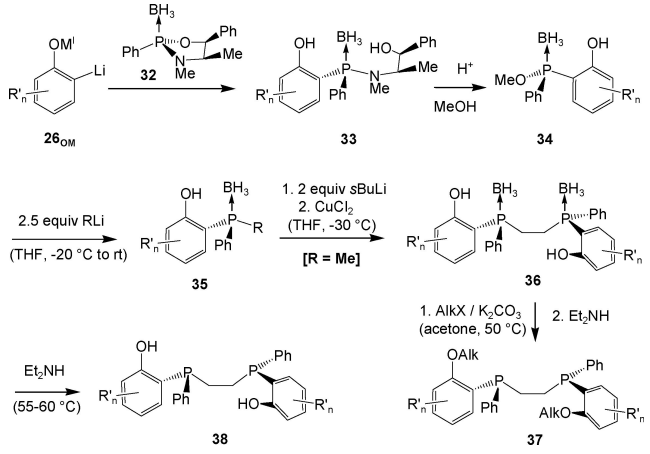
Scheme 8. Syntheses of *o*-phosphanylphenols via *o*-lithiophenolates **26**$_{OLi}$ or **26**$_{ONa}$.

sible by the same route, likewise 2′-phosphanyl-1,1′-biaryl-2-silyl ethers (R^1 = Ph, R^2 = Ph, Me, *i*Pr, *t*Bu)[97a] as well as related *o*-arsanylphenyl silylethers, exemplified by *t*BuAs($C_6H_4OSiMe_3$)$_2$.[95] With methanol the O-$SiMe_3$ derivatives may easily be converted to the phenols, without the necessity of pH control and possible formation of hydrates.[89] By reaction with MeOH in the absence of traces of acids and moisture (best in the presence of Et_3N to avoid side products by H^+-catalyzed Arbuzov reaction) the NR_2 groups of **29** are replaced by OMe groups and allow reduction by $LiAlH_4$ to PH-functional *o*-phosphanylphenols.[77,79] The silyl ethers can also be used for O-lithiation, O-acylation,[97b] reactions with $ClER_n$ reagents, with transition metal halides and the preparation of (*P*,*O*)-nickel ethylene polymerization catalysts.[98]

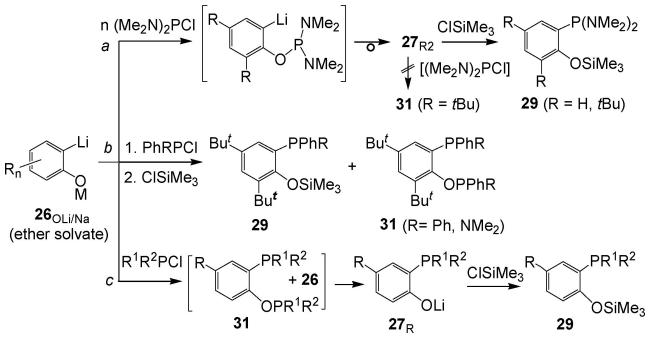
The *o*-lithio-phenolates and -naphtholates **26**$_{OM}$ (M=Li or Na; R_n = H and 5,6-C_4H_4) were also applied to stereospezific syntheses of *P*-asymmetric *o*-hydroxyarylphosphanes, using the Jugé-Stephan route. Reaction in THF (−20 °C to rt) with the (2*S*,4*R*,5*S*)-(–)-1,3,2-oxazaphospholidine **32**, obtained from $PhP(NEt_2)_2$, (+)-ephedrine and BH_3·THF,[99] provides the P–O ring-opening product (R_P)-**33** with retention of configuration (Scheme 9). The acid-catalyzed methanolysis with MeOH/H_2SO_4 or BF_3·Et_2O proceeds also stereospecifically, but with inversion of configuration at phosphorus to (S_P)-**34**, proved by its crystal structure analysis as well as by O-methylation to (S_P)-**35** and comparison of the specific optical rotations with those of the known methoxy-derivatives.[100,101] Replacement of the *P*-methoxy group by reaction with excess MeLi, *t*BuLi or dilithiated ferrocene leads again to *P*-inversion and formation of the corresponding P-asymmetric compounds (R_P)-**35** (R=Me,[101a] *t*Bu[14]) R_n = H, C_4H_4) and (R_P)-(*o*-$HOC_6H_4PPh(BH_3)Cp)_2Fe$.[102] Lithiation of the *P*-methyl group of **35** (R=Me) by *s*BuLi in THF (−30 °C), followed by oxidative homo-C–C-coupling with $CuCl_2$ (−30 °C), provides the ethane-bridged diphosphane-boranes (R_P,R_P)-**36**. These may be O-methylated to the well-known (*R*,*R*)-DIPAMP **37** (Alk = Me, R_n = H), initially developed by Knowles et al.,[103] and to its naphtho-analogues (*R*,*R*)-**37** (Alk = Me, R_n = H and 5,6-C_4H_4). O-Alkylation leads to so-called (*R*),(*R*)-SMS-Phos-ligands (*R*,*R*)-**37**. These exhibit exceptional features in Rh-catalyzed hydrogenations of olefins. Removal of the BH_3 group by heating (*R*,*R*)-**36** with Et_2NH furnishes the free homochiral ethylene-bis(*o*-hydroxyarylphenylphosphanes) (*R*,*R*)-**38**.

Use of mixed *o*-Li-aryl-ONa reagents **26**$_{ONa}$ is advantageous in the case of a bulky substituent adjacent to the OM^I group, for example 6-*t*Bu. It may provide higher yields of the respective *o*-phosphanylphenols **1** (($R^{1=2}$ = Ph, R_n = 4-Me, 6-*t*Bu; R^1 = Ph, R^2 = Ph, *i*PrPh, *t*BuPh, R_n = 4,6-tBu_2,[27] $R^{1=2}$ = Ph, *p*Tol, R_n = 6-*t*Bu)[87]) in 1:1 conversions with chlorophosphanes and diminish side reactions in the case of steric hindrance, for example competing metal-halogen exchange of *t*BuPhPCl to *t*BuPhPLi, leading to *meso*- and *rac*-(*t*BuPhP)$_2$ besides the substitution of 2-Li-4,6-$tBu_2C_6H_2OM^I$.[89] Problems may arise, however, by incomplete conversion of the *o*-OH group with NaH before addition of BuLi or by too long metalation time before addition of the chlorophosphane to **26**$_{ONa}$. In the latter case the *o*-Li-arylONa reagent, a reactive Lochmann/Schlosser-type base,[104] may slowly react with ether, without hindrance by an adjacent 6-*t*Bu group obviously faster, and replace the metal at the *o*-C-atom by a proton.[89]

To get more information on the mechanism, the reaction of **26**$_{OLi}$ with $ClP(NMe_2)_2$ was monitored by NMR. A single signal at $\delta(^{31}P)$ 134.5 ppm immediately after addition of the chlorodiaminophosphane indicated formation of a OPN_2 species, repetition after 2 h at ambient temperature displayed a single signal at $\delta(^{31}P)$ 99.6 ppm, accounting for rather slow and clean rearrangement of the primary O-substitution product to *o*-$(Me_2N)_2PC_6H_4OLi$ (**27**$_{R2}$, R=H) (Scheme 10a).[96] This mechanism may be preferred in all clean 1:1 conversions of **26**$_{OLi/Na}$ with equivalent amounts of similar α-branched $(Alk_2N)_2PCl$ reactants by steric hindrance and possibly a slow-down effect of the electron lone-pair at the α-N atom to the attack by a δ⁻-charged carbanion. However, reactions between equimolar amounts of **26**$_{OLi}$ (R_n = 4-Me) and $ClP(NMe_2)Ph$ or of **26**$_{ONa}$ (R_n = 4,6-tBu_2) and Ph_2PCl or $ClP(NMe_2)Ph$ provided mixtures of the corresponding C-mono- and *C*,*O*-disubstitution products **29** and **31**, in the latter case mainly **31** (R=Ph, NMe_2) (Scheme 10b).[77,79] This resembles the behavior of Me_3SiCl, reacting with an equimolar amount of **26**$_{OLi}$ mainly by *C*,*O*-disubstitution, leaving the



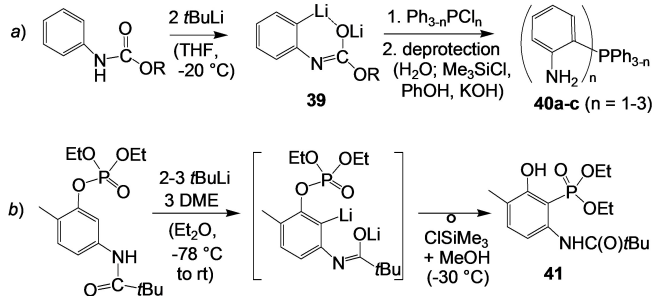
Scheme 9. Synthesis of chiral BH_3 protected *o*-hydroxyarylphosphanes using the Jugé-Stephan asymmetric route with *o*-lithio-aryloxyM^I reagents (M^I = Li or Na) and conversions to ethylene-bridged bis-*o*-hydroxyarylphosphanes and their OAlk-derivatives.



Scheme 10. a–c. Detected (*a*,*b*) and proposed additional mechanism (*c*) for slower rearranging, sterically hindered O–P(III) species (in analogy to the reaction of **26**$_{OLi}$ with $ClSiMe_3$).[95]

residual dilithium reagent unconverted[95] and suggests, that besides the stepwise mechanism also an alternative mechanism should be considered. Break of a relatively stable, to the best of my knowledge still unknown LiC/OM^{I} cluster structure of **26**$_{OLi}$ or **26**$_{ONa}$, and polarization of the C–Li bond by interactions with O-M^{I}[104] might cause sufficient activation for a preferred second substitution at the same molecule to afford **31**. Subsequent cleavage of its arylO–P bond by still unconverted LiC/OM^{I} reagent could then more or less rapidly provide the *o*-phosphanylphenolate **27**$_{R}$ (Scheme 10c). Finally, it should be mentioned that the 4,6-di-*t*Bu-substituted bis(dimethylamino)phosphanylphenolate **27**$_{R2}$ (R = *t*Bu, Scheme 10a) was found unable to react with a second equivalent of $ClP(NMe_2)_2$ at the O-atom, whereas trimethylsilylation to 2-$(Me_2N)_2$P-4,6-$tBu_2C_6H_2OSiMe_3$ (**29**, R = *t*Bu) was still possible.[79] This and low yields of 2-PhRP-4,6-$tBu_2C_6H_2OSiMe_3$ (**29**, R = *i*Pr, *t*Bu) hint at unfavorable steric effects of α-branched substituents at the P-atom in reactions with **26**$_{OLi}$ or **26**$_{ONa}$, significantly strengthened by the additional steric influence of the 6-*t*Bu-group. Detected side reactions are competing metal-halogen exchange reactions of CLi with the chlorophosphane, leading to diphosphanes, detected for $(tBuPhP)_2$, or base-induced HCl-elimination of oligomerizing phosphaalkenes from slowly reacting ClPR*i*Pr reagents, made probable by several $(RPCH_2)_n$ peaks in the mass spectra of byproducts.[89]

Another type of C,O-dilithium reagents (**39**) is formed by reaction of *N*-acylanilides with *t*BuLi in THF (−20 °C), including directed *o*-lithiation and lithiation of the NHC(O) fragment to a delocalized (NCO)Li group. Subsequent C–P coupling with *a*) Cl_nPPh_{3-n} or *b*) an *o*-O-bound PO_3Et_2 group via 1,3-anionic O–C rearrangement was used for the synthesis of related *o*-phosphanylaniline derivatives **40**[105] or of compound **41** with an additional *o'*–OH group[106] (Scheme 11). Reduction of **41** with excess $LiAlH_4$ did not lead to an OH– and NH-functional primary phosphane but, by intramolecular attack of PH_2 or PHLi at the adjacent N=C(OLi)*t*Bu group, to a 1*H*-1,3-benzazaphosphole, the so far only example of a P=C-NR-heterocycle with OH-group in *o*-position to the (relatively π-electron rich) σ^2-P-atom.[106]

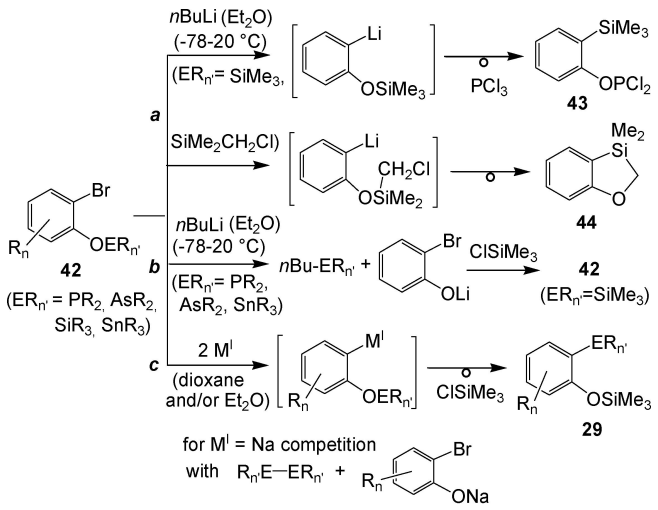


Scheme 11. P–C coupling reactions with acylanilide-based C,O-dilithium reagents.

2.4. o-Hydroxyarylphosphanes via anionic 1,3-O-C rearrangement of o–metalated aryl-O-PRR′ intermediates

The above mentioned use of the bulky TBS as towards BuLi stable *O*-protection group[60,62] (*cf.* Scheme 5a) in starting materials for organometallic C–P couplings proved not applicable for *o*-Me_2RSi-substituents with less bulky R at silicon. Lithiation of $SiMe_3$- or $SiMe_2CH_2Cl$-substituted phenolates via metal-halogen exchange of *n*BuLi with *o*-bromophenyl silyl ethers **42** leads to intramolecular Si–O bond cleavage and anionic 1,3-O–C migration of the $SiMe_2R$ group. Workup by hydrolysis, reaction with $ClSiMe_3$ or PCl_3 or intramolecular ring closure in the case of a $SiCH_2Cl$ group, affords the corresponding silylphenol, its O-trimethylsilylether[107] or O-substitution products (e.g. **43** with PCl_3) and the dihydro-1,3-benzoxasilole **44** (Scheme 12a).[108] Attempts to transfer this route to R_2P-substituted *o*-bromophenol derivatives and related R_nE compounds failed. *o*-Bromophenyl-OPR_2, similarly -$OAsR_2$ and also -$OSnR_3$ analogues undergo more rapid O-ER_n bond cleavage than lithium-bromine exchange (at −78 °C), resulting in lithium *o*-bromophenolates and the respective *n*BuER_n species (Scheme 12b).[108] However, direct metalation, first reported for *o*-chlorophenyl silyl ethers with sodium suspension (2 equiv) in toluene,[109] can be applied for reactions of *o*-bromoaryloxy organo main-group element compounds **42** ($ER_n = SiR_3$[81,110] and PR_2, AsR_2, SiR_3, SnR_3)[111] with sodium in toluene or 1,4-dioxane if more bulky alkyl or NMe_2-substituents at P, As, or Sn prevent or disfavor the competing reductive cleavage of the O–E bond of the *o*-bromoaryl reactant. With lithium in refluxing diethyl ether the reduction is suppressed, but the metalation-rearrangement reaction of **42** ($ER_{n'} = PiPr_2$, $R_n = H$) is rather slow and the yield of the corresponding phosphanylphenyl silyl ether **29** still moderate (55%).[108] Magnesium can be used for metalation if activated by prior reaction with anthracene.[112]

Stability to preferred reduction provided, the rearrangement of the *o*-Na-phenoxy-PRR′-species in 1,4-dioxane is faster than



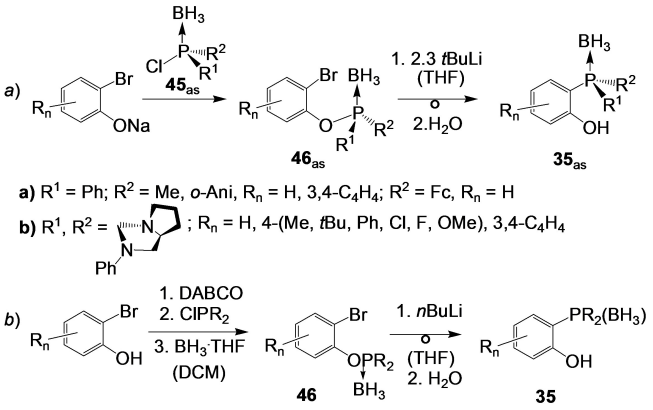
Scheme 12. a–c. Metalation/O,C-rearrangements of *o*-bromophenyl-$ER_{n'}$ compounds (*a*, *c*) versus main-group element-O bond cleavage leading to *n*-Bu$ER_{n'}$ and *o*-bromophenolate (*b*); in (*c*) competing reduction of **42** by sodium to $R_{n'}E$-$ER_{n'}$ (for temperature and steric effects see discussion).

of *o*-Na-phenoxy-$SiMe_3$ as shown by much lower yields of *o*-trimethylsilylphenols in this ether due to competing reaction of the sodium aryl intermediates with the solvent (Na–H exchange with formation of $PhOSiMe_3$). Final conversion of the *o*-phosphanylphenolates with Me_3SiCl allows good to moderate yields of the corresponding *o*-phosphanylphenyl silyl ethers. Closer studies of structural features controlling the metalation/reduction ratio indicated that the disturbing reduction to diphosphanes is particularly preferred in 2-haloaryl-$OPPh_2$ species, generally stronger in slower metallating 2-chloro- compared to 2-bromophenyl-OPR_2 compounds, still significant in the reactions of 2-haloaryl-OPPhR (R=NMe_2, *t*Bu) derivatives, but diminish with increasing steric hindrance at the O-PR^1R^2 group by the size of R^1/R^2 ($Me_2 < Et_2 < Me/tBu < iPr_2 \sim NMe_2$) and an additional adjacent *t*Bu group in 4,6-di-*t*Bu derivatives, then reaching yields up to 89% for **29** ($R^{1=2} = NMe_2$, $R_n = 4,6\text{-}tBu_2$)[113,114,77] (Scheme 12c). Finally, it shall be mentioned that the metalation-rearrangements with sodium are also applicable to prepare analogous *N*-secondary *o*-aminophenyl-phosphonous-bis(dimethylamide)s from *o*-$ClC_6H_4NMeP(NMe_2)_2$, however with rather low yields (ca. 35%).[108]

2.5. o-Hydroxyarylphosphanes via o–metalated aryloxy-P(BH_3)RR′ intermediates

Limitations by competing cleavage of the (2-bromoaryl)O–P(III) bond or other reasons, preventing defined products in metalation attempts of an asymmetric 2-bromophenoxy-substituted bicyclic *N*-phenyl-1,3,2-diazaphospholidine,[115] can be circumvented by BH_3-protection of O–P(III) compounds, which besides air-oxidation also avoids easy P–O bond cleavage by LiR reagents or $LiAlH_4$. This improvement was introduced by Jugé and coworkers.[116] Starting from a resolved asymmetric chlorophosphane borane **45**$_{as}$ and coupling with *o*-NaO-substituted arylbromides, the resulting *o*-bromoarylphosphinite boranes **46**$_{as}$ (R^1=Ph, R^2=Me, *o*-anisyl) were lithiated with excess *t*BuLi (THF, −78 °C to r.t.), which induced a stereoselective 1,3-O–C migration of the $R^1R^2P(BH_3)$ group, after workup providing the *o*-hydroxyarylphosphane boranes **35**$_{as}$ with retention of configuration (*ee* 72–99%) (Scheme 13a). The BH_3 group was finally cleaved by treatment with EtOH.[116] An electron-rich asymmetric (*S*)-*o*-(ferrocenylphenylphosphanyl)phenol (**35**$_{as}$, R^1=Ph, R^2=ferrocenyl), applied as organocatalyst for aza-Morita-Baylis–Hillman reactions of ketimines, was synthesized by the same strategy, starting from (*S*)-ClP(Fc)Ph·BH_3, coupling with 2-BrC_6H_4OH/NaH, metalation (*t*BuLi)/1,3-O,C-rearrangement, acidification and final BH_3-deprotection by DABCO (1,4-diazabicyclo[2.2.2.]octane).[117] Analogous conversions are reported for *o*-bromoaryloxy derivatives of asymmetric 1,3,2-diazaphospholidine boranes **45**$_{as}$ to the respective 2-(*o*-hydroxyaryl)-diazaphospholidine boranes **46**$_{as}$ (R_n=H, 4-(Me, Ph, *t*Bu, Cl, F, OMe), 3,4-C_4H_4) likewise proceeding stereoselectively and with retention of the configuration.[115]

The lithiation of the BH_3-protected *o*-bromophenylphosphinite precursors **46** can be performed without P–O bond scission also with the non-bulky *n*BuLi (1.5 equiv) in THF at 0 °C



Scheme 13. a–c. Lithiation of BH_3-protected aryloxy-phosphinites and -diamidophosphites, leading to 1,3-anionic O,C-rearrangements, for chiral compounds solvent-dependent and usally, but not always, with retention of configuration.

and is applicable for syntheses of a wide variety of different substituted 2-hydroxyarylphosphane-boranes **35** (R=Ph, R_n=6-Me, 5,6-Me_2, 3,6-Me_2, 6-Et, 6-*i*Pr, 6-*t*Bu, 4,6-tBu_2, 6-*t*Pent, 4,6-$tPent_2$, 6-Ph; 5,6-C_4H_4; R=*i*Pr, R_n=6-Ph; R=C_6H_2-3,5-Me_2-4-OEt, R_n=6-Ph; R=*p*-$MeOC_6H_4$, R_n=6-*i*Pr; R=3,5-Me_2-4-$MeOC_6H_2$, R_n=6-Ph). The reaction sequence to these compounds (Scheme 13b) comprises iPr_2NH-catalyzed *o*-bromination of suitable phenols with NBS, O-substitution with $ClPAr_2$ in the presence of a suitable tertiary amine (DABCO), protection with BH_3·THF, lithiation with *n*BuLi and quenching the rearranged product with water. Cleavage of BH_3 by DABCO was combined with the O-substitution step to various types of chiral *o*-phosphanylaryl phosphites,[118a–e] like the aforementioned chiral compounds **35**$_{as}$,[115–117] to study its use in enantioselective transition-metal catalyzed organic reactions.

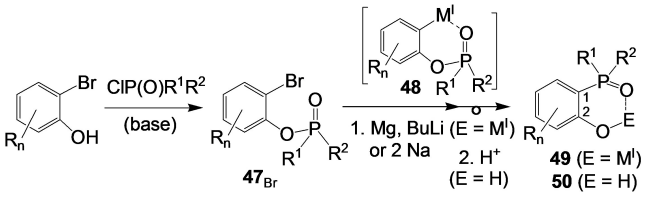
2.6. o-Hydroxyarylphosphonates, -phosphinates and selected o–hydroxyaryl phosphine oxides via o–metalated aryloxy-P(O)RR′ intermediates

Despite the focus of this review to *o*-hydroxyaryl-P(III) compounds *o*-hydroxyaryl-P(O)(OR)R′ compounds (R′=OR, H, alkyl, aryl), used as or being potential precursors of PH-functional *o*-hydroxyarylphosphanes, are also included, likewise selected *o*-hydroxyaryl phosphonodiamides and phosphine oxides with respect to mechanistic aspects.

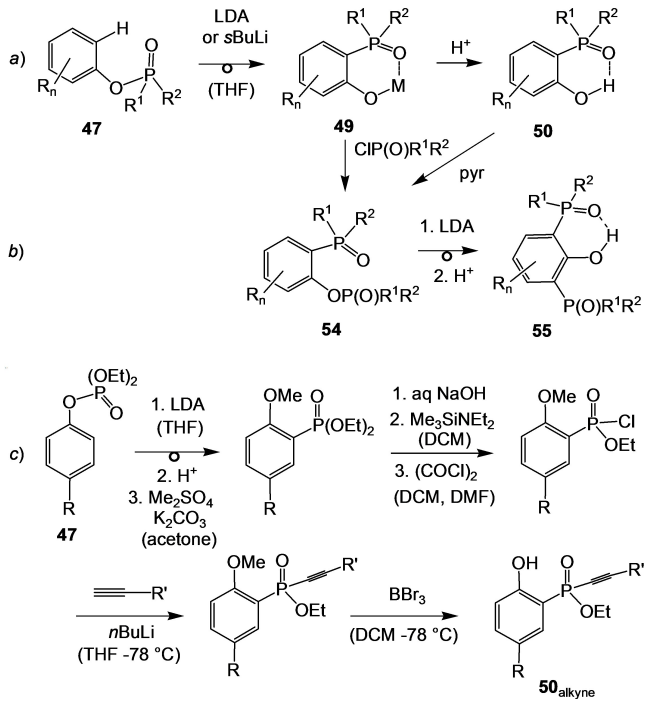
Compared to the P–O bonds of Lewis-basic tri-coordinated P(III)-compounds those of tetracoordinated phosphorus are less easily cleaved by reactive main-group organometallic reagents. Like as for the aforementioned phosphane borane Lewis acid-base-adducts this allows (di)alkyl *o*-bromoaryl-phosphates, -phosphonates or -phosphinates **47**$_{Br}$ to form organometallic intermediates **48** with Mg,[21,77,119] lithium (with BuLi in ether)[4,21,120,121] or, in suitable cases, sodium (in dioxane).[21,119] These undergo rapid 1,3-O,C-migration, also referred to as anionic phospho-Fries-rearrangement,[122,123] affording the respective 2-oxyarylphosphonate, -phosphinate or phosphine

oxide salts **49**, after acidification the respective *o*-hydroxy compounds **50**. The reactions work also for *O*,*O*-diethyl phenylthiophosphates, with *n*BuLi in THF delivering diethyl *o*-hydroxyphenylthiophosphonates in high yield.[124] The route via intermediate Grignard-reagents, proceeding less exothermic than usual RMgBr preparations, depends on solubility of the resulting Mg-phenolates in the reaction mixture (e.g. $R^{1=2}$ = OEt) to not block the Mg surface. It is obviously supported by intramolecular Mg…O=P(OEt)$_2$ interactions in the intermediates **48** and thus regioselective for reactions with 2-Br atoms, leaving 4-Br or 4-Cl of the precursors **47** unconverted.[21] The same regioselectivity of *o*- vs. *p*-Br was observed for lithiation, likewise hinting at intermediate P=O…Li chelate stabilization.[121] For the metalation of *o*-chloro-, better of diethyl *o*-bromophenyl phosphates, also sodium may be used, in this case unselective with 2,4-dichloro precursors. The reaction with sodium was performed in dioxane/diethyl ether or in 1,4-dioxane with temperature control (< 50 °C) to suppress or diminish reduction and Na–H exchange of intermediate sodium aryls with the solvent.[21] This procedure was also useful for the metalation and rearrangement of diisopropyl *o*-chlorophenylphosphinate to *i*Pr$_2$P(O)C$_6$H$_4$ONa whereas the analogous diethyl phosphinate and diethyl phosphate gave lower yields than the alternative metalation with Mg (Scheme 14).[119]

The P=O···LiR-directed *o*-metalation of dialkyl aryl phosphates (**47**, $R^{1=2}$ = OAlk) or alkyl aryl organophosphonates (**47**, R^1 = OAlk, R^2 = alkyl or aryl) is more convenient than the aforementioned Li–Br exchange unless disturbed by unsuitable substituents.[122] It is usually carried out with LDA or *s*BuLi in THF (−78 °C to r.t.) and followed by rapid anionic 1,3-O,C-migration. Mild acidic workup of **49** affords then the corresponding *o*-hydroxyarylphosphonates **50** ($R^{1=2}$ = OAlk) or -phosphinates (R^1 = OAlk, R^2 = alkyl or aryl) (Scheme 15a). This route was first reported by Melvin (**50**, $R^{1=2}$ = OEt, R_n = H, 3- and 5-Me, 5- and 6-OMe, 4,6-(OMe)$_2$)[125] and later further explored by many other groups to various *o*-hydroxyphenyl-P(O)R^1R^2 compounds (R^1 and/or R^2 = OAlk, OAr, OH, Alk, Ar) of type **50**[119,121,126,127a–e,128,129,130,131] as well as to 2-R_2P(O)-naphth-1-ols (**51**) and isomeric 1- and 3-R_2P(O)-naphth-2-ols (**52** and **53**).[127f,132] Aryl phosphonates[127a,132,133] or phosphinates,[127c] and also ferrocenyl phosphates or phosphonates[134a–c] react analogously, affording the corresponding *o*-hydroxyaryl-P(O)R^1R^2 moieties. The reaction works also for diethyl phenylthiophosphate, but by a much lower *o*-directing effect of sulfur compared to oxygen, only with excess *t*BuLi in THF and much lower isolated yield compared to starting from the *o*-bromoprecursor.[124] Replacement of X=O by S or BH_3 in ferrocenyl-OP(X)(OEt)$_2$ lowered the yields of the respective *o*-HO-FcP(X)(OEt)$_2$ compounds (94, 50, 37 %).[134c]



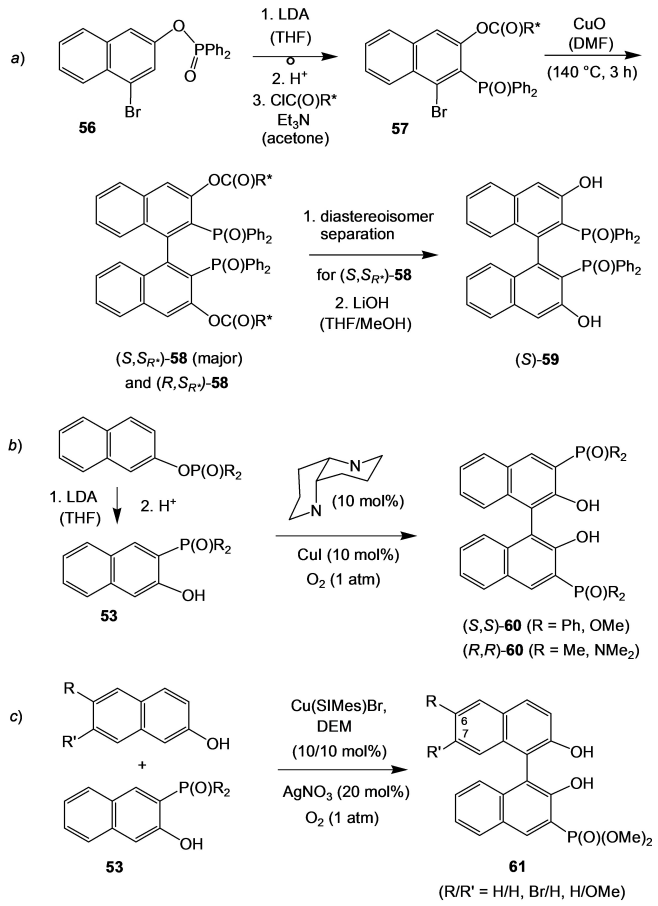
Scheme 14. Syntheses of *o*-bromoaryl phosphates, -phosphorodiamides, -phosphonates, and -phosphinates and metalation-rearrangements with Mg, BuLi or Na (R^1 and R^2 belong to any of the following groups: alkoxy, alkyl, aryl; R_n = H, 5-Me, 3,5-*t*Bu$_2$, 5-Cl or 5-Br).



Scheme 15. a–c. Examples for *a*) mono- and *b*) stepwise 1,3-bis-*o*-lithiation, each followed by rapid anionic 1,3-O,C-rearrangement and *c*) a route to bypass problems of direct use of the Melvin procedure by incompatible (alkynyl) substituents.

Direct OLi phosphorylation or alkylphosphonylation of the primarily formed product **49** to compound **54** and subsequent treatment with LDA, initiating a second rearrangement, may allow a stepwise one-pot 1,3-bis-phosphonylation or -phosphinylation to compounds of type **55**.[127a,e,134a,b] Substitution of **50** ($R^{1=2}$ = OEt, Ph) at the *o*-hydroxy group by R_2P(O)Cl / pyridine and subsequent treatment with LDA in THF is an alternative route to **55** ($R^{1=2}$ = Ph)[75] (Scheme 15b). An alkynyl group at phosphorus in the target molecule **50$_{alkyne}$** proved incompatible with direct synthesis by the *Melvin* procedure. A strategy to bypass this problem consists in replacing a *P*-ethoxy by an alkynyl group (Scheme 15c).[135]

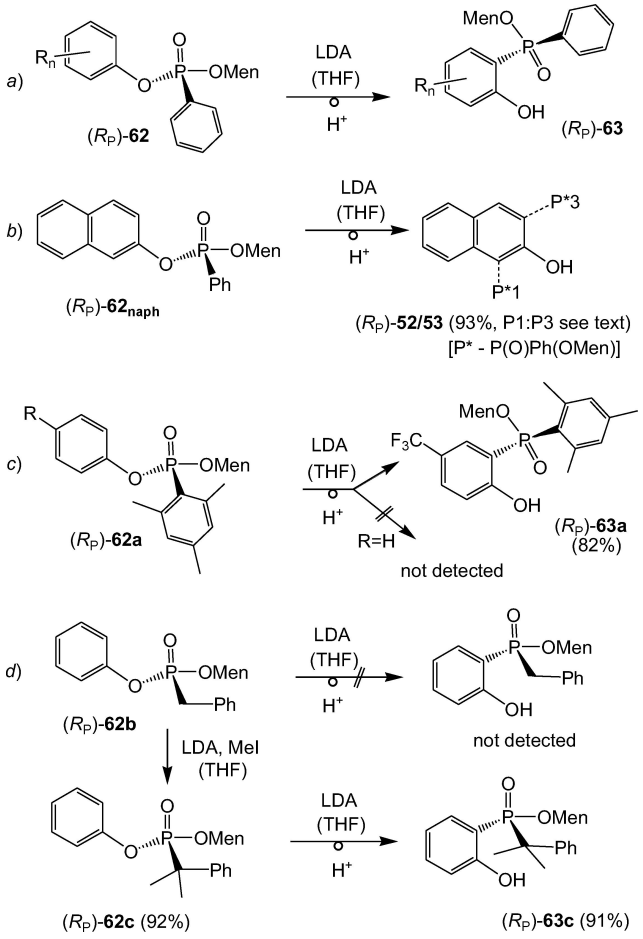
An interesting reaction of 2-hydroxy-, 3-phosphono-substituted naphthalenes is their conversion to BINAP or BINOL derivatives. This is achieved by Cu-mediated or catalyzed oxidative couplings, visualized in Schemes 16a–c. The first reaction sequence (*a*) involves *o*-lithiation of bromonaphthyl-diphenylphosphinate **56**, obtained from 4-bromonaphth-2-ol and ClP(O)Ph$_2$/Et$_3$N, and exploits the 3-OH group of the resulting rearrangement/acidification product for substitution with a (*S*)-lactic acid derivative ClC(O)R* (R* = (*S*)-CHMeOAc). This group acts upon the moderate stereoselective Ullmann coupling of **57** as chiral auxiliary for separation of the diastereomers of **58**. Saponification of the major product (*S*,S_{R*})-**58** provides (*S*)-**59**. This was used for the preparation of 3,3′-



Scheme 16. a–c. Examples of conversions of (O-acylated) 3-hydroxynaphth-2-yl-P(O)R_2 compounds to binaphthyls with *o*-OH/P(O)R_2 substituents (R=Ar, Alk, OAlk, NMe_2).

bis(methoxy)-BINAP ligands by O-alkylation and subsequent reduction with $HSiCl_3/Bu_3N$ (in xylenes) and finally evaluated in Rh-catalyzed asymmetric hydrogenations of 2-acetamidoacrylates.[136] A broad study of enantioselective Cu/chiral amine catalyzed oxidative biaryl couplings opened a route (*b*) also to 3,3′-bis-P(O)R_2 substituted BINOLs. Variously substituted 2-hydroxynaphthalenes showed for the hydroxynaphthyl-P(O)R_2-derivatives **53** (R=Ph, Me, OMe, NMe_2) moderate to good coupling yields (29–76%) and with one exception good *ee*'s (82–96%) of **60**, the best for the bis(*o*-hydroxy)-bis(phosphonate) **60** (R=OMe) (yield 76, *ee* 92%). The oxidative couplings were performed with O_2 in the presence of CuI (10 mol%) and chiral 1,5-diaza-*cis*-decaline (10 mol%).[137] Oxidative heterocoupling of electronically dissimilar 2-naphthols (*c*) proved challenging but succeeded using an optimized catalyst. A mixture of dimesityl-imidazolin-2-ylidene Cu complex Cu(SIMes)Br (10 mol%), diethyl malonate (DEM) (10 mol%) to prevent overoxidation and $AgNO_3$ (20 mol%) activated O_2 for regioselective oxidative 1,1′ combination of various 2-naphthols (6-R/7-R′=H/H, Br/H, H/OMe) with HO-naphthalene-P(O)$(OMe)_2$ **53**, applied in equimolar amount, delivered **61** in 50–77% yield.[138] Another direct oxidative coupling of various 2-hydroxynaphthalenes to the corresponding BINOL moieties was accomplished by dry microwave heating with $FeCl_3 \cdot 6H_2O$, for example affording the 3,3′-bis(diethyl phosphonate) **60** (R=OEt) in moderate yield.[139] The much better performance in the absence of solvent may be due to stronger local heating of the water- and probably also twice 2-OH-coordinated Fe(III) for the oxidative coupling in the neighbor positions. (A similar moisture effect was observed for example in microwave-activated Suzuki–Miyaura couplings of *o*-bromophenol and 1-bromonaphth-2-ol in the presence of moist compared to dry K_3PO_4.[140])

A variety of chiral mixed aryl menthyl (R_P)-phenylphosphonates is accessible from (R_P)-HP(O)(OMen)R and phenol by Atherton-Todd reaction with Et_3N/CCl_4 and proceeding with stereoinversion.[132a] This proved suitable to study the stereochemistry and compatibility of *o*-lithiation/rearrangement reactions, performed via LDA in THF, with various functional substituents at the phenoxy group of the reactants **62** (e.g. R_n = *o,m,p*-Me, *p*-(*n,t*)Bu, *p*-CF_3, *m,p*-OMe, *m,p*-NO_2) (Scheme 17a). The rearrangements proceed intramolecularly, demonstrated by cross-experiments, and with retention of configuration. The 1-naphthoxyphosphonate reacts regioselectively to the 1-hydroxynaphth-2-ylphosphinite **51** (R^1=Ph, R^2=Men, R_n=3,4-C_4H_4) whereas in the case of the 2-naphthoxyphosphonate a mixture



Scheme 17. a–d. *a*) *o*-Lithiation/rearrangements of (R_P)-menthylarylphosphonates **62** to *o*-hydroxyarylphosphinates **63** and *b-d*) limitations by steric reasons or competing metalations.

is formed, attributed to formation of the regioisomers **52** and **53** (Scheme 17b). The ^{13}C NMR data, given in the supporting information,[132b] and close values of P-C coupled key signals (C_qP, C_qO etc.) of the major isomer with those of related 3-hydroxynaphthyl-2-phosphonate or 2-phosphinate in 1,3/2,3-isomer mixtures[127f,133,165b] account for a general dominance of the 2,3-isomers, here **53** to **52** (82:18, opposite to the ratio listed in Table 4[132b]), and more upfield shifted ^{31}P signals compared to their 3-isomers (comment added in proof correction). For *o*-lithiation/rearrangements of related mesityl phosphonates **62a** activation of the phenoxy group by an electron-withdrawing *p*-CF_3 group is necessary, demonstrated by good yield of compound **63a**. Otherwise no diarylphosphinite was detected, possibly by lithiation at an *o*-methyl group of the mesityl substituent (Scheme 17c). With *P*-benzyl phosphonates **62b** lithiation at CH_2 of benzyl is preferred to *o*-lithiation of the aryloxy group, but introduction of Me groups to replace benzyl by CMe_2Ph (**62c**) gives high yield of the subsequent *o*-lithiation/1,3-O,C-rearrangement product **63c** (Scheme 17d).[132b] Low yield of 2-$HOC_6H_4P(O)(OEt)CH(OEt)_2$ was attributed to partial deprotonation of the acetale-protected aldehyde group, which like the aforementioned benzyl group competes with the *o*-lithiation or the rearrangement step.[133] Further limitations for the phospho-Fries rearrangement may occur by −M-groups in the reactant, for example *p*-COO*t*Bu[121] or *o*-O_2N,[141] which disfavor the rearrangement step of *o*-lithiated aryl-dialkylphosphonates or even prevent it in combination with steric congestion by a $P(O)(OtBu)_2$) group.[121] The basic N-atom in 2- or 4-pyridyl phosphates does not disturb the *o*-lithiation-rearrangement reaction sequence. Only a second lithation/rearrangement step of 4-phosphonato-3-pyridyl phosphate to 3-hydroxy-pyridine-2,4-phosphonate could not be achieved.[142]

In a study of mixed OR-substituted chiral ferrocenyl phosphates use of cyclohexyloxy or related chiral substituents (menthyloxy, fenchyloxy etc.) requires a non-polar solvent (hexane) and activation of LDA by TMEDA or (−)-sparteine for smooth *o*-lithiation and good yields of *o*-methoxyferrocenyl phosphonates, isolated after quenching the crude product with Me_2SO_4.[143]

Application of the *o*-lithiation-rearrangement strategy to tri- and diaryl phosphates may lead to triple and double rearrangements, affording tris-(*o*-hydroxyaryl)phosphine oxides **64**[127f,134b,c,144] or bis-(*o*-hydroxyaryl)phosphinates **65**.[145,146] Double lithiation-rearrangements of catechol-, hydroquinone- and naphth-1,5-diyl-bis(phosphates),[127a,147] naphth-2,3-diyl-bis(phosphonates),[148] 1,1′-biphenyl-2,2′-bis(diethyl phosphate)s,[24] 6,6′-alkylene-bridged 1,1′-biphenyl-2,2′-bis(phosphates),[149a] and (*R*)-BINOL bis(phosphates) or bis(phosphorodiamides)[149b,c] deliver a variety of bis-(*o*-hydroxy)aryl-bis(phosphonates) **66–69** and the non- or 6,6′-alkylene-bridged 2,2′-dihydroxy-1,1′diphenyl- as well as BINOL-3,3′-bis(phosphonates) or -bis(phosphonodiamides) **70**, **70a,b** and **60**. Me_2C-, S- and SO_2-bridged[150,151] or spirocyclic bridged bis(aryl phosphates)[150] react in the same way to the correspondingly bridged bis(*o*-hydroxyarylphosphonates) $\mathbf{71}_Z$ and **72**[150] (Figure 4).

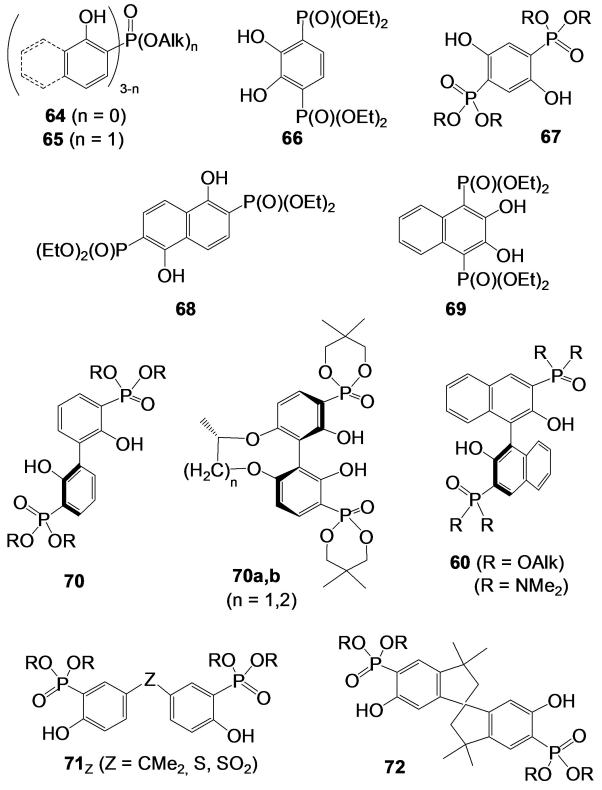
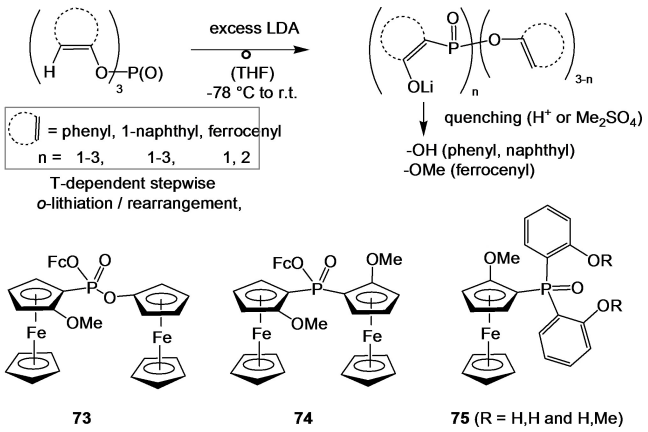


Figure 4. Examples of *o*-hydroxyaryl-$P(O)R_2$ compounds, obtained by concomitant triple (**64**) or double lithiation/1,3-O,C-migration (**60** and **65**–**72**) from the corresponding aryl phosphate precursors.

A detailed reviewed[122] study of triaryl, mixed aryl ferrocenyl and triferrocenyl phosphates[134b,c] confirmed for concomitantly performed conversions also bis- and in part even tris *o*-metalation/rearrangements. In-depth investigations by temperature-dependent NMR proved, however, that these reactions proceed by a sequential mechanism. Thus, treatment of triphenyl phosphate with excess LDA at −80 to −70 °C and final acidic quenching displayed mainly the mono-*o*-lithiation/rearrangement product and minor amounts of (o-$HOC_6H_4)_2P(O)(OPh)$. Their molar ratio varied with the excess of LDA and the reaction temperature from 75:24 to 55:45, indicating competing subsequent *o*-lithiation/rearrangement of the primarily formed product. The third *o*-lithiation/rearrangement to $(LiOC_6H_4)_3P(O)$ occurred only at 0 °C. The reactivity of triferrocenyl phosphate towards excess LDA is lower, according to cyclovoltametric studies due to the higher electron-density of the Fc-backbone. The first two steps to **73** and **74** need less low temperature, and the formation of tris-ferrocenylphosphine oxides was not achieved. For the electron-rich ferrocenyloxy compounds O-methylations are strongly favored compared to related phenoxy moieties and therefore preferred to aqueous quenching. For mixed phenyl-/ferrocenyl-substituted phosphates $(PhO)_{3-n}(FcO)_nP(O)$ (n = 1, 2) the primary attack was only moderately preferred for phenyl, but the final metalation-rearrangement limited to the phenyl group, leading to **75** (Scheme 18).[134b,c] Replacement of the OEt by $Nalk_2$ groups prevents *o*-lithiation of the ferrocenyl-$P(O)R_2$ compounds by

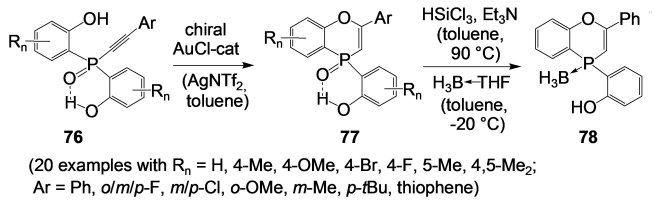


Scheme 18. Stepwise mechanism of concomitantly performed bis- and tris-*o*-lithiation/rearrangements and products **73**–**75**, formed by tris-lithiation/rearrangements of $(FcO)_3P(O)$ and $FcOP(O)(OPh)_2$ and final quenching with Me_2SO_4 or acid.

LDA. Ortholithiation of $FcP(O)(NEt_2)_2$ can still be achieved by use of *s*BuLi in THF, but does not lead to the 1,3-anionic rearrangement as detected by *o*-C-methylation after quenching with Me_2SO_4.[134c] Mixed phenoxy- and methylanilido-substituted phosphates are preferably *o*-lithiated at the phenoxy group, after acidic quenching resulting in *o*-$HOC_6H_4P(O)(NMePh)_2$ or (*o*-$HOC_6H_4)_2P(O)NMePh$. Directed *o*-lithiation also at the anilido group for formation of mixed *o*-hydroxyphenyl- and *o*-methylaminophenyl-substituted phosphine oxides required a large excess of LDA and gave poor yield (25%).[134d]

The conversion of *o*-hydroxyaryl phosphonates, phosphinates and phosphine oxides to PH-functional or P-tertiary *o*-hydroxyarylphosphanes is reviewed below (chapter *2.11*). In the following, some examples of other reactions and hints to potential applications are presented.

Various bis(*o*-hydroxyphenyl)alkynyl phosphine oxides **76**, obtained via the bis(MOM)-*o*-lithiation route, undergo enantioselective intramolecular hydroetherification to compounds of type **77**, catalyzed by a chiral gold complex. The subsequent reduction of **77** (R_n = H, Ar=Ph) with $HSiCl_3/Et_3N$ in toluene (90 °C) and BH_3 protection by H_3B-THF to **78** exemplifies catalytic cycloadditions of unsaturated *o*-hydroxyarylphosphinates to asymmetric *o*-OH-functional phosphine oxides and its reduction to phosphanes (Scheme 19).[146] Phosphane protection by BH_3 is long known[152] but is so far very rarely applied in combination with reduction to *o*-hydroxyaryl phosphanes.



Scheme 19. Example for catalytic transformation of *o*-hydroxyarylphosphine oxides and their reduction to (BH_3-protected) *o*-hydroxyarylphosphanes.

Biaryl-bis(*o*-hydroxy)-bis(phosphonates or phosphonodiamides) of type **60** (R,R = alkyl ester or NMe_2) were used as catalysts in enantioselective Alk_2Zn additions to aldehydes,[149a–c] those of type **70a,b** as components of conformationally flexible chiral supramolecular catalysts for enantioselective Diels–Alder reactions.[149a] Other applications concern mainly reactions at the P-atom or the OH-group. Thus, conversions to *o*-hydroxyarylphosphonic or -phosphinic acids are studied,[74,127a,b,d,e,f] which in the case of 2-$HOC_6H_4PH(O)(OH)$ are showing analgesic activity.[74] The combination of the CMe_2-bridged bis-hydroxyphenylphosphonic acid **79** (Figure 5) with glycidol, methacrylate and photo-polymerizing substances may lead to new dental materials.[151,153] Tests of ion-selective properties of *o*-hydroxyaryl-phosphonates and related phosphine oxides exhibit potentiometric selectivity to cesium cations.[131] In podands with *o*-phenoxyarylphosphonate end groups (**80**), obtained by base-promoted etherification of the OH groups with $Br(CH_2)_5Br$ or $TsO(C_2H_4O)_nTs$ (n = 1, 2), the charge and size dependent coordination of metal cations is useful for efficient and selective extraction of f-metal cations.[154] Crown ethers for extraction of alkaline metal cations from the aqueous into a $CHCl_3$ phase were analogously obtained by heating 4-decyl-2-$HOC_6H_3P(O)(OEt)_2$ with tosylmethyl-crown ethers (15-Crown-5 to 24-Crown-8) and NaH in THF (72 h reflux). The best extracted cation fitted with the predictions based on the crown ring size.[126 155] Alternative 2-phenoxyphosphonate crown ethers **81** are obtained from $(2\text{-}HOC_6H_4)_2P(O)OR$ with KH and $X–CHR'(CH_2OCH_2)_3CHR'\text{-}X$, in part chiral (X=I, Tos; R=Et, Me; R' = H, Me), and display high affinity for cations with radii <1 Å whereas attempts at discrimination of chiral organoammonium cations failed so far.[156] Etherification of 2-$HOC_6H_4P(O)(OEt)_2$ (**50**) with 4-nitrophthalonitrile and subsequent conversions to a variety of phthalocyanines with *o*-phenoxyphosphonate substituents and Li and Zn complexes thereof were studied with respect to the UV-VIS properties.[157] Fluorosulfonylation of variously 4-substituted 2-hydroxyphenyl phosphonates with R_fSO_2F ($R_f = –(CF_2)_2O(CF_2)_2H$) and subsequent Pd(II)/CuI catalyzed C–C cross-coupling with monosubstituted alkyl- and arylalkynes in the presence of Et_3N opened a route to *o*-alkynylphenyl phosphonates via replacement of R_fSO_3.[141] Etherification of di(α-fenchyl) *o*-hydroxyferrocenyl phosphonate by heating with C_6F_6 in DMF furnished the corresponding pentafluorophenyl ether.[158]

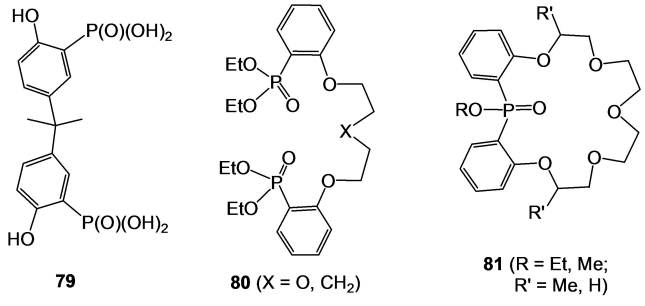
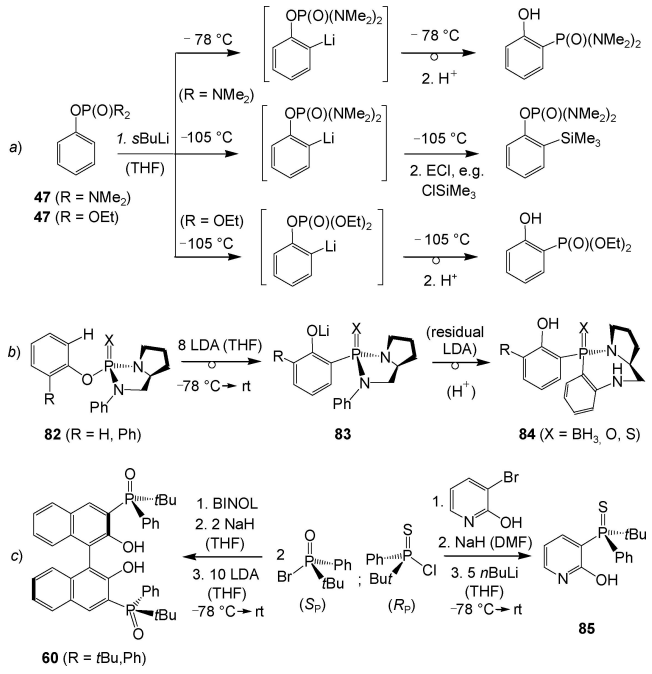


Figure 5. Selected examples for compounds, obtained from *o*-hydroxyarylphosphonates for use in dental materials (**79**), separation of f-metals (**80**) or complexation of alkaline or earth alkaline metals (**81**).

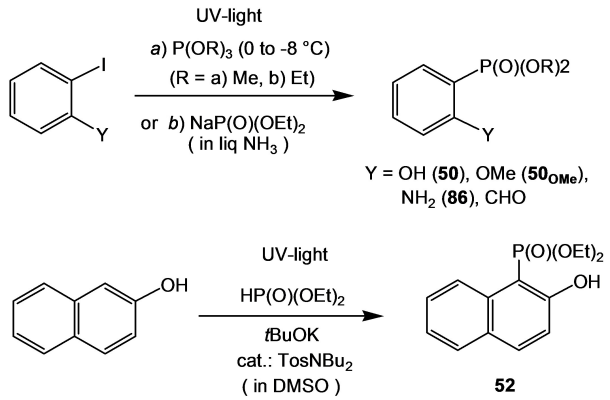
Some studies on *o*-hydroxyarylphosphonodiamides are quite informative with respect to mechanistic questions and limitations. The phenylphosphorodiamide **47** (R=NMe_2) requires *s*BuLi in THF for *o*-lithiation. The rearrangement proceeds still at −78 °C but is frozen in at −105 °C, allowing then trapping by electrophiles like Me_3SiCl, disulfides, aldehydes or ketones. The analogous phosphate **47** (R=OEt) rearranges still at −105 °C (Scheme 20a).[128] In this connection it shall be noted that treatment of the C-analogous *O*-arylcarbamates with *s*BuLi (−78 °C) also leads to 1,3-O,C-rearrangement whereas reaction with *s*BuLi/TMEDA/THF (−78 °C) furnishes obviously TMEDA-stabilized *o*-lithiated carbamates, switching to classic trapping reactions with organic electrophiles or Me_3SiCl.[159] In the case of *P*-asymmetric *p*-methoxyphenyl phosphoroesteramides (RR′= 1,3,2-oxazaphospholidine with ephedrine backbone)[160] and aryl phosphorodiamidates **82** (aryl = phenyl, biphenyl, naphthyl, pyridyl) with 2-oxo-*N*-phenyl-1,3,2-diazaphospholidine group, obtained by transamination of $(NMe_2)_3$ with 2-(phenylaminomethyl)proline, replacement of the remaining NMe_2 group by reaction with aryl-OH and oxidation with *t*BOOH, the directed *o*-lithiation/rearrangement with LDA proceeds stereoselectively with total retention of the configuration (Scheme 20b).[161a–d,162a,b] If the 2-oxybiphenyl group in **82** (R=Ph) contains a substituent in 3-position, blocking the 1,3-rearrangement, an alternative 1,5-O,C migration to an *o*′-position of the second phenyl ring, known for lithiation of 3-substituted biphenyl-2-yl diethylcarbamide,[163] was not observed.[161d] Except excess LDA also *s*BuLi or *t*BuLi give high yields and stereoselectivity in the *o*-lithiation and rearrangement whereas *n*BuLi was found unsuitable. If for **82** (R=H, Ph) a large excess (8 equiv) of LDA is used, the anionic 1,3-O,C-rearrangement to **83** is followed by *o*-lithiation of the *N*-phenyl ring and a stereoselective internal 1,3-N,C-shift via attack of *o*-CLi at P and *o*-phenylene insertion leading to **84**.[161b] Compounds of type **83** are efficient catalysts in the asymmetric addition of Et_2Zn to benzaldehyde.[164a] Analogous applications are reported also for the 3,3′-$Ph_2P(O)$-substituted BINOL-derivative (*R*)-**60** (R=Ph), synthesized by concomitant double *o*-lithiation/1,3-O,C-rearrangement of the (*R*)-BINOL bis(diphenylphosphinate).[164b] Finally, it shall be mentioned, that *o*-lithiations of *P*-asymmetric BINOL-derived (S_P,*R*,S_P)-bis(phosphinates), naphthyl phosphinates and few thiono- and *N*-heterocyclic phosphinates proceed by completely enantioselective 1,3-rearrangements with strict retention of configuration (Scheme 20c). The yields of the resulting asymmetric phosphine oxides are in most cases high, ee's excellent (for **60** and **85** 88 and 76% yield, ee >98 and 97%). In the reaction of the naphth-2-yl phosphinate the formation of the 2,3-hydroxynaphthylphosphine oxide (confirmed by XRD) was preferred to the 1,2-isomer (by ^1H and ^{31}P NMR 84:14% yield). For the synthesis of the pyridylphosphine oxide **85** Li–Br exchange with *n*BuLi was used because the thionophosphinate group is less effective in inducing *o*-lithiation than is phosphinate.[165a,b]



Scheme 20. *a*) Peculiarities in *o*-lithiation/rearrangements of aryl-phosphorodiamidates compared to dialkyl aryl phosphates; *b*) lithiation of **82** with a large excess of LDA, leading to stereoselective 1,3-O,C- and N,C-rearrangements; *c*) examples for *o*-lithiation/stereoselective 1,3-rearrangements of asymmetric phosphinates to phosphine oxides.

2.7. o-Hydroxy- and related arylphosphonates via light induced arylation of phosphites

In contrast to facile alkylations, the arylations of phosphides, phosphanes, phosphites or phosphonites require activation by strongly electron withdrawing substituents such as nitro groups or σ^2-N-atoms within N-heteroaryl rings, for example,[166,167,168,169a,b] or alternatively, activation by UV-light, transition metal support or catalysis. Photochemically induced *P*-arylations are established for coupling of aryliodides with excess trialkyl phosphites,[170] a photolytic modification of the Michaelis–Arbuzov reaction, eliminating alkylhalide via an intermediate trialkoxyphosphonium salt,[171] or with potassium dialkyl phosphites in liquid ammonia,[172,173a,b] for bromoanilines in DMF.[174] Both protocols are working also for +M-substituted hydroxy-, methoxy- or aminoaryl iodides. Thus, they provide a short route to *o*-$HOC_6H_4P(O)(OR)_2$ (**50**, R=Me, Et), related *o*-methoxy- and *o*-amino compounds $\mathbf{50_{OMe}}$ and **86**. As a hint at a general applicability the synthesis of the *o*-aldehyde with –M-group is also included in Scheme 21.[170,172] A mechanistically different oxidative synthesis of 2-hydroxy-naphthalene-1-phosphonic acid diethyl ester **52** from 2-naphthol, excess KO*t*Bu and diethyl phosphite in DMSO with UV-irradiation in the presence of a catalytic amount of *p*-tolyl-SO_2NBu_2 ($TosNBu_2$) to support a radical course, proceeds with an optimized yield of 66%.[175] A recent report describes high-yield C–H phosphonylations of electron-rich (hetero)arenes including mono- to three-methoxybenzenes with excess triethyl phosphite by visible-light photoredox catalysis with $(NH_4)_2S_2O_8$/$Ru(bpz)_3(PF_6)_2$ (2.2 equiv/2 mol%, bpz=2,2′-bipyrazine) in acetonitrile.[176] If this reaction would work also with acetonitrile-soluble phenolate salts, it



Scheme 21. Photochemically induced syntheses of *o*-hydroxyarylphosphonates and related compounds.

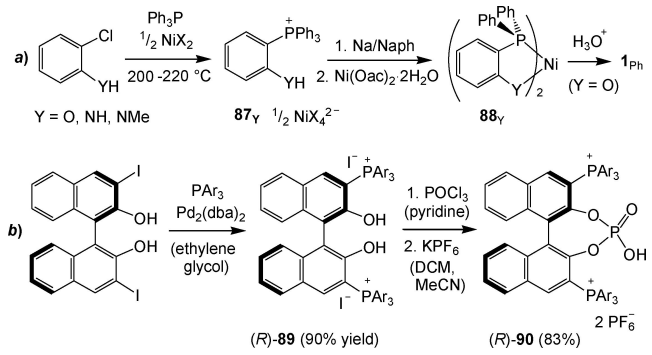
might open an interesting new route to electron-rich 2-hydroxyaryl phosphonates.

2.8. o-Hydroxy- and related +M-substituted aryl-phosphanes, -phosphonates, -phosphinates and selected phosphine oxides via transition-metal mediated or catalyzed P-arylation

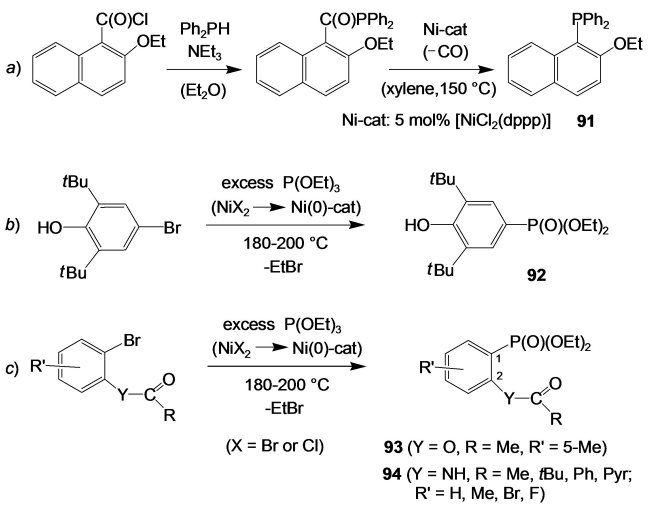
Transition-metal mediated stoichiometric or catalytic reactions of tertiary phosphanes with arylhalides to phosphonium salts require harsh reaction conditions but are still compatible with *p*-OMe and *p*-NMe_2 groups[177] and have also been used in the syntheses of *o*-$Ph_2PC_6H_4OH$ ($\mathbf{1_{Ph}}$) and few *o*-phosphanylanilines (Scheme 22a).[178] The first steps in the so far only examples of such arylations with OH or NHR-substituents require heating of *o*-chlorophenol or *o*-chloroanilines with Ph_3P and $NiCl_2$ (0.5 equiv) at 200–220 °C (4 h) to obtain the phosphonium salts (*o*-$HYC_6H_4PPh_3^+)_2$ $NiCl_4^{2-}$ ($\mathbf{87_Y}$). Subsequent reductive cleavage of a phenyl group is best performed using sodium naphthalenide (Na/Naph) at low temperature. Separation of the product from naphthalene is achieved by reaction with nickelacetate dihydrate in hot ethanol and precipitation of the $(Ph_2PC_6H_4Y)_2Ni$ chelate complexes $\mathbf{88_Y}$. The decomplexation is different for Y=O and Y=NR/NH, for the phosphanylphenolate complex simply by treatment with 3 *N* aqueous HCl and extraction of $\mathbf{1_{Ph}}$ with ether.

P-Arylation of triphenylphosphane, later extended to further triarylphosphanes, $(p\text{-}RC_6H_4)_3P$ (R=Me, Et, *n*Pr), is possible under much milder conditions (130 °C for 24 h) as shown by the $Pd_2(dba)_3$-catalyzed reaction with the chiral (*R*)-3,3′-diiodo-2,2′-dihydroxy-binaphthyl in ethylene glycol. The resulting chiral (*R*)-bis(phosphonium) salts **89** (Scheme 22b) were used to prepare chiral electrostatically-enhanced phosphoric diester acids **90** as organocatalysts for asymmetric Friedel–Crafts reactions.[18,179a,b]

NiX_2 (X=Br, Cl) catalyzed P–C coupling reactions of arylbromides with functionally substituted diphenylphosphane derivatives Ph_2PY (Y=H, SR, NEt_2)[180] require similar harsh conditions (long heating to 200 °C) and lead to $ArPh_2PY^+$ X^- species, stable for Y=NEt_2, but decomposing for Y=H or SR to tertiary phosphanes. The latter may react with still unconverted or excess arylbromides to stable $Ar_2Ph_2P^+$ salts. Milder conditions (100 °C for 2–3 d) are required in the optimized stereospezific bis-substitution of chiral 1,1′-binaphthyl-2,2′-bis-triflate with Ph_2PH in the presence of DABCO and 10 mol% dppe (1,2-bis(diphenylphosphanyl)ethane).[181] Examples with functional groups are not yet reported for this protocol. Another route for arylation of diphenylphosphane involves its acylation with the corresponding aromatic acid chloride (ArC(O)Cl) and subsequent decarbonylation, catalyzed by heating with 5 mol% $NiCl_2$(dppp) in xylene at 150 °C (dppp = 1,3-bis(diphenylphosphanyl)propane). The applicability to *o*-hydroxyarylphosphanes has still to be checked but the compatibility of the method with +M-substituted reactants was demonstrated for 1-diphenylphosphanyl-2-ethoxy-naphthalene (**91**) and *p*-$Ph_2PC_6H_4OMe$ (yield 45 and 70%) (Scheme 23a).[182] Reactions of arylhalides (aryl-X) with trialkyl phosphites in the presence of catalytic amounts of anhydrous $NiBr_2$ or $NiCl_2$, performed at 150–160 °C (for X=I, Br; for X=Cl at higher temperature), were first reported by Tavs[183] and proceed with elimination of alkylhalides, analogously as Arbuzov-reactions with alkyl halides.[171] The catalytically active species are $Ni(0)(P(OEt)_3)_n$



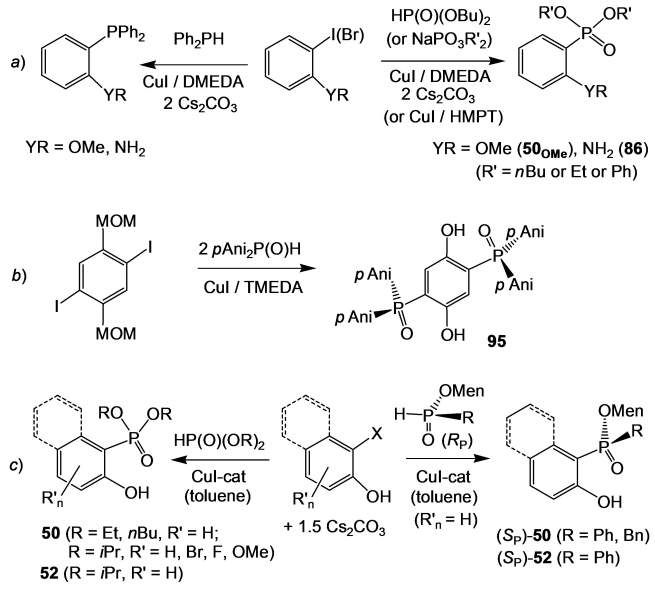
Scheme 22. a,b. *a*) Metal mediated arylations of Ph_3P with *o*-chlorophenol and analogous *o*-chloroanilines and *b*) metal catalyzed syntheses of BINOL-bis(triarylphosphonium) salts.



Scheme 23. a–c. Examples of Ni-catalyzed C–P cross-couplings of *O*- or *N*-functional substituted aryl halides with P(III)-compounds.

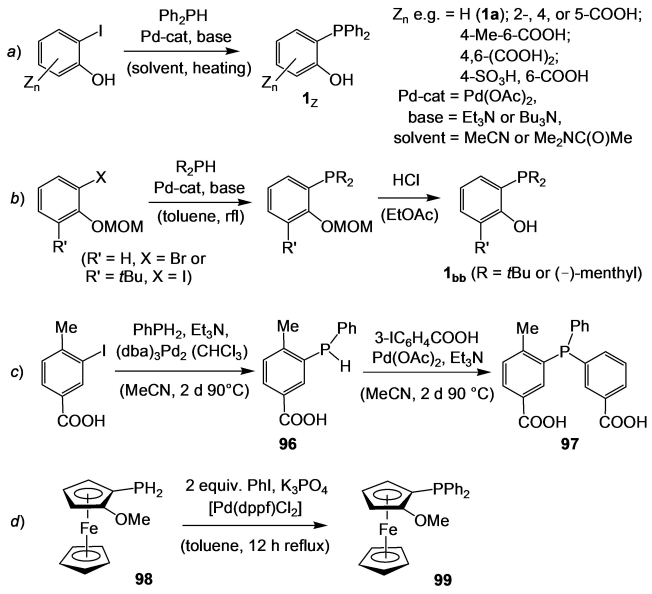
complexes (n = 3,4), formed in situ from NiX_2 and $(EtO)_3P$ on heating.[184–186] Free OH or NH_2 groups disturb reactions according to the Tavs-protocol unless hindered by steric reasons, for example in 4-bromo-2,6-di(*tert*-butyl)phenol, affording the corresponding 4-hydroxyphenylphosphonate **92** (Scheme 23b).[183] The latter suggests that coupling problems are due rather to catalyst deactivation than to the electronic + M- or –M-effects, illustrated also by more or less efficient couplings of a variety of π-donor- or π-acceptor-substituted bromobenzenes (*p*-R=AcO, MeO, Et_2N or NC, EtOOC) with $P(OEt)_3$[183] or of *o*-IC_6H_4COOEt with $MeP(OEt)_2$.[184] Saponification of 4-$AcOC_6H_4P(O)(OEt)_2$ with Et_2NH to 4-$HOC_6H_4P(O)(OEt)_2$[183] hints at a possible route to *o*-hydroxy-substituted arylphosphonates. A first test to couple acetic acid 2-bromo-4-methylphenyl ester with triethyl phosphite in the presence of $NiCl_2$·dioxane (175 / 204 mmol / 1 g; 15 min 210 °C) furnished the 2-acetoxy-5-methylphenylphosphonate **93** in modest yield (10 g, 27%)[187] but should be improvable by use of the respective aryliodide, a bulkier acyl group and a more efficient catalyst. Analogous secondary *NH*-acyl-*o*-bromoanilides **94** (except formylamides) display good to almost quantitative conversions in comparable $NiBr_2$-catalyzed P–C couplings with $MeP(OEt)_2$[188] or $P(OEt)_3$[186,189] (Scheme 23c). C–P cross-couplings of *p*-hydroxy- or *o*/*m*/*p*-NH_2-functionalized bromo- or iodobenzenes with $Ph_2P(O)H$ using the $NiCl_2 \cdot 6H_2O$/bipyridyl/Zn catalyst system can even be performed in water.[190]

Cu(I)-catalysts, stabilized by suitable donor ligands or the P-reactant itself, are more functional group tolerant[191–193,132] (Scheme 24a). Studies with + M-group substituted aryl iodides showed that CuI/DMEDA ($MeNHC_2H_4NHMe$) catalyzed reactions of 2-iodoanisol or -aniline with Ph_2PH or $(nBuO)_2P(O)H$ in the presence of two equivalents of Cs_2CO_3 give high yields (86-91%) of the corresponding *o*-methoxy- or *o*-aminophenylphosphanes or the corresponding phosphonates $\mathbf{50_{OMe}}$ and **86**.[192] Likewise good results are obtained in early CuI/HMPT catalyzed syntheses of 2-MeO- and 2- and 4-$H_2NC_6H_4P(O)(OR)_2$ from *o*-bromoanisol or *o*- and *p*-bromaniline with sodium phosphites (R=Et, Ph)[193] or in CuI/*N*-methylpyrrolidine-2-carboxamide catalyzed couplings of 2-bromo- or 2-iodo-trifluoroacetanilides with phosphites or PH-functional phosphine oxides under mild conditions (45–55 °C).[194] 2,5-Bis[(*p*-$MeOC_6H_4)_2P(O)]_2$-hydroquinone (**95**) was obtained by CuI/TMEDA catalyzed reaction of bis-MOM-protected 2,5-diiodo-hydroquinone with (*p*-$MeOC_6H_4)_2P(O)H$ and subsequent HCl-mediated cleavage of the MOM group.[195] O-Silylated derivatives thereof were of interest by their simultaneous phosphorescence and fluorescence (Scheme 24b). A recent investigation of Cu-catalyzed P–C cross-couplings to synthesize *o*-hydroxyphenyl- and 2-hydroxynaphthyl-1-P(O)-compounds (type **50** and **52**) comprised optimization of the conversion of *o*-iodophenol and diisopropyl phosphite with respect to copper salts, ligand additive, base, solvent and temperature, followed by screening of various *o*-halophenols for couplings with dialkyl phosphites, menthyl phosphonites and two secondary phosphine oxides under the optimized condition (Cs_2CO_3 1.5 equiv, no ligand additive, 10 mol% CuI, toluene, 80 °C/14-20 h) (Scheme 24c). The yields of the P–C coupling products decrease in the following order: for *o*-XC_6H_4OH and $(iPrO)_2P(O)H$: X=I > Br ≫ Cl (97–99, 87, 0%); for *o*-BrC_6H_4OH and RR'P(O)H: RR' = Ph_2 ≈ *t*BuPh ≈ $(OnBu)_2$ > $(OEt)_2$ ≈ $(OiPr)_2$, > (–)-OMenPh; for *p*-substituents: H ≈ F > OMe ≫ NO_2 (0%). In the case of two *o*-Br only one is replaced by $(iPrO)_2P(O)$ with good yield. *o*-OMe- or *o*-SH-substituted or unsubstituted bromobenzene did not undergo CuI-catalyzed coupling with $(iPrO)_2P(O)H$ whereas iodobenzene or *o*-iodoaniline gave still high conversions (94 and 91% of 2-$YC_6H_4P(O)(OiPr)_2$ (Y=H, H_2N). 1-Bromo-naphth-2-ol displayed lower coupling yields with $HP(O)(iPrO)_2$ or HP(O)Ph(OMen) (27 or 53%) than *o*-bromophenol. The conversions of iodo- or bromophenol or 1-iodonaphth-2-ol with the *P*-asymmetric (R_P)-HP(O)(OMen)R reactants proceed with stereoretention to the corresponding (S_P)-2-hydroxyphenyl- or 1-naphthylphosphinates **50** or **52**.[132b]



Scheme 24. a–c. Examples of CuI catalyzed C–P cross-couplings of *a*) Ph_2PH or H/NaP(O)$(OR)_2$ with *o*-OMe or NH_2 functional aryl iodides, *b*) MOM-protected diiodo-hydroquinone with di-(*p*-anisyl)phosphine oxide and *c*) $HP(O)(OR)_2$ or chiral arylphosphinites HPR'(O)(OR*) with mainly *o*-OH substituted aryl halides.

For Pd-catalyzed C–P cross-couplings of aryliodides or -bromides with P–H functional phosphanes as well as with phosphites or hypophosphites likewise high functional group tolerance was demonstrated. Stelzer and coworkers used this strategy to synthesize a wide variety of functionally substituted and in part water-soluble phosphane ligands from Ph_2PH and in part also $PhPH_2$ and the correspondingly substituted aryl iodides. The substituents include electron-donating *o*- or *p*-hydroxy-, alkoxy- and the analogous NH_2- and *N*-acylamido groups, electron-withdrawing (–M)-COOH and water-solubility mediating SO_3Na groups as well as multifunctional combinations thereof,[105,196a–c] illustrated by selected examples of $\mathbf{1_Z}$ with acidic substituents (Scheme 25a). The scope of this strategy was later extended by other groups, beyond $Ph_2PC_6H_4OH$ ($\mathbf{1_{Ph}}$)[197] to a variety of further, in part very bulky substituents. Thus, 2-(3,5-$(CF_3)_2C_6H_3)_2PC_6H_4OH$, used to evaluate the influence of P-electron-withdrawing substituted ligands on the dehydrocou-

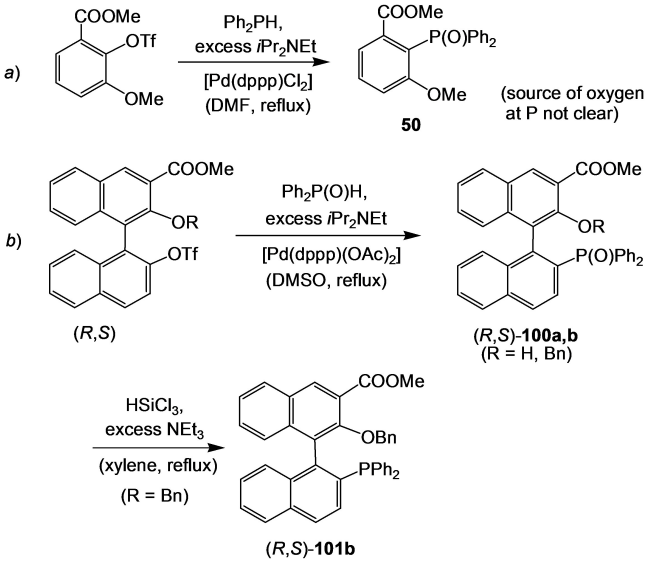


Scheme 25. a–d. Examples of Pd-catalyzed C–P cross-couplings to *a*) $\mathbf{1}_{Ph}$ and $\mathbf{1}_{Z}$ with various additional functional groups, *b*) bulky and P-basic *o*-PR_2- and *o'*-substituted phosphanylphenols $\mathbf{1}_{bb}$; *c*) stepwise C–P cross-coupling of $PhPH_2$ to the *P*-asymmetric phosphanes **96** and **97** and *d*) double P-arylation of the *o*-methoxy-ferrocenylphosphane **98** to **99**.

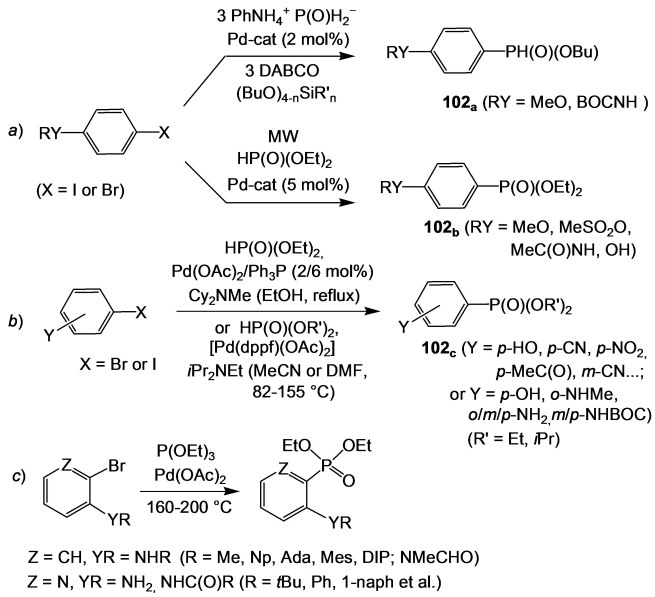
pling of amine-boranes by cationic Zr-phosphanylphenolate catalysts, was prepared via a multistep procedure, using $Pd(OAc)_2$ catalyzed coupling of *o*-iodophenol with $(3,5\text{-}(CF_3)_2C_6H_3)_2PH$ as the last step.[198] Other examples are rather P-basic and bulky dialkylphosphanylphenols $\mathbf{1}_{bb}$, accessible by $Pd_2(dba)_3$/DPEphos (dba = dibenzylideneacetone; DPEphos = bis[(*o*-diphenylphosphanyl)phenyl]ether) catalyzed coupling of dimenthylphosphane or tBu_2PH with $2\text{-}BrC_6H_4OMOM$ or 2-I-6-$tBuC_6H_3OMOM$ and subsequent deprotection by HCl/EtOAc (Scheme 25b).[65] Primary phosphanes like $PhPH_2$ may undergo stepwise arylation to form *P*-asymmetric phosphanes **96** and **97**, probably favored by the *o*-methyl group in **96** (Scheme 25c), but also undergo double *P*-arylation. An example is the coupling of the *P*-primary *o*-methoxy-ferrocenylphosphane **98** with two equivalents of iodobenzene, catalyzed by $[Pd(dppf)Cl_2]$ (4 mol%) in toluene in the presence of K_3PO_4, affording compound **99** in 52% yield (Scheme 25d).[134a] Microwave heating shortens the reaction time for coupling of iodoarenes including 3-iodoanisol and 2 iodoaniline with Ph_2PH, at 180 °C to 5–20 min, although yields of 3-MeO- and $2\text{-}H_2NC_6H_4PPh_2$ (catalysts 2 mol% Pd/C and 3.5 mol% $Pd(PPh_3)_4$, resp.) remain rather moderate.[199] The Stille-coupling with Me_3SiPR_2 or Me_3SnPR_2 instead of PH-functional phosphanes works with the protected MeO- and (slowly) with *N*-acylamino derivatives but is not compatible with a free OH or NH_2 group in the aryliodide by preferred Si–P or Sn–P bond cleavage.[200] It should also be mentioned that the Ph_2P-group of *o*-phosphanylphenyl esters of aromatic acids, used for example in traceless-Staudinger couplings of labeled aryl-C(O) groups with biomolecules, can be introduced via Pd-catalyzed reaction of Ph_2PH with the corresponding *o*-iodophenyl esters.[201]

Phenyltriflates are also usable for arylation of R_2PH (R=Ph, Et) but furnish like as in the couplings with $Ph_2P(O)H$ the respective phosphine oxides, for example **50** with *o*-COOMe and *o'*-methoxy substituents, by refluxing in DMF in the presence of $[Pd(dppp)X_2]$ and iPr_2NEt as a base. As a related 2'-OH or 2'-OBn-substituted binaphthyl-2-triflate undergoes P–C coupling only with $Ph_2P(O)H$, then providing similar phosphine oxides $\mathbf{100}_{a,b}$, it was assumed that the oxidation step occurred before or in connection with the coupling step and that this might be due to coordinative interactions of the Pd-catalyst in *o*-OR and 2,2'-OR aryl-P surrounding. *o*-OR and *o*-COOMe functional groups are compatible with the coupling method and also with the reduction of the coupling product $\mathbf{100}_{a,b}$ by refluxing with $HSiCl_3/Et_3N$ in xylene to the corresponding phosphane $\mathbf{101}_{b}$ (Scheme 26a,b).[202]

In contrast to the above mentioned results with Ph_2PH, examples of Pd-catalyzed C–P cross-couplings of *o*-iodo- or *o*-bromophenols or *O*-acyl derivatives thereof with hypophosphites, di- or triethyl phosphite are rare and require acetate additives.[203a] However, reports on PH-functional *O*-butyl-phenylphosphinites with *p*-MeO- and *p*-BOC-NH-substituents $\mathbf{102}_{a}$ are known. These are accessible by arylation of anilinium hypophosphite with the corresponding phenyliodides in the presence of butoxysilanes, excess DABCO and 2 mol% $[Pd(dppp)(OAc)_2]$.[203] Likewise, studies including microwave-supported arylation of diethyl phosphite with *p*-iodoanisol and *O*- or *N*-acyl-protected *p*-bromophenol or *p*-iodoaniline to $\mathbf{102}_{b}$, catalyzed by 5 mol% $[Pd(Ph_3P)_2Cl_2]$ have been reported (Scheme 27a).[204] Optimized couplings of diethyl phosphite with *p*-bromophenol, *p*-bromoanisol and arylbromides with various –M- or –I-substituents to $\mathbf{102}_{c}$ indicate a rather small influence of electronic effects. In the presence of Cy_2NMe (1.5 equiv) and $Pd(OAc)_2/Ph_3P$ (2/6 mol%) in boiling EtOH yields reach 80 (*p*-OH) to 92% (*p*-CN) (Scheme 27b).[205] Examples for Pd-catalyzed cross-couplings of dialkyl or trialkyl phosphites with *o*-(+M)-aryl



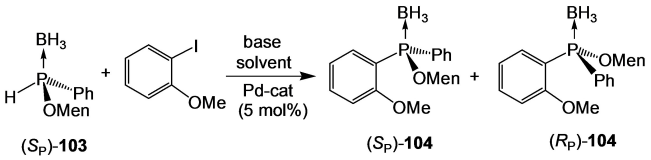
Scheme 26. a,b. Pd-catalyzed C–P cross-couplings of Ph_2PH or $Ph_2P(O)H$ with COOMe and OR functional aryltriflates.



Scheme 27. a–c. Pd-catalyzed C–P cross-couplings of functionally substituted aryliodides or bromides with *a*) anilinium hypophosphite or with dialkyl phosphite (MW stimulated), *b*) dialkyl phosphite (according to *Hirao*-protocol) and *c*) trialkyl phosphite (*Tav*s-protocol).

substituents other than OH are reactions of *o*-bromo- or *o*-iodoanilines[206,207,208a,b] and *o*-bromo-*N*-acylamidobenzenes or -pyridines.[189,206,208b] For small *o*-donor groups working according to the *Hirao* protocol is more advantageously. This method is using usually diethyl or diisopropyl phosphite and catalyst systems optimized for the target molecules,[209] for example [Pd(dppf)(OAc)$_2$] (1 mol%) for *o*/*m*/*p*-NH$_2$ or *p*-OH substituted aryliodides or bromides (Scheme 27b, below arrow).[206,207] Higher yields for bulky *N*-alkyl or *N*-aryl *o*-anilinophosphonates[208a] and *o*-bromo-*N*-acylamidopyridines[208b] allow using the simpler *Tav*s-protocol with triethyl phosphite as reactant (including reduction of Pd^{II} to Pd^0) and catalyst ligand (cat. 4 mol% Pd(OAc)$_2$) (Scheme 27c).

Arylations of chiral tetracoordinated P–H functional organophosphorus compounds usually proceed with retention of configuration. However, for the coupling of the asymmetric air-stable (S_P)-(menthyloxy)phenylphosphane-borane ((S_P)-**103**) with *o*-iodoanisol in the presence of Pd(PPh$_3$)$_4$, using various bases and solvents, dependence of the stereoselectivity for formation of (*S*)- and (*R*)-**104** on the solvent and base was demonstrated. Reactions in MeCN (K_2CO_3, K_3PO_4 or Ag_2CO_3), toluene (Ag_2CO_3), THF (Ag_2CO_3) or DMF (K_2CO_3) proceed almost completely or strongly preferred with retention of configuration whereas in THF, THP or dioxane (K_2CO_3) inversion is dominant. In THF and in the presence of various strong bases the stereoselectivity is lost.[210] Few examples are presented in Scheme 28.

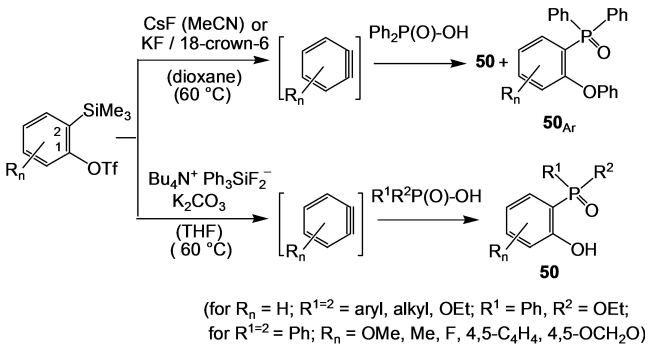


solvent	base	time	temp.	yield (S_P)-**104**	:	(R_P)-**104**
MeCN	K_2CO_3	16 h	50 °C	96 %	100 :	0
dioxane	K_2CO_3	16 h	50 °C	61 %	10 :	90
THF	K_2CO_3	48 h	50 °C	76 %	4 :	96
THF	Ag_2CO_3	12 h	50 °C	67 %	99 :	1

Scheme 28. Examples of solvent- and base-dependent stereoselectivity of Pd-catalyzed P–C cross-couplings of (S_P)-**103** and *o*-iodoanisol.

2.9. o-Hydroxyarylphosphanes, -phosphonates and selected phosphine oxides via addition of phosphorus compounds to benzynes or quinones

Rare examples for syntheses of *o*-hydroxyarylphosphine oxides, -phosphinates or -phosphonates are the recently discovered insertions of benzynes, generated by fluoride-mediated *o*-elimination of Me$_3$SiOTf from *o*-trimethylsilyl-phenyltriflates, into the P–O bonds of phosphinic, phosphonic or dialkoxy phosphoric acids (Scheme 29). The simultaneous formation of C–P and C–O bonds occurs regioselectively in one step, transition-metal free and with good yields up to 86%. In first experiments with Ph$_2$P(O)OH and CsF in MeCN or KF/[18]-crown-6 (2 equiv) in dioxane, the O-phenyl ether **50**$_{Ar}$ (all R=Ph) was the only or the main product. This indicates insertion of a second benzyne into the O–H bond of **50**. Optimization experiments proved that nBu$_4$N$^+$ Ph$_3$SiF$_2^-$ (TBAT) with weaker basicity of the anion is well suited for the only or strongly preferred formation of the *o*-hydroxyaryl phosphine oxides, -phosphinates or -phosphonates **50**. Variation of substituents (R$_n$ = H, R$^{1=2}$ = 4-R'C$_6$H$_4$ (with R' = H, OMe, Me, F, CF$_3$), alkyl (*i*Pr, *n*Pent, cyclopentyl, Bn, Vin), OEt; R^1 = Ph, R^2 = OMe, OEt; R$_n$ = one or two MeO, two Me or F, 4,5-benzo-, cyclopentene- or 1,3-dioxolene annulation with R$^{1=2}$ = Ph) proved minor influence of electron-donating groups and steric hindrance whereas electron-withdrawing groups in *p*- or *o*-position diminished the

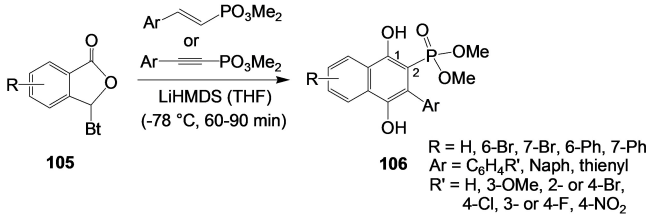


Scheme 29. Formation of *o*-hydroxyaryl-phosphonates, -phosphinates and phosphine oxides by insertion of benzynes into the P–O bond of R^{1}R^{2}P(O)OH compounds.

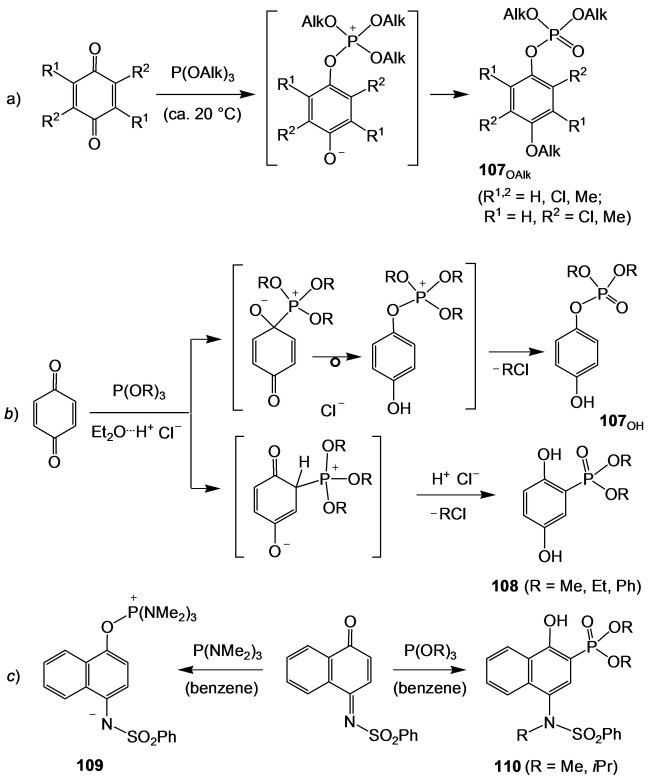
yields. Few examples of methylation or triflation at the *o*-OH group and Pd-catalyzed substitutions of OTf demonstrate the potential of the *o*-hydroxyarylphosphine oxides for transformations to other types of *o*-substituted arylphosphorus compounds.[211]

Also the other way round, reaction of vinyl- or alkynyl phosphonates with suitable precursors for cycloadditions, was recently established. Various isobenzofuranones (phthalides) **105** with an electron-withdrawing Bt-substituent (Bt = benzotriazolyl) react with both, phosphonate-activated styryl- or arylalkynyl moieties, via Hauser-annulation to a variety of benzo- and 3-aryl-substituted 1,4-hydroquinone-2-phosphonates **106**. The moderate to good yields with the double and triple bond precursors are comparable (Scheme 30). A mechanism to explain the formation of the same products was proposed. The tolerance of a variety of aryl substituents displays some leeway concerning the unsaturated phosphonates. Oxidations with NBS to various corresponding 2-phosphonyl benzoquinones were reported and disclose the properties of these compounds and lack of tautomerism.[212]

Studies of the addition of tri- and dialkyl phosphites towards *p*-quinones started in contrast to the aforementioned investigations already more than 60 years ago. Ramirez et al.[213] found that tri-*n*-alkyl phosphites react with several *p*-quinones to give dialkyl 4-alkoxyphenyl phosphates **107$_{OAlk}$**, probably via zwitterionic intermediates, which like the alkoxyphosphonium intermediates of Michaelis–Arbuzov-reactions[171] transfer Alk$^+$ to a suitable electrophile, here to 4-O$^-$, resulting in a 1,6-addition product (Scheme 31a). Saponification under basic conditions leads to the corresponding 1,4-hydroquinone-monoalkylesters. Only minor amounts (6–8%) of phenolic side products were observed in the reaction of *p*-quinone with $(EtO)_3P$, and no substantial replacement of Cl of *p*-di- or tetrachloroquinone occurred.[213] Analogous reactions were reported for *p*-naphthoquinones,[214] *p*-quinone-dibenzenesulfonimides, *p*-chloranil- and 2,3-dichloro-*p*-naphthoquinone dibenzenesulfonimides[215a,b] whereas *o*-quinones delivered cyclic phosphate orthoesters.[214] If the reaction of triethyl phosphite with *p*-benzoquinone was performed in the presence of HCl in dry ether two products were reported. Based on analytical and ^{31}P NMR data ($\delta = 7$ and -20 ppm, roughly 1:1) they were described as diethyl *p*-hydroxyphenyl phosphate **107$_{OH}$** and diethyl 1,4-dihydroxybenzenephosphonate **108** (R=Et). The reaction was explained by competing attacks of the Lewis basic $P(OEt)_3$ at the electrophilic CO-carbon and its neighbor atom, activated by conjugation with the *p*-CO group.



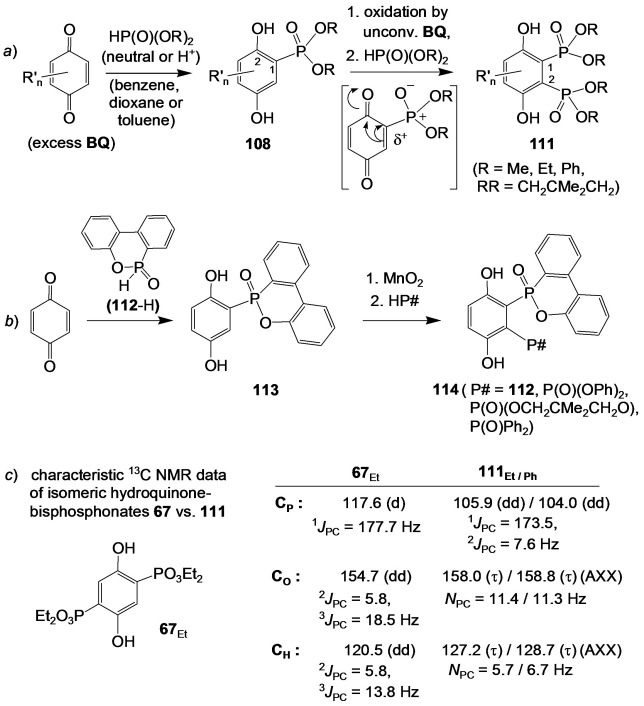
Scheme 30. Synthesis of 1,4-dihydroxynaphthaline-2-phosphonates via Hauser-annulation of unsaturated phosphonates with phthalides.



Scheme 31. a–c. Reaction of *p*-quinones or imino derivatives with $(RO)_3P$ (*a-c*) or $P(NMe_2)_3$ (*c*).

The first intermediate undergoes 1,2-C,O migration of the triethoxyphosphonium to O$^-$ and then transfer of an ethyl$^+$ group to chloride (of $Et_2OH^+Cl^-$). The alternative 1,4-Michael intermediate with CH–$P(OEt)_3^+$ group similarly transfers ethyl$^+$ to chloride (Scheme 31b).[216] For the reaction of trimethyl- and triisopropyl phosphite with 1,4-naphthoquinone-benzenesulfonimine in benzene the 1,4-addition products with Et$^+$-translocation to the N-atom (**110**) were precipitated, the methyl compound in low yield (25%), the *i*Pr-derivative after addition of petroleum ether in 95% yield. Reaction with $P(NMe_2)_3$ instead of phosphite furnished directly the stable zwitterionic 1,6-addition product **109** (Scheme 31c).[217]

Studies with the PH-functional dialkyl phosphites proved that the addition to *p*-benzoquinone depends on the reaction conditions. In the presence of alkali metal alkoxides[218] or Et_3N[219,220] only 1,6-addition to **107$_{OAlk}$** is observed. Under neutral conditions or in the presence of acids (HOAc) the phospha-Michael-addition delivers 1,4-hydroquinone phosphonates **108** (R=Me, Et, Ph, R'$_n$ = H and others, see below) and minor amounts of 1,4-bis-addition products **111**.[219–222] The formation of the latter was attributed to oxidation of **108** by benzoquinone (**BQ**), acting dual as enone and oxidizing agent, followed by a second 1,4-addition step of $HP(O)(OR)_2$ (Scheme 32a).[219] The heterocyclic PH-functional biphenylphosphinate **112-H** and **BQ** formed in high yield the mono-adduct **113**. This was synthesized to transfer the flame retarding properties of **112-H** via reaction at the two OH groups of **113** to (oligomer) building blocks for integration into polymers.[223a,b] A



Scheme 32. a–c. Addition of *a*) $HP(O)(OR)_2$ or *b*) **112-H** to *p*-quinones and, after oxidation of the primarily formed 2-phosphono-hydroquinones, addition of a second equivalent H-P#-reagent, H-P(O)$(OR)_2$ or H-P(O)Ph_2; *c*) comparison of characteristic ^{13}C NMR data allowing to distinguish regioisomers of type **67** and **111**.

procedure for direct 1,4-bis-addition of **112-H** to *p*-benzoquinone, claimed in a patent,[224] could not be reproduced. Tests showed that **113** is stable to oxidation by **BQ** but is oxidized by MnO_2 to the corresponding quinone. This then allowed subsequent conversion with **112-H** or, alternatively, three other $R_2P(O)H$ compounds to **114** (P# = **112**, P(O)$(OCH_2CMe_2CH_2O)$; P(O)$(OPh)_2$, P(O)Ph_2) (Scheme 32b). XRD analyses of various products of type **111** and of **114** proved the *o*-position of the $P(O)R^1R^2$ groups to each other and give closer information also on structural features such as inter- and intramolecular hydrogen bridges between OH and P=O groups within the crystals.[219] The high yield of **108** (R=Ph, R_n = H, 96%) in the monoaddition of $Ph_2P(O)H$ to *p*-benzoquinone[225] will go back to low sensitivity for competing oxidation by **BQ** or a much slower oxidation rate. Oxidation of 1,4-hydroquinone phosphine oxides with iodine(III) acetate[36b] or Fremy's salt[226] (potassium nitrosodisulfonate $K_2NO(S_2O_6)$) delivers the corresponding Ph_2P-(O)-substituted quinone.

Another, quite extensive study on the mono-addition reactions of various types of $R_2P(O)H$ substrates towards *p*-benzoquinones[220] includes additive, solvent and temperature tuning possibilities and effects by steric (**BQ**- and P-OAlk substituents) and electronic [$(AlkO)_2P(O)H$ vs. (AlkO)PhP(O)H and $Ph_2P(O)H$] influences (Scheme 32a). Using diethyl phosphite/**BQ** (1:1) the following trends were detected: *i*) increasing reactant concentrations (0.1–1.0 M) cause increasing yields of 1,4-addition products (**108**) and slight decrease of the mono-/bis-adduct ratio; *ii*) water (0.2–1.0 equiv) > HCOOH (0.2 equiv) > HOAc (0.2–1.0 equiv) additives (compared to its absence, referred to c = 0.5 M) increase the yields of **108** with slight increase of the mono/bis-addition ratio for water (up to 92–95%); *iii*) solvent variation (in the presence of 0.5 equiv H_2O, 80 °C) indicated highest yields and mono-/bis-adduct ratios for toluene 85 (94/6) > benzene 83 (92/8) > Ph_2O 75 (90/10) > hexane 71 (78/22) > no solvent 56 (63:37) > MeOPh, EtOAc, dioxane and acetone. DMF and DMSO favored bis(1,4-addition) (29/80 and 33/67). Et_3N additives (1–50 mol%) confirmed the known 1,6-addition with excellent selectivity and highest yields (94–97%) at room temperature. The results of the 1,4-mono-addition of diethyl phosphite to R'_n-substituted benzoquinones don't display clear trends except in the case of strong steric hindrance (yields in % for R'_n = 4,6-Me_2 (91), 3,6-Ph_2 (87), H (85), 3,4-C_4H_4 (55), 3,6-Me_2 (45), 4,6-*t*Bu_2 (15)). The influence of the substituents at the $R_2P(O)$ group on the yield of **108**, evaluated by addition to **BQ** in toluene in the presence of water (1:1:0.5 equiv), indicated best results for R=Ph (98%) followed by R=OEt, Ph/OEt, O*i*Pr (85–81%), $(CH_2)_4Ph$ (77%), OMe (51%).

The synthesis of the bis(1,4-addition) products was optimized based on the above trend analyses (Scheme 32b). Heating **BQ** with diethyl- and diisopropyl phosphite overnight in DMSO (80 °C) delivered adducts of type **111** in good yields (72 and 65%), respectively. HP(O)(MeO)Ph and $HP(O)(MeO)_2$ proved less favorable (34 and 22%). Because the mono-adduct is stable to oxidation by **BQ** under "the same conditions", a stepwise mechanism was excluded and a mechanism for simultaneous 1,4-addition and subsequent oxidation by the second half of **BQ** proposed. (Use of DMSO should have explicitely be mentioned because hot DMSO also may act as oxidizing agent, for example converting phosphanes to phosphine oxides – author comment). Unfortunately, the proposed isomer assignment,[220] following older reports,[221,222] is not correct. Despite it seems sterically unfavorable, the bis(1,4-addition) delivers the two P-substituents in *o*-position to each other. This is shown by similar characteristic ^{13}C NMR data (J_{PC} almost equal), for example of **111** (R=Et)[220] to those of **111** (R=Ph), reported by Mueller et al.,[219] who in addition presented XRD analyses of **111** (R=Ph) and several related 1,4-bis-adducts of type **111**. The NMR data of the bis-adducts (Scheme 32c), erroneously assigned to type **67**,[220] differ clearly by characteristic ^{13}C chemical shifts and ^{31}P-^{13}C coupling constants from those of 2,5-dihydroxybenzene-1,4-bis(phosphonates) **67** (*cf.* Figure 4), prepared by another route.[127a] So far resolved, also a different ^{31}P-^{1}H coupling pattern for the two ring-H atoms is observed for compounds of type **67** and **111** (both with R=Et in $CDCl_3$/TMS), δ = 7.00 (q, $^3J_{PH}$ = 15, $^4J_{PH}$ = 8 Hz) in **67**[127a] vs. δ = 7.10 (t, $^3J_{PH}$ = 4 Hz) in **111**[220]). The reasons for the attack at the sterically less favorable position are probably the polarity of the P=O bond and inductive effects of $P^{\delta+}$ at the α- and β-C atoms, that favors attack of $(RO)_2P(O)H$ in this position, possibly via a DMSO-induced tautomeric associate (DMS=O···H··O-PR_2).

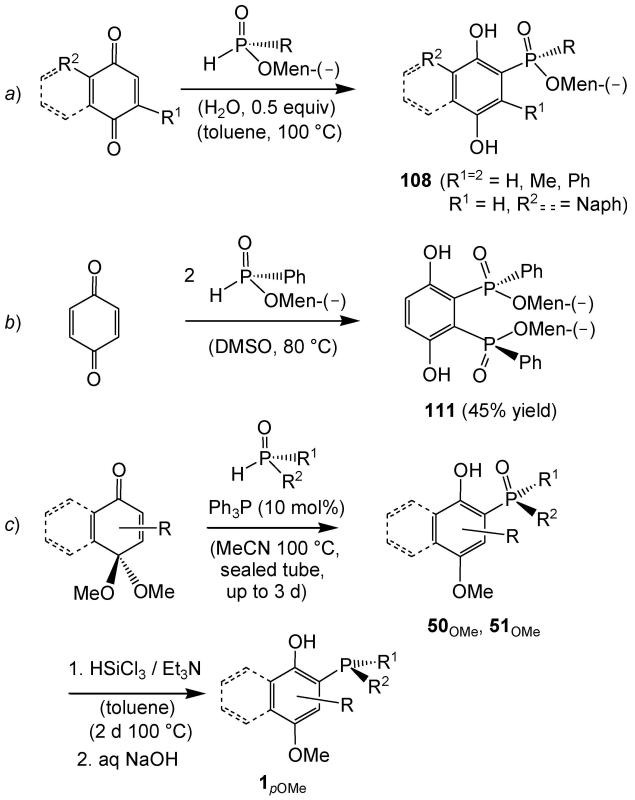
Of particular interest is the detection of stereospecific 1,4-additions of easily accessible optically active H-phosphinates, for example menthyl phenylphosphinate. These proceed with retention of configuration in toluene (water 0.5 equiv) and are applicable not only for **BQ** but also for the 2,5-Ph_2- and 2,5-Me_2-

substituted BQ-derivatives as well as 1,4-naphthoquinone (yields of **108** (R=Men) up to 97–81%) (Scheme 33a). Besides (R_P)-menthylphenyl- also (R_P)-menthylbenzyl- and (R_P)-menthyl-4-vinylbenzylphosphinate exhibited useful coupling yields with **BQ** and 2,5-Ph_2**BQ** to the corresponding derivatives of **108** (R=Men). By heating in DMSO also chiral bis-adducts of the type **111** (R=Men) are formed, depicted in Scheme 33b, whereas Et_3N promotes 1,6-addition products.[220]

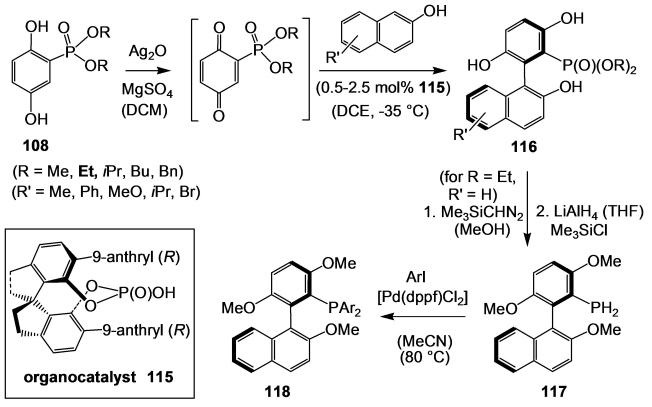
In a related study, 1,4-addition reactions of variously substituted secondary phosphine oxides to *p*-benzoquinone-dimethyl acetale, to substituted derivatives thereof as well as to 1,4-naphthoquinone-dimethylacetale were explored (Scheme 33c).[31] These acetals are conveniently available by oxidation of the corresponding *p*-methoxyphenols and -naphthols with $PhI(OAc)_2$, subsequent acetalization with methanol and neutralization with $NaHCO_3$. For the addition reactions various additives, solvents and reaction conditions were tested to optimize yields and selectivity. Triphenylphosphane (0.1 equiv) and acetonitrile proved beneficial for a multitude of reactants. Advantages of the 1,4-addition reactions are *i*) the metal-free procedure, *ii*) excellent regioselectivity, *iii*) tolerance of electron-withdrawing (F, CF_3) or donating (OMe) aryl substituents and/or bulky or unsaturated alkyl groups at phosphorus, *iv*) compatibility with *t*Bu, AcO, Br, PhC≡C and OCH_2O groups at **BQ**, and last not least high yields for various substitution pattern. This allows access to a large number of new *o*-hydroxy-methoxyphenyl and naphth-2-yl phosphine oxides of type $\mathbf{50}_{OMe}$ and $\mathbf{51}_{OMe}$, demonstrated by many examples.[31] Thus, this route offers a large potential for further transformations at the OH group, reactions with functional groups at the aryl rings or reduction of the $P(O)R^1R^2$ group to *o*-hydroxyaryl phosphanes $\mathbf{1}_{pOMe}$ or O-substituted derivatives thereof, widely useable in coordination chemistry or catalysis.

A related arylation by 1,4-addition should also be mentioned in this place. The 1,4-hydroxy groups of **108** allow oxidation with Ag_2O in DCM to the corresponding quinones, which after separation by filtration could directly be coupled with 2-naphthol to the trihydroxy-biarylphosphonate **116** (Scheme 34).[227] Optimization with various BINOL- and related chiral diaryloxy phosphoric acid catalysts indicated best yields and enantioselectivities with the spiro-organocatalyst **115**. This was then applied for coupling of a variety of hydroquinone phosphonates **108** with 2-naphthols, showing mostly good to excellent yields and enantioselectivities, in a 3 g-scale experiment with **108** (R=Et), unsubstituted naphthol and 0.5 mol% catalyst **115** 94% yield of **116** (R=Et) with 94% *ee*. Yields varied with the substituents at the naphthol, were rather low with Br in various positions, moderate for 6-MeO, good for 6-Ph, very good for 7-Ph or without substituent and excellent for various 7-alkoxy substituents. For different alkoxy groups yields ranged from 77 (OBn) to 95% (OEt), and *ee*'s reached mostly 90 up to 95%. Reaction of the initially studied 1,4-$(HO)_2C_6H_3P(O)Ph_2$ with 2-naphthol delivered only 50% coupling product with 24% *ee*. Besides the coupling studies few examples for useful transformations of **116** (R=Et) were presented, thus the syntheses of **117** and **118**, included in Scheme 34.

Reactions of phosphanes with quinones are known since long and not discussed here in all details. Whereas $PhPH_2$ reduces *p*-benzoquinones in benzene (ca. 20 °C) to the corresponding hydroquinones,[228] secondary and tertiary arylphosphanes may form addition products. These phosphanes react like the aforementioned $R_2P(O)H$ compounds depending on the substituents in the quinone or phosphane and the reaction conditions to products with P–O or with P–C-bonds.[229]

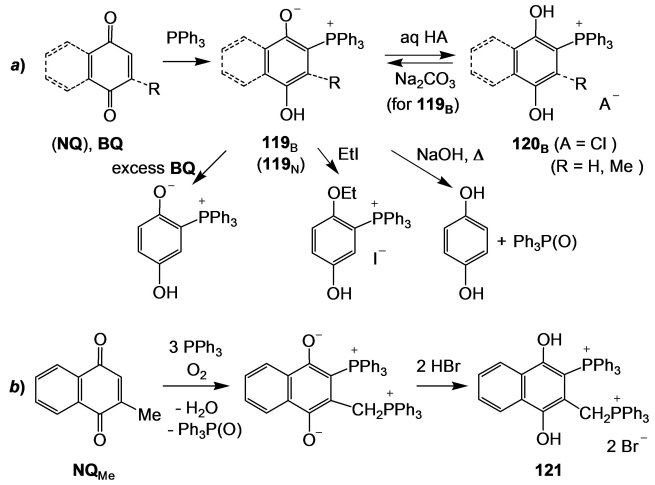


Scheme 33. a–c. Examples of stereospezific *a*) mono- and *b*) bis-(1,4-additions) of chiral menthylarylphosphinates to *p*-benzo- or naphthoquinones affording **108** and **111** (isomer assignment according to NMR data - *cf.* Scheme 32c); *c*) monoadditions of secondary phosphine oxides to quinone-dimethylacetals inclusive so far rarely used direct reductions of *o*-hydroxyaryl phosphine oxides to *o*-hydroxyarylphosphanes $\mathbf{1}_{pOMe}$.

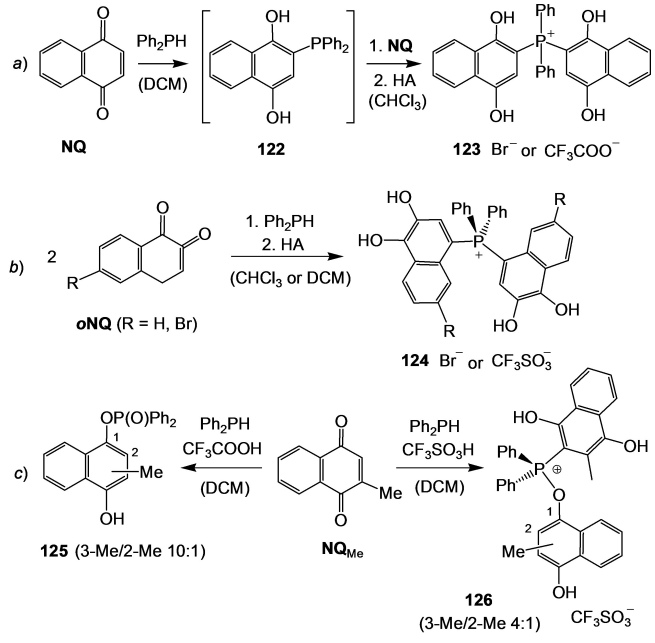


Scheme 34. Enantioselective oxidative coupling of **108** and 2-naphthols to the biaryl derivatives **116** and examples for further transformation to **117** and **118**.

Examples for 1,4-additions of Ph_3P to *p*-benzoquinone (in benzene) and 1,4-naphthoquinone, delivering the zwitterionic (ylidic) products **119**$_B$[230] and **119**$_N$,[231] are displayed in Scheme 35a. The compounds are easily oxidized by excess quinone, proved for **119**$_B$ by ESR,[232] and form with acids the corresponding 1,4-dihydroxyaryl-2-triphenylphosphonium salts **120**$_B$. Air contact of the 2-methyl substituted phosphonium-hydroxynaphtholate **119**$_N$ (R=Me), formed in conversions of **NQ**$_{Me}$ with excess Ph_3P, led to oxidative substitution at the methyl group with Ph_3P and after addition of HBr (2 equiv) in CH_2Cl_2 to precipitation of the bis-hydroxynaphthyl-bis(phosphonium) salt **121** (Scheme 35b), in the crystal forming centrosymmetric dimers with O–H···Br hydrogen bonds.[233]



Scheme 35. ab. Examples for formation of *o*-hydroxyarylphosphonium salts from Ph_3P and *p*-quinones.



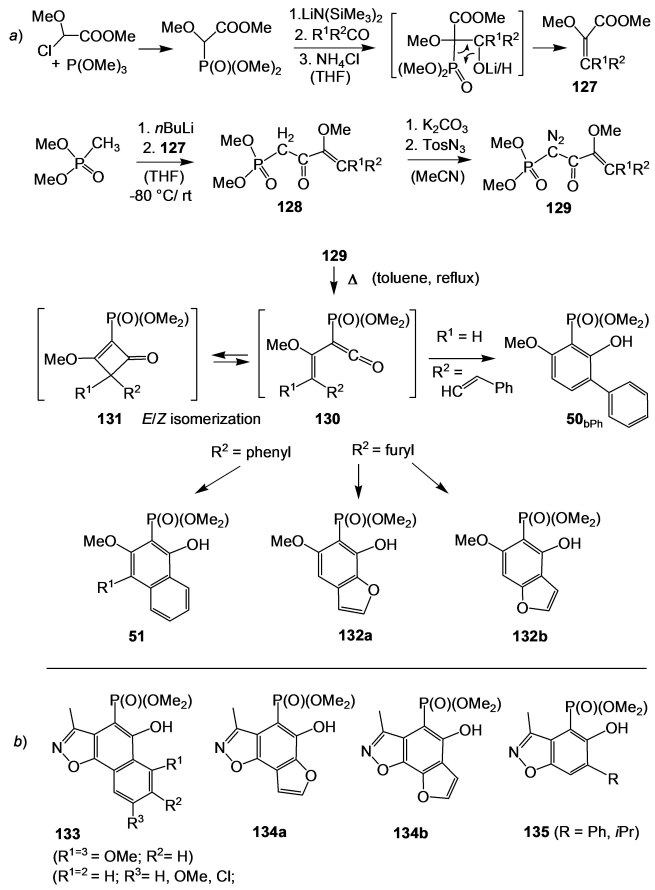
Scheme 36. a–c. Examples (and limits) for 1,4-addition reactions of Ph_2PH with *p*- and *o*-naphthoquinones.

Examples for addition of Ph_2PH to 1,4- and 1,2-naphthoquinones (**NQ** and ***o*NQ**) are depicted in Scheme 36. The reactions proceed probably through highly reactive mono-adducts (e.g. **122**) that rapidly add a second naphthoquinone (Scheme 36a,b) to sparingly soluble zwitterions, which with gaseous HBr, CF_3COOH or CF_3SO_3H form the corresponding bis(dihydroxynaphthyl)phosphonium salts **123** and **124**.[234a,b] Steric hindrance of [1,4]-addition by a 2-Me group favors [1,6]-addition, in the presence of CF_3COOH leading to the 4-hydroxynaphthylphosphinate **125**, in the presence of the stronger acidic triflic acid with [1,4]- and [1,6]-addition providing the aryloxyphosphonium salt **126**. For both, **125** and **126**, the isomers with the less hindering Me-3 position are preferred (Scheme 36c).[235]

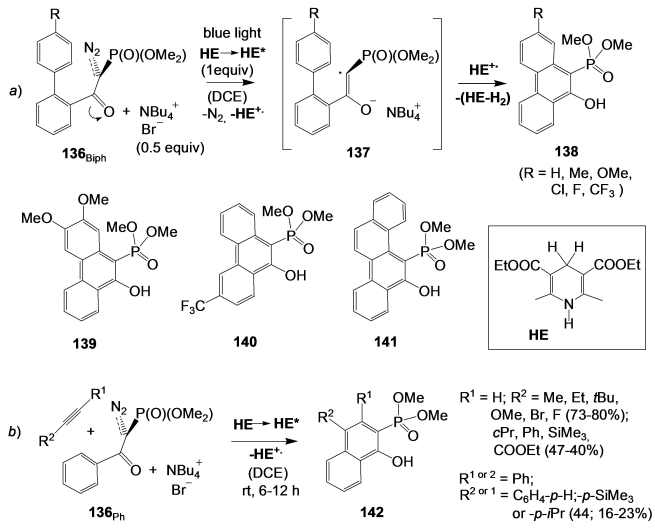
2.10. o-Hydroxyarylphosphonates via thermal or photoinduced decomposition of vinyl- or aryl-substituted α-diazo-β-ketophosphonates

A suitable alternative to the aforementioned strategies for syntheses of annulated *o*-hydroxyarylphosphonates was developed by Doutheau and Dehayes. This is based on thermolyses of vinyl- or (hetero)aryl-substituted α-diazo-β-ketophosphonates **129**.[236a–c] Compounds of type **129** are available in four steps, starting by Michaelis–Arbuzov reaction of trimethyl phosphite with MeOCHClCOOMe,[237] subsequent Horner–Wadsworth–Emmons olefination to the 2-methoxy-2-alkenoates **127**, coupling with dimethyl lithiomethylphosphonate to β-ketophosphonates **128** and reaction with tosylazide in the presence of K_2CO_3 to **129**. These α-diazo-β-ketophosphonates are stabilized by the EWG-effect of the phosphonate substituent, but on heating in toluene they extrude N_2 and undergo Wolff-rearrangement to the ketene acetals **130**. These may isomerize via **131** to the *trans*-configuration, detected for R^2 = Ph by trapping with methanol, or react with unsaturated substituents R^2 to give raise to an electrocyclization. With R^2 = styryl and phenyl the *o*-hydroxybiphenylphosphonates **50**$_{bPh}$ and **51**, with furyl group the annulated hydroxyarylphosphonates **132a** and **132b** were formed (Scheme 37a). The methoxy group proved crucial for the *E*/*Z* isomerization, allowing electrocyclization for both of the isomers. Compounds of type **131** with H, Me or NMe_2 instead of the OMe group may be obtained by another route and also used for electrocyclization, in this case needing $Rh_2(OAc)_4$ as a catalyst.[236a,c] In a related route via thermal decomposition of methylisoxazolyl-2-oxo-1-diazo-ethylphosphonates (instead of **129**), triggering a tandem Wolff rearrangement-benzannulation sequence, various novel isoxazole-annulated *o*-hydroxyarylphosphonates **133**–**135** (Scheme 37b) were prepared.[236b]

A related strategy, recently reported by Nagode, Kant and Rastogi,[238] is using a light-induced and $Bu_4N^+Br^-$/Hantzsch-ester (0.5/1.0 equiv) mediated N_2-extrusion from diphenyl-substituted α-diazo-β-ketophosphonates **136**$_{Biph}$ in DCE (dichloroethane) and finishes in intramolecular cyclization to annulated *o*-hydroxyarylphosphonates **138**–**141**. Yields are ranching from 68 to 82% with CF_3 and F substituents at the low and OMe at the high end (Scheme 38a). Extension of this



Scheme 37. a,b. Syntheses of biphenyl-type and annulated *o*-hydroxyarylphosphonates via thermally induced Wolff-rearrangement of vinyl- or (hetero)aryl-substituted α-diazo-β-ketophosphonates.



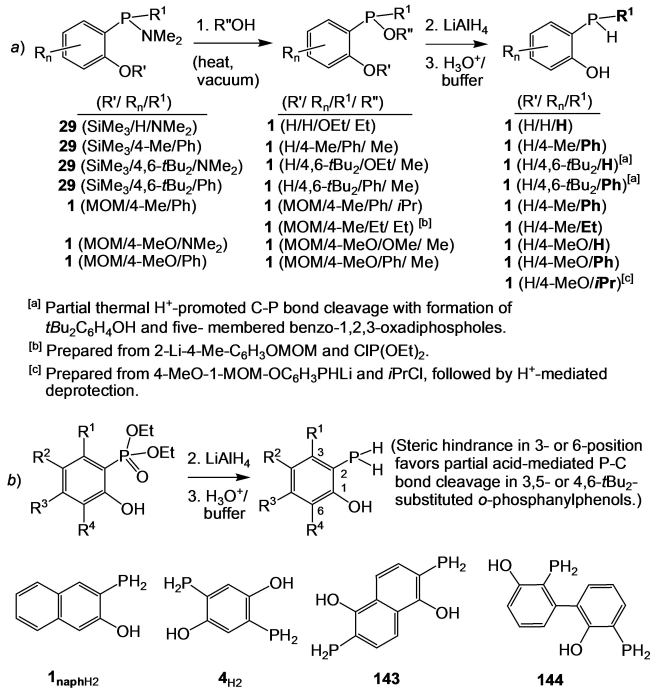
Scheme 38. a,b. Annulated *o*-hydroxyphenylphosphonates by light induced and $Bu_4N^+Br^-$ / HE mediated N_2-cleavage of α-diazo-β-ketophosphonates and *a*) intramolecular cyclization of biphenyl derivatives or *b*) intermolecular tandem alkyne addition-cyclization reaction.

reaction to phenyl-substituted α-diazo-β-ketophosphonates **136$_{Ph}$** in the presence of alkynes lead in an intermolecular tandem addition-cyclization reaction to a range of variously substituted dimethyl 1-hydroxy-naphthylphosphonates **142**, including biaryl-type- and bis-aryl-substituted derivatives. Experiments without light and with light in the presence and absence of a "triplet quencher" gave rise to suggest a SET mechanism with radical ring-closure of **137**, mediated by the strongly reducing light-activated Hantzsch ester (HE*) and electron uptake after cyclization (Scheme 38b).

2.11. PH-functional and P-tertiary o–hydroxyarylphosphanes by reduction of P(III)- or P(V)-precursors

The first PH-functional *o*-phosphanylphenol **1$_{H2}$** was initially prepared in low yield (20%) by $LiAlH_4$ reduction of a mixture of mono-, di- and trisubstituted products, formed by unselective conversion of 2-LiC_6H_4OLi (**26$_{OLi}$**) with chlorophosphites or $P(OEt)_3$.[20a] Selective coupling of **26$_{OLi}$** with $ClP(NMe_2)_2$ to **29** (R^1 = NMe_2), methanolysis and reduction of the resulting *o*-hydroxyphenyl phosphonites with $LiAlH_4$ delivered good yields of **1$_{H2}$**.[20b] Few 4-methyl-, 4-methoxy- and 4,6-*t*Bu-substituted primary and secondary *o*-hydroxyphenylphosphanes were obtained analogously (Scheme 39a).[77,79]

Much more convenient for the synthesis of primary *o*-hydroxyarylphosphanes is the reduction of the air and moisture stable *o*-hydroxyarylphosphonates by $LiAlH_4$.[21,130] In combination with suitable routes to the precursors this method allows the preparation of a range of primary *o*-hydroxyarylphosphanes including the 3-phosphanylnaphth-2-ol **1$_{naphH2}$** and the bis(*o*-OH/PH_2)-substituted benzene, naphthalene and biphenyl compounds **4$_{H2}$**, **143** and **144** (Scheme 39b), used for the access to a



Scheme 39. a,b. PH-functional *o*-hydroxyarylphosphanes by reduction of *a*) P(III)-precursors and *b*) *o*-hydroxyarylphosphonates.

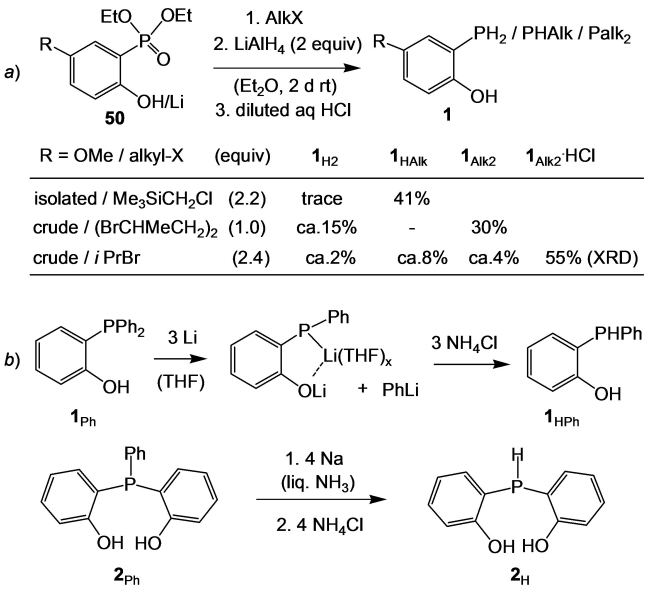
multitude of annulated 1,3-oxaphospholes and a detailed study of their luminescent and electronic properties.[3,24,147,239a–d]

Attempts to obtain 1-phosphanyl- or 1-phenylphosphanyl-naphth-2-ol by the aforementioned route resulted in complete P–C(naphthyl) bond fission and formation of PH_3 or $PhPH_2$ and 2-naphthol.[4] Partial P–C bond cleavage was also observed by acid catalyzed deprotection of a MOM-protected primary phosphanylphenol[77] and acidic workup or distillation of primary *o*-hydroxyphenylphosphanes with *t*Bu groups in 4,6-[79] or 3,5-position.[3] For the latter several experiments and quantum chemical calculations have been performed to explain the formation of $tBu_2C_6H_3OH$ and PH_3 and find reasons by the small H–P-H angles, high *s*-character of the P-lone electron pair, preferred conformations (see also[240]) or the energy of SOMO or frontier orbitals, but the situation seems to be rather complex.[3] The detection of 1,2,3-benzoxadiphospholes during similar acid-mediated partial decompositions of 2-HO-4,6-$tBu_2C_6H_2PHR$ (R=H,Ph) may formally be explained by extrusion of "PhP", insertion of 2 PhP or PhP=PPh into the P–H bond of an undecomposed molecule and ring closure with elimination of $PhPH_2$.[79] The real mechanism is not clear, but the transfer of "PhP" from one to another molecule suggests, that the decomposition involves intermolecular interactions between the sterically hindered PH-functional *o*-phosphanylphenols.

Reduction of crude 2-LiO-5-$MeC_6H_3P(O)(OEt)_2$, prepared via Li/Br exchange of the *o*-bromo-precursor with *n*BuLi without removal of the resulting *n*BuBr, led to isolation of the P-secondary *o*-HO-4-MeC_6H_3PHBu (30%) besides *o*-HO-4-$MeC_6H_3PH_2$ and inspired few tests of the reduction of *o*-hydroxyphenyl phosphonates **50** with $LiAlH_4$ in the presence of alkyl halides. The results show that this protocol can be applied for suitable alkylhalides to prepare secondary or tertiary *o*-hydroxyphenylalkylphosphanes $\mathbf{1}_{HAlk}$ and/or $\mathbf{1}_{Alk2}$ as the main product[130] (Scheme 40a) without separate metalation/alkylation steps.[77]

Another route to PH-functional *o*-hydroxyphenylphosphanes consists in the reductive cleavage of a phenyl group from *o*-diphenylphosphanylphenol ($\mathbf{1}_{Ph}$) with lithium in THF or from tertiary phenyl-bis(*o*-phosphanylphenol) ($\mathbf{2}_{Ph}$) with sodium (4 equiv) in liquid ammonia. After neutralization of PhM^{I} and the phenolate group with NH_4Cl *o*-HOC_6H_4PHPh ($\mathbf{1}_{HPh}$) and (*o*-$HOC_6H_4)_2PH$ ($\mathbf{2}_{PH}$) were isolated in each 90% yield. The reaction of *o*-$HOC_6H_4PPh_2$ with sodium in liquid NH_3 followed by NH_4Cl led to much lower yield (43%) of $\mathbf{1}_{HPh}$. The reason is competing Birch (over)reduction of the phenyl to a dihydrophenyl group (50%) (Scheme 40b).[241]

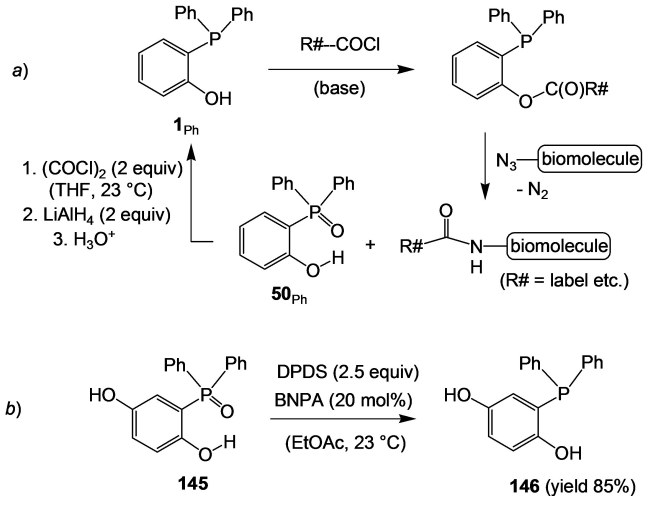
An early report by Horner and coworkers[242] showed that the reduction of phosphine oxides with $LiAlH_4$ or sodium requires harsh conditions. This is valid also for various strategies developed since then for stereoselective reduction of asymmetric phosphine oxides with retention or inversion of configuration, mainly with use of silanes, presence of borane or borohydrides or with $LiAlH_4$ after conversion of the P-oxides by oxalyl chloride to chlorophosphonium salts,[152] recently also reduction with Hantzsch ester in the presence of trimethylamine.[243] Examples for the reduction of *o*-hydroxyarylphosphine oxides are still rare with first reports only few years ago.



Scheme 40. a,b. Examples of *a*) tandem reduction-alkylation of 2-hydroxyphenyl phosphonates **50** with $LiAlH_4$/alkyl halides to *P*-mono- and/or *P*-dialkylated *o*-phosphanylphenols $\mathbf{1}_{HAlk}/\mathbf{1}_{Alk2}$ or PH-phosphonium salts thereof ($\mathbf{1}_{Alk2}$·HCl with P^{+}-H…O hydrogen bonds) and *b*) of reductive cleavage of a *P*-phenyl group from *o*-hydroxy-substituted triphenylphosphanes.

A procedure, based on the chlorophosphonium/$LiAlH_4$ strategy of Gilheany and coworkers,[244] allows the recovery of $\mathbf{1}_{Ph}$ from its P-oxide $\mathbf{50}_{Ph}$, produced in traceless Staudinger couplings between O-acylated derivatives of $\mathbf{1}_{Ph}$ with azide-substituted diagnostic or biomolecules (Scheme 41a).[19,30] The reduction proceeds via replacing the oxygen at P(O) by Cl-atoms and possible esterification of the *o*-OH group by oxalyl chloride followed by reduction with $LiAlH_4$ (2 equiv).[30]

Other examples are 4-methoxy-1-hydroxynaphth-2-yl-phosphine oxides and analogous phenylphosphine oxides, reduced in the classic way by $HSiCl_3/Et_3N$ in boiling toluene and



Scheme 41. a,b. Examples for reduction of hydroxy-substituted triphenylphosphine oxides $\mathbf{50}_{Ph}$ and **145** to the corresponding phosphanes $\mathbf{1}_{Ph}$ and **146**.

workup with diluted aqueous NaOH (cf. Scheme 33c),[31] and the reduction of (*R*)-BINOL-3,3′-$(P(O)Ph_2)_2$[164b] with $HSiCl_3$/$PhNMe_2$ (10/40 equiv) in refluxing toluene to (*R*)-BINOL-3,3′-$(PPh_2)_2$.[164b] A recent improvement is the use of 1,3-diphenyldisiloxane (DPDS), which selectively reduces tertiary as well as secondary phosphine oxides with retention of configuration, even in the presence of various functional groups including hydroxy groups. This was exemplified by the high-yield reduction (85%) of 2-diphenylphosphinoyl-hydroquinone **145** to the corresponding phosphane **146** by DPDS (2.5 equiv) in the presence of BNPA (bis-(*p*-nitrophenyl)-phosphoric acid) in ethyl acetate. The acidic additive BNPA (20 mol%) accelerates the reduction to an extent, that it can be carried out at room temperature (Scheme 41b).[32]

Conclusions and Outlook

Several strategies for the synthesis of *o*-hydroxyarylphosphanes have been developed within the ca. fifty years since the first reports on such species. This allowed access to a steadily growing number of such compounds with a large variety of different substitution pattern and steric and electronic properties, covering a wide range of properties and offering chances for tuning and optimizing of these three-valent phosphorus compounds for a multitude of applications. Recent developments of very bulky ligands for transition metal copolymerization catalysts, chiral organocatalysts, procedures to materials with interesting physical properties etc. underline the potential of these compounds for further developments. The author hopes that this review on various strategies to the title compounds, including also remarks on limits and advantages as well as hints on methods not yet reported for *o*-OH-substituted arylphosphanes are helpful in the selection of suitable known or development of new routes for further ligand optimization and progress in the application of *o*-hydroxyarylphosphanes.

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Conflict of Interests

The author declares no conflict of interest.

Data Availability Statement

Old XRD data of $[Ni_4(o\text{-}Cy_2C_6H_4O)_6]^{2+}$ $2SbF_6^-\cdot CDCl_3$ (F048), belonging to and supplementing the information to compound **3b** in ref.[29] have been refined for structure proof and deposition (C. Schulzke). Deposition number CCDC 2289358 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access structures Service. Scans of ^{31}P, ^{13}C and ^{1}H NMR spectra of compound **93** (data see Ref. [187]) can be obtained from the author.

Keywords: catalyses · phosphanes · P,O ligands · synthetic methods · P,O heterocycles

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