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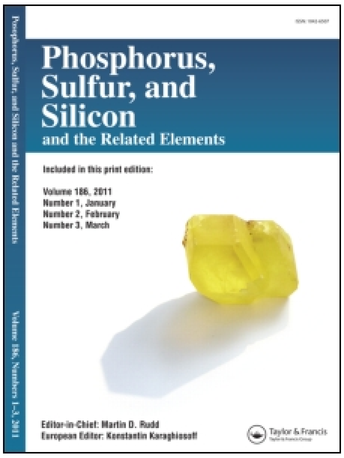

Phosphorus, Sulfur, and Silicon and the Related Elements

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2-Hydroxy- and 2-Amino-Functional Arylphosphines—Syntheses, Reactivity, and Use in Catalysis

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We present the synthesis, resolution, structures and catalytic activity of selected representatives of 2-(1S)-camphanoyloxy-phenyl- and biphenylphosphines and the access to novel asymmetric P,N-heterocyclic ethylenebis(phosphine) ligands.

Keywords Chiral phosphines; hybrid ligands; phosphino amino acids; catalysis

The chemistry of chiral phosphines began with the pioneering work of Horner and coworkers, who in the early 1960s synthesized optically active methylpropylphenylphosphine by reductive cleavage of the resolved asymmetric benzylphosphonium salt[1] and recognized its configurational stability.[2] Furthermore, Horner et al. studied the use of (+)-(*S*)-methylphenylpropylphosphine in asymmetric synthesis[3] and in rhodium-catalyzed homogeneous asymmetric hydrogenations of styrenes.[4] The potential of resolved methylpropylphenylphosphine for catalytic applications was rapidly realized by other groups. Knowles et al.[5] published their first paper on Rh-catalyzed asymmetric hydrogenation in 1968—a few months earlier than Horner. However, the breakthrough to highly enantioselective hydrogenation of α-phenylacrylic acid and, later, α-amino acid precursors, was the innovative use of the

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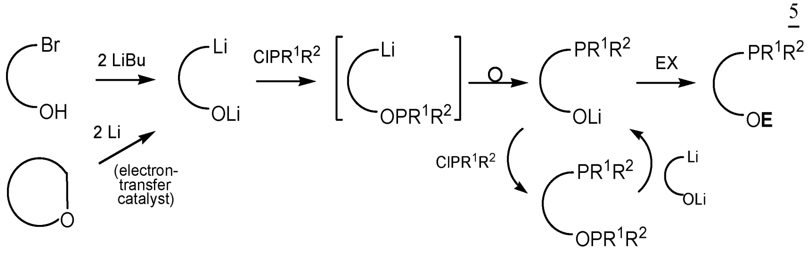
o-anisyl group as a P-substituent by Knowles et al. PAMP and CAMP provided 58 and 88% ee, whereas the corresponding dimer diPAMP gave as much as 95% ee in the asymmetric hydrogenation.[5] With the discovery by Kagan (DIOP),[6] and later by many other groups including Noyori et al.,[7] that chirality at phosphorus is not necessary and a chiral carbon backbone or axial chirality is sufficient to induce high asymmetry in catalysis, the interest turned to these new types of phosphine ligands.[8] However, alkoxy or amino groups in *ortho*- or β-position often remain important in terms of their directing effects or hemilabile coordination.[9]

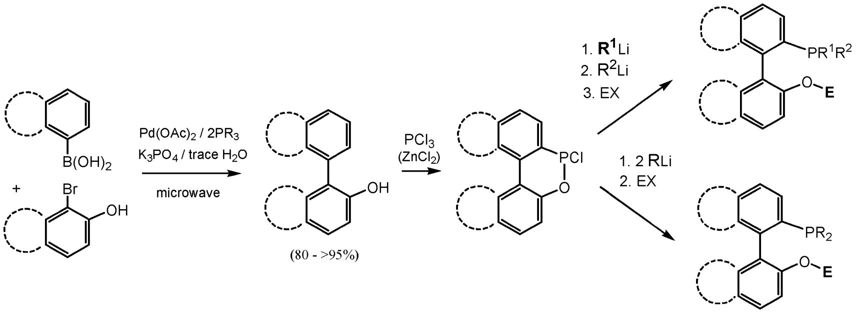
The research interest of the authors (Greifswald group) was directed to 2-hydroxy- and 2-amino-functional phosphines as building blocks for heterocycles and later as ligands for coordination compounds or catalysts, in part including *P*-asymmetric derivatives. 2-Hydroxyarylphosphines were first synthesized from 2-alkoxyarylphosphines by ether cleavage and used to synthesize R_2P,O-chelate complexes.[10] Primary 2-phosphinophenols required by us for the investigation of P=C—O heterocycles[11] were not available by ether cleavage because of extensive concomitant P—C fission.[12] Therefore, more generally applicable strategies were developed. The first was the replacement of C,O-dilithium reagents by R^1R^2PCl derivatives[13] (Scheme 1) and the second the ortho-metalation of 2-bromophenyl-OPR^1R^2 derivatives with sodium, which is followed by an anionic 1,3-O,C phosphine shift.[14] R^1 and R^2 indicate organic or $NAlk_2$ substituents. The latter allows the generation of P—H bonds (alcoholysis, $LiAlH_4$ reduction).



SCHEME 1 Synthesis of *o*-hydroxyaryl- and –biarylphosphines.

In general, the first procedure is applicable for diphenyl- and non-bulky alkylphenylphosphino groups and also provides access to 1-phosphino-2-naphthols[15] and 2-hydroxy-2'-phosphino-biaryls.[16] However, the mechanism is less simple than it looks at first sight, and negative effects are associated with bulky groups—either at the dilithium or chlorophosphine reagent. The behavior can probably be explained by primary reaction of OLi, subsequent rapid intramolecular 1,3-O→C phosphine shift, repeated OLi-substitution unless strongly hindered, and reaction of residual C,OLi_2 with the C,O-diphosphinylated species if not sterically hindered. Further complications arose with $t$$Bu_2PCl$ by metal-halogen exchange leading to ($t$$Bu_2P)_2$, and with some dialkylchlorophosphines, probably by C,OLi_2-induced HCl elimination. The second above-mentioned procedure is sensitive to competing reduction at the P—O bond (by sodium) if sterically unhindered, but useful for bulky P- and 6-tBu-substituted compounds and thus supplementary to the first method. A novel one-pot procedure, reductive alkylation of 2-lithiumoxyphenyl-phosphonates (from arylphosphates and LDA[17]) by $LiAlH_4$ in the presence of an alkyl halide, provides secondary 2-alkyl- and/or tertiary 2-dialkylphosphinophenols, dependent on relative rates of reduction and alkylation of 2-LiO-arene-PH_{2-n}/M^I_n intermediates (M^I = Li, Al).[18]

Separation of *P*-asymmetric 2-phosphinophenols was achieved by esterification of an isopropylphenyl derivative with (–)-(1*S*)-camphanoyl chloride. One diastereoisomer ((+)-R_P-CPIP) crystallized much more rapidly from diethyl ether than the other[13] and was later characterized by X-ray crystal structure analysis (Figure 1). We recently applied this method to the separation of 2-hydroxy-biarylphosphines, prepared by reaction of anellated 2-chloro-dihydro-1,2-oxaphosphorines with RLi (Scheme 2)[19,20] to circumvent the C,O-Li_2 strategy and its inherent problems.



SCHEME 2 Synthesis of P,O-biaryls (bold R^1= bulky substituent: tBu, Mes; R^2= Me, pTol; R = Ph, o-Ani; E = H, $SiMe_3$, (1*S*)-camphanoyl).[20]

The intended double substitution by two equivalents of tBuLi, as claimed in a patent,[19a] was not achieved. Similarly, MesLi failed to give the dimesityl derivative, whereas less bulky organolithium reagents (MeLi, PhLi, *o*-anisyl-Li) react cleanly to disubstitution products. The anellated 2-*tert*-butyl- and 2-mesityl-dihydro-1,2-oxaphosphorines react with less hindered RLi to *P*-asymmetric

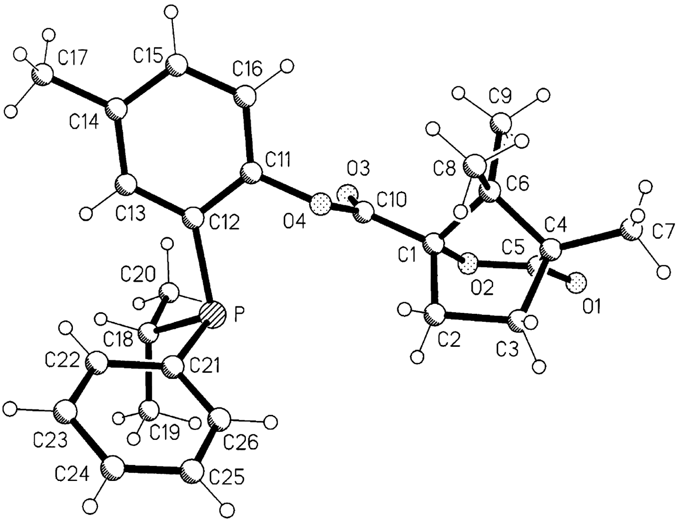


FIGURE 1 Structure of R_P-CPIP.

2-lithiumoxy-biaryl-2′-phosphines, which were converted to the 2-(1S)-camphanoyloxy biaryl-2’-phosphines via the O-trimethylsilyl derivatives (for purification by distillation). These phosphines crystallized easily, possibly because of the roughly ball-like shape of the camphanoyl groups. This may also be responsible for the easy co-crystallization of two—and in another case even four—diastereoisomers detected by crystallography in one unit cell. This disables separation by crystallization, but (1S, S_P, R_{ax})-2-camphanoyloxy-diphenyl-2′-*tert*-butylmethylphosphine (S_P, R_{ax}-CPP*t*BuMe, Figure 2), formed in excess, was obtained enantiopure after co-crystallization of other isomers.[20]

The access to *P*-asymmetric *o*-aminofunctional arylphosphines was not studied systematically, but investigations on the reactivity of P=C-N heterocycles derived from 2-phosphinoanilines led to an interesting novel path to P,N-heterocyclic ethylene-1,2-bis(phosphines). N-Alkyl 1,3-benzazaphospholes and *t*BuLi usually react to the 2-lithiobenzazaphospholes that allow coupling with electrophiles.[21] This holds also for the *N*-neopentyl derivative, as demonstrated by the synthesis of the 2-carboxylic acid (BAPCA), but under certain conditions addition is preferred. The resulting 3-*tert*-butyl-2,3-dihydro-1,3-benzazaphosphol-2-yllithium reagent adds to a second molecule of benzazaphosphole in an inverse mode, forming on hydrolysis the heterocyclic ethylenbis(phosphine) diHBAP (Scheme 3). The reaction proceeds with high diastereoselectivity. Only two doublets were observed for the two different phosphorus atoms in solution ^{31}P NMR spectra of the product.

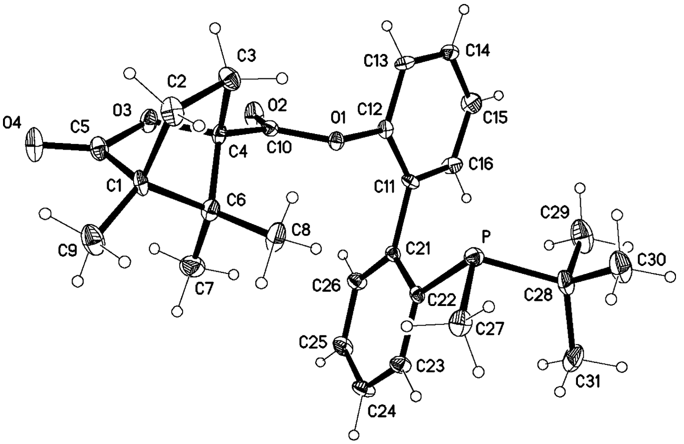


FIGURE 2 Structure of S_P, R_{ax}-CPP*t*BuMe.

The crystal structure analysis of isolated single crystals indicated each two molecules with *S*, *S*, *S*, *S*- (Figure 3) and *R*, *R*, *R*, *R*-configuration in the unit cell.

SCHEME 3 Synthesis of benzazaphospholes, BAPCA and diHBAP.

Catalytic screenings in asymmetric catalyses were performed with S_P, R_{ax}-CPP*t*BuMe. Hydrogenation of *N*-(1-phenylvinyl)acetamide in the presence of a catalyst formed from $[Rh(cod)_2]BF_4$ and two ligand molecules (M:L:substrate 1:2.1:100) (Scheme 4) provided excellent yields (97–>99%) at 30°C/6 h and 2.5–10 bar hydrogen pressure in toluene, DCM or MeOH and furnished the *S*-enantiomer with ee's of 52–59% in toluene, 42–45% in DCM and 42% in MeOH. Interestingly, the ee's did not markedly decrease at higher temperatures (50, 70°C, 59 and 54% ee) in toluene.

Tests with the isomer mixture containing mainly S_P, R_{ax}- and R_P, S_{ax}-CPP*t*BuMe displayed only 5% ee, thus indicating that the effect of the chiral camphanoyl group is low and that the higher ee's are caused by either the axial or phosphine chirality. Hydrogenation of 1-acetamidocinnamic or -acrylic acid methyl esters at 30°C /1.3 bar in the presence of this catalyst was less efficient and led to low conversion and ee's. A catalyst formed from S_P, R_{ax}-CPP*t*BuMe and $[Rh(cod)Cl]_2$ was tested in the hydrosilylation of acetophenone with diphenylsilane using a M:L:substrate:silane ratio of 1:1:200:320 (Scheme 5). Yields (78%) were similar as in the absence of the ligand (75%), but 48% ee was induced according to HPLC analysis of the 1-phenylethanol isomers on a chiral column. Finally, unresolved CPPtBu was used in Suzuki-Migaura Coupling of 2-bromophenol with aryl boranic acids.[22]

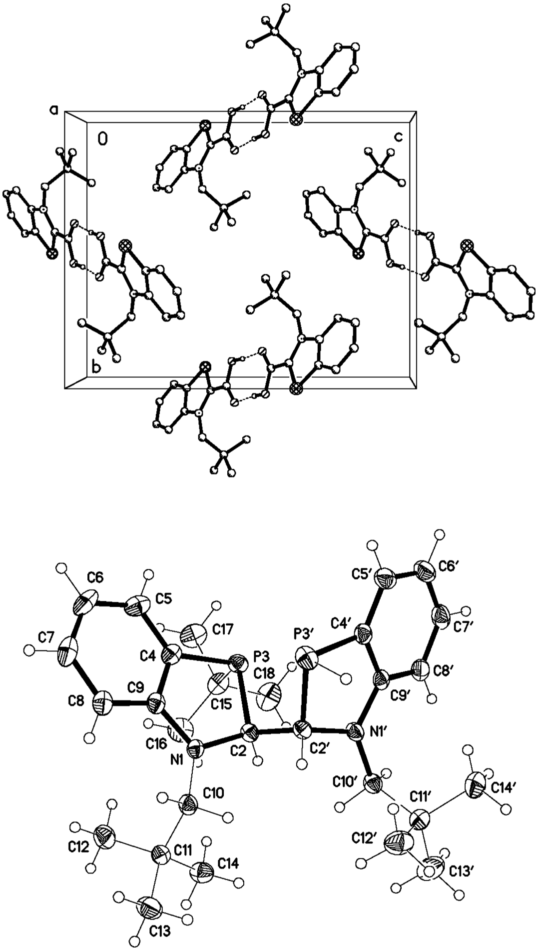
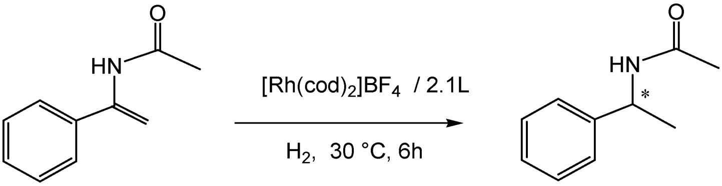
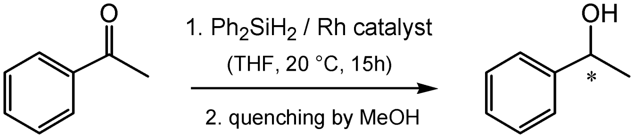


FIGURE 3 Molecular structures of BAPCA and diHBAP.

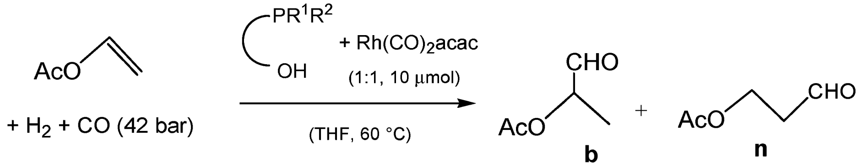


SCHEME 4 Hydrogenation of N-(1-phenylvinyl)acetamide in the presence of Rh-catalyst containing ligand *Sp*, *Rax*-CPP*t*BuMe.



SCHEME 5 Hydrosilylation of acetophenone in the presence of Rh-catalyst containing ligand *Sp, Rax*-CPP*t*BuMe.

The O-unsubstituted 2-hydroxybiphenyl-2'-phosphines are configurationally unstable by slow rotation around the C—C axis,[16] but 2-hydroxy-1,1'-binaphthyl-2'-diphenylphosphine is stable, and after separation on a chiral column it was tested in the Rh-catalyzed hydroformylation of vinylacetate ([Rh(CO)$_2$acac]:L:substrate 1:1:10) at 60°C, 42 bar (Scheme 6). The yield was 80–90% after 24 h and 96% after 70 h with high selectivity for the branched product (>98%) but low ee.[16]



SCHEME 6 Hydroformylation of vinylacetate in the presence of Rh-catalysts containing various 2-hydroxy(bi)aryl ligands.

Tests for Rh-catalyzed hydrogenation of 1-acetamido-cinnamic acid ester with 2-phosphinophenol ligands at normal pressure failed. Even under hydroformylation conditions, 50–60 bar and the presence of CO as well as H$_2$, the catalyst deactivation was not overcome. Only steric bulk by *tert*-butyl groups or a naphth-1-yl backbone enabled low activity. Since 2-phosphinophenol ethers provide active catalysts, catalyst deactivation is probably caused by formation of stable P,O$^-$-chelate complexes. Therefore, no further attempts were made to separate *P*-asymmetric 2-phosphinophenols, and catalytic studies were focused on ethylene oligomerization by phosphinophenolate nickel P,O chelate complexes. These are structurally related to the nickel-phosphinoenolates, used in the Shell Higher Olefin Process,[23] but they allow wider variation by substitution, and the ligands are more stable. Indeed, all 2-phosphinophenols including *P*-secondary and even O-basic (by 4-MeO groups or 4,6-tBu$_2$ groups) primary derivatives formed active polymerization catalysts with high selectivity for linear α-olefins and high tolerance towards water. Catalysts based on 2-dicyclohexylphosphinophenolate give rise to higher chain lengths, and in the presence of α-olefins to random-copolymers, but the highest molecular weights (M_w) in bimodal distribution were observed with 4-methoxy-substituted secondary phosphinophenol ligands. Phosphine additives allow shifting of the selectivity to lower oligomers. Furthermore, oligomers are formed if carboxylic acid esters of 2-phosphinophenols are used as ligands, whereas 2-phosphinophenol ethers do not form catalysts with Ni(cod)$_2$. Syntheses and studies of several single-component catalysts gave evidence that the active catalysts contain P,O-Ni chelate complexes. Deactivation occurs by formation of colloidal nickel or nickel-bis(P,O-chelate) complexes, but the detection of a Ni$_3$-P,O cluster complex hints at possible alternative deactivation routes.[24] Catalytic studies on amino-functional arylphosphines are planned for future work.

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