Architecture and synthesis of P,N-heterocyclic phosphine ligands
Wisdom A. Munzeiwa¹, Bernard Omondi*² and Vincent O. Nyamori¹

Abstract
Diverse P,N-phosphine ligands reported to date have performed exceptionally well as auxiliary ligands in organometallic catalysis. Phosphines bearing 2-pyridyl moieties prominently feature in literature as compared to phosphines with five-membered N-heterocycles. This discussion seeks to paint a broad picture and consolidate different synthetic protocols and techniques for N-heterocyclic phosphine motifs. The introduction provides an account of P,N-phosphine ligands, and their structural and coordination benefits from combining heteroatoms with different basicity in one ligand. The body discusses the synthetic protocols which focus on P–C, P–N-bond formation, substrate and nucleophile types and different N-heterocycle construction strategies. Selected references are given in relation to the applications of the ligands.

Introduction
Phosphines constitute a large percentage of ligands in organometallic chemistry and over the years, they have received enormous attention. The main interest towards this class of compounds is attributed to aspects such as, the good electron-donating ability of the phosphorous atom, and the ease of optimizing steric and electronic properties. Additionally, properties like chirality can be conferred to the backbone of the ligands to generate C-stereogenic [1] and P-chirogenic [2] compounds. Furthermore, the 31P-nucleus abundance allows the use of NMR for reaction monitoring and in situ speciation. In addition, phosphine ligands have found various applications as auxiliary ligands in organometallic transition-metal complexes. A great number have exhibited potential application in organic light-emitting devices (OLEDs) [3], medicine [4–6] and catalysis [1,7,8] among other fields (Table 1). There is a number of review articles in the literature [9–11] which explore deeper into the applications of P,N-phosphine ligands. Besides, the inclusion of other heteroatoms in the phosphine ligand skeleton opens up many possibilities for metal coordination [12]. Thus, their use in catalysis is the basis of this review article with the main focus on the synthesis of N-heterocyclic phosphines.
Table 1: Selected works on the applications of P,N-phosphine ligands.

| Type of ligand   | Application                          | References |
|-----------------|--------------------------------------|------------|
| pyridyl phosphines | OLEDs                               | [13]       |
|                  | Heck coupling                        | [14]       |
|                  | metal organic frameworks             | [15]       |
|                  | polymerization of lactides           | [16]       |
|                  | alkene hydroxylation                 | [17]       |
|                  | addition reaction                    | [18]       |
|                  | ethylene                             | [19]       |
|                  | oligomerization                      |            |
|                  | synthesis of pyrazolines             | [20]       |
| triazolyl phosphines | Suzuki cross coupling               | [21]       |
|                  | asymmetric hydrogenation             | [22]       |
|                  | luminescence                         | [23]       |
|                  | hydroformylation                     | [24]       |
| pyrazolyl phosphines | coordination polymers               | [25]       |
|                  | Heck coupling                        | [26]       |
| imidazolyl phosphines | Suzuki coupling                     | [27]       |
|                  | hydroamination                       | [28]       |
|                  | OLEDs                               | [29]       |
|                  | ethylene                             | [30]       |
|                  | oligomerization                      | [31]       |
|                  | amination                            | [32]       |
|                  | olefin metathesis                    | [33]       |
| pyrrolyl phosphines | hydroformylation                     | [34,35]    |
|                  | ethylene                             | [36]       |
| oxazolyl phosphines | asymmetric cycloaddition             | [37]       |
|                  | asymmetric hydrogenation             | [38]       |
|                  | carbonylation of alkynes             | [39]       |
|                  | allylic substitution                  | [40]       |
|                  | asymmetric addition                  | [41]       |
|                  | allylic amination                     | [42,43]    |

The presence of soft donor atoms such as phosphorus results in the formation of hemilabile ligands. These are multidentate ligands having hard P-donor and soft N- and/or O-donor atoms [44]. During catalysis the weakly coordinating hard donor atom detaches to give way for the incoming substrate to coordinate to the metal center [45]. This behavior also aids in ligands being able to stabilize low-valent metal states and promote oxidative addition reactions [45,46]. The complimentary effect of P and N can help stabilizing different catalytic species that are produced during catalytic transformations [11,47].

P,N-phosphine ligands can effect regioselective control, due to the trans-effect as exhibited in π-allyl metal complexes, where substitution occurs selectively on the end opposite to the phosphorus donor atom [48]. This is because the position trans to the heteroatom, with greater π-acceptor character, is more electrophilic than the one opposite the σ-donor atom [9]. One can modify this electronic imbalance by attaching vicinal heteroatoms. The π-acceptor character of phosphorus can be reinforced by the presence of oxygen and/or nitrogen whilst σ-donating potency of nitrogen can be manipulated by switching between sp³ and sp² hybridization [9,49,50].

The synthesis of phosphines is quite delicate because when exposed to air, some of them are easily oxidized, hence the reactions are often conducted under inert conditions. Alternatively, the phosphine can be protected as a borane adduct and thereafter, the protecting group is ultimately removed to liberate the free ligand. This method has been developed by Imamoto et al. [51,52] were the phosphine boranes were prepared by reacting phosphines with sodium borohydride. Alternatively, the reduction of phosphine oxide byproducts with lithium tetrahydridoaluminate, calcium aluminum hydride, and hydrosilanes can also be used to regenerate the phosphine ligands. Hydrosilane reagents usually lead to stereoselective reduction products, hence, they are used for the synthesis of chiral phosphines from chiral oxides [53]. Lithium tetrahydridoaluminate is used for the reduction of achiral phosphines because its action on optically active phosphine oxides leads mainly to the optically inactive phosphines ascribed to pseudo rotation of the pentacoordinated transition intermediates [52]. Despite this, researchers have synthesized many efficient phosphine ligands, though fast and easy synthetic methods which are principal in the development of flexible ligands are still needed.

Review

Preparation of N-heterocyclic phosphines via P–C bond formation

Nucleophilic substitution of halogens

There are different methods that have been reported for the construction of the P–C bonds. Two approaches are possible using halogenated precursors. The first one is the organometal-halogen-phosphine route where the metalated organohalogen compound is reacted with the halogen phosphine. Alternatively, the metal phosphide can be reacted with an organohalogen compound leading to the desired product. The most commonly used trans-metalation reagents are Grignard [54] or organolithium reagents [55] and other suitable bases. The metalation reaction is prone to side reactions when carried out at higher tempera-
tures and as such, the reaction must be carried out below 0 °C. For example, pyridyllithium derivatives as intermediates can be subjected to deprotonation, substrate addition and pyridine formation due to lithium halogen elimination, halide migration, and ring-opening reactions [56,57]. Butylphosphines are also formed alongside the main product, and in most cases pure phosphine pyridines are obtained using column chromatography followed by extractions adding to the number of synthesis steps.

This method has proven handy in the synthesis of phosphine pyridyl-type ligands. Jasen et al. [58] reported on the synthesis of picoline analogs by reacting the organohalide 1 with a lithium phosphide generated from chlorodiphenylphosphine (2) (Scheme 1). The resulting phosphine ligands 3 were obtained in relatively good yields. Notably, a low isolated yield was reported when starting from 2-(4-chlorobutyl)pyridine (n = 4) and this was attributed to the competing cyclization reaction affording cyclic pyridinium salts. The prominent 2-(diphenylphosphine)pyridine (4) has proved to be an interesting building block for the assembly of homo and hetero-organometallic complexes. The 3- and 4-pyridylphosphine derivatives 5 have also been successfully used as templates for assembling supramolecular structures and coordination polymers [54,59]. Halogenated ring-fused pyridine reagents can also be used to generate bipyridyl- (6), quinolinyl- (7), phenanthrolinyl- (8) and terpyridinyl- (9) phosphate ligands (Figure 1) [60].

Trofimov et al. [61,62] reported on an alternative reaction pathway using microwave heating for the synthesis of tris(2-pyridyl)phosphine in which white and red phosphorus were used. On treating the red phosphorus with 2-bromopyridine in potassium hydroxide/dimethyl sulfoxide emulsion, pyridylphosphine was obtained in moderate yields. Traces of phosphine oxide were present as evidenced by the observation of two phosphorus peaks in the $^{31}$P NMR spectrum.

An optimized method via Grignard reagents has been reported by Kluver et al. [54], by which the product was isolated in excellent yield (71%). It was noted that the magnesium ions

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**Scheme 1:** Synthesis of pyridylphosphine ligands.

**Figure 1:** Pyridylphosphine ligands.
increase the water partition coefficient of these compounds since they coordinate stronger to the nitrogen atoms as compared to lithium ions. In this case, common extraction with dichloromethane was not applicable, hence solid–liquid extraction with diethylamine was used. Low yields were reported for the 3- and 4-pyridyl analogs due to the difficulty associated with their extraction compared to their 2-pyridyl counterparts [54,55].

Dai and co-workers [63] also used the Grignard route to synthesize phosphine ligands that are stable to oxidation as described in Scheme 2. The organomagnesium intermediate 11 produced from 2-(N-piperidyl)bromobenzene (10) was trapped with appropriate halo-phosphine reagents to generate derivatives 12. The 2-(N-piperidyl)phenyl-substituted phosphine (X = CH$_2$, n = 1) was obtained in relatively good yield while the 2-(N-morpholinyl)phenyl derivatives (X = O, n = 1, 2, 3) were obtained in moderate yields. The reactions were complete within 3 h despite the fact that the Grignard substrate contains an ortho-substituent. This methodology was also faster than the metal-catalyzed phosphorylation route reported by the same authors.

The use of multiply halogenated compounds opens up opportunities to synthesize multidentate ligands. Zhang et al. [64] reported on a sequential synthetic route of multichelate pyridylphosphines 15, 16 and bis(2-pyridylpheny1phosphino)methane (dpypm, 19) as shown in Scheme 3. Ligands 15 and 16 were prepared from intermediate 14, which in turn was obtained upon treating 2,6-dichloropyridine (13) with the generated lithium phosphide reagent. The phosphine ligand 15 was obtained by reacting chloropyridylphosphine 14 with PhPLi$_2$. In a similar manner, the hexadentate pyridylphosphine 16 was synthesized: Firstly, PhPH$_2$ was treated with an equivalent amount of n-BuLi to afford LiPHPh. The latter was then reacted with 14, followed by deprotonation with n-BuLi and reaction with 0.5 equiv CH$_2$Br$_2$ to afford hexadentate compound 16 in 73% yield.

The synthesis of 19 (Scheme 3B) was achieved in moderate to high yield, firstly, by reacting equimolar amounts of LiPHPh and 2-chloropyridine (17) to give (2-pyridyl)phenylphosphide 18. Secondly, compound 18 was bridged by reaction with a half molar equivalent of dibromomethane to furnish the desired ligand 19.
The nature of the halide in the precursors also influences the reaction progress. Fluorine and chlorine usually require strong bases for the metal–halogen exchange, while relatively mild bases can be used for bromo and iodo derivatives. Structurally inflexible chiral acetal ligands have been reported by Lyle et al. where the fluorine–metal exchange was achieved by treatment with potassium tert-butoxide for a relatively long period (24 h) (Scheme 4) [65]. Acid-catalyzed condensation of compound 20 with enantiomerically pure C$_2$-symmetric 1,2-tosylate analogs 21 (R = Me, iPr and Ph) in benzene produced chiral acetal 22. Subsequent palladium-catalyzed C–C coupling of the acetal with 4-fluorophenylboronic acid (FPBA) in the presence of caesium carbonate and tri-tert-butylyphosphine afforded aryl fluorides 23. Pure ligands 24 (63–72%) were obtained by phosphorylation with diphenylphosphine in the presence of potassium tert-butoxide and 18-crown-6.

The use of silyl and dialkylamine as reagents
Organosilyl, silylphosphine derivatives, along with dialkylamines can also be used as alternative substrates to halogen-based reagents. These compounds are more stable nucleophiles compared to organometallic or metal phosphides generated through metalation processes. Hayashi et al. [66] used tris(trimethylsilyl)phosphine to control the nucleophilic substitution in the preparation of P,N-(phosphino)triazine ligands (Scheme 5). It was shown that the use of other nucleophiles failed to give controlled products, i.e., when lithium phosphide was used in a 1:1 ratio a mixture of products was obtained. A reaction between one molar equivalent of cyanuric chloride (25) and tris(trimethylsilyl)phosphines formed the unstable monophosphine intermediate 26, which was isolated as amino and/or alkoxy derivatives 29–31. Selectively varying the molar ratio of the silylphosphine nucleophile and the starting reagent 25
resulted in the corresponding bis- and tris(diphenylphosphine)triazine motifs 27 and 28. A subsequent nucleophilic substitution reaction of 27 gave compounds 32 and 33.

Changing the silylated substrate can also influence the product formed. Thus, when reacting P(SiMe₃)₃ with 3 equivalents of 2-picolylic chloride (34) in DCM ligand 35 was obtained in low yield (33% based on 34). Alternatively, when 3 equivalents of 2-(trimethylsilylmethyl)pyridine (36) with an equivalent of phosphorous trichloride were reacted, compound 37 was obtained with relatively good yield of about 76% (based on PCl₃, Scheme 6) [67]. The byproduct Me₃SiCl can be easily be removed by distillation or in vacuo.

A facile substitution of dimethylamine with phosphine in the synthesis of P,N,P and P,N,N,P pyrrolylphosphine ligands 40 and 43 was reported by Kumar et al. [68] (Scheme 7). The condensation of pyrrole (38) with formaldehyde and the amine gave the bis(diaminomethyl)pyrrole 39, which on reaction with Ph₂PH gave diphosphine pyrrole ligand 40 in good yield (90%).

Following a different route, condensation of pyrrole (38) with diphenylketone gave diphenyl(dipyrrolyl)methane 41. Subsequent Mannich condensation reaction resulted in the pyrrole diamine 42. Refluxing a toluene solution of intermediate 42 and diphenylphosphine gave dipyrrolyldiphosphine ligand 43 in very good yield (92%). Generally, high temperatures are involved, and the reaction requires relatively longer times compared to the organometallic route.

**Reaction of metal phosphides with cycloalkanes**

Cyclopropane easily undergoes nucleophilic substitution reactions because of its high ring strain. Tan et al. [69] reported the...
preparation of 9-(2-(diphenylphosphine)ethyl)-4,5-diazafluorene ligand 47 which includes a cyclopropylated intermediate (45, Scheme 8). The ligand was prepared by an initial cyclopropanation of diazafluorene 44. For this, 44 was treated with a dibromomethane solution in THF in the presence of sodium hydride under reflux for four hours to obtain cyclopropyl intermediate 45. The latter was converted into compound 46 by reaction with lithium diphenylphosphide in dry THF. Finally, the desired ligand 47 was obtained after quenching the intermediate compound 46 with a saturated solution of ammonium chloride. Ligand 47 was investigated for its ability to undergo ligand transfer reactions.

Ethylene sulfide has also been used as precursor for the synthesis of phosphine ligands. Kuang et al. synthesized a thioether-functionalized pyridine-based diphosphine ligand starting from diphenylphosphine and ethylene sulfide (Scheme 9) [70]. Thus, the diphosphine ligand 51 was obtained in good yield by reacting 2,6-bis(chloromethyl)pyridine (50) with phosphine lithiothiolate 49. The latter was obtained by treatment of
diphenylphosphine (48) with n-BuLi and ethylene sulfide in tetrahydrofuran at very low temperatures.

**Metal–proton exchange from α-C–H bond activation in heterocycles**

The α-position to a heteroatom in a cyclic compound is activated because of the difference in electronegativity with carbon. This presents an opportunity to readily generate organometallic nucleophiles. Chelucci et al. [71] used this fact to synthesize the monoterpene-derived pyridylphosphine ligand 58 (Scheme 10).

The key step was a Kröhnke annulation reaction. The Kröhnke salt 52 was pre-synthesized from ethyl bromoacetate and pyridine and then reacted with (−)-pinocarvone (53) in the presence of ammonium acetate. The obtained keto intermediate 54 was then treated with triflic anhydride to afford the corresponding triflate 55. Microwave-assisted reduction of compound 55 with pyridinium chloride afforded the α-chloropyridine derivative 56, which was further catalytically dehalogenated with palladium on carbon and formic acid to generate the pyridine scaffold 57. Coupling of 57 with Ph$_2$PCl·BH$_3$ resulted in the boron-protected ligand 58, which was deprotected with Et$_3$N. Alternatively, 1,1′-bis(diphenylphosphino)ferrocene (dppf) with palladium(II) acetate was used to catalyze the reduction of 55 generating the pyridine scaffold 57. Subsequent lithiation and addition of chlorophosphine resulted in the desired ligand 58. However, the overall yield was lower than the yield obtained through the other method.

Imidazole can be regioselectively deprotonated at the more acidic C$_2$ position. The mono- and diphosphine imidazole ligands 62 and 63 were conveniently synthesized by Milde et al. (Scheme 11) [8]. The imidazole intermediates 61 were obtained by coupling iodoaniline (59) with the dialdehyde 60.

Selective metalation of the imidazole ring and subsequent treat-
ment with the phosphine gave the imidazolylphosphine ligands 62 and 63 (46–64%).

The fast and clean alkyne–azide cycloaddition reaction has been applied successfully to prepare click-phosphine ligands [72]. The presence of three nitrogen atoms within the five-membered ring results in a high activation of the α-position and the highly acidic nature of the proton makes it easy for abstraction. Sharpless et al. [73] reported on the synthesis of 1,5-disubstituted triazoles and Liu et al. [74] used this procedure to synthesize triazolylphosphine ligands with the phosphorous substituent in the α-position (Scheme 12). For this, the aryl azide 64 was reacted with bromomagnesium acetylides 65 to generate magnesium-containing triazoles 66 which, upon quenching with ammonium chloride, afforded the triazoles 67. Lithiation followed by coupling with the appropriate chlorophosphines resulted in the desired 1,5-disubstitued triazolylphosphine ligands 68. The procedure could be performed in one pot by directly quenching the metalated triazole 66 with chlorophosphate. However, a separation of the triazole before phosphorylation makes purification of the final ligand easier [74].

The direct ortho-metalation of pyridyltriazole 69 and subsequent reaction with chlorophosphines gave the isomeric ligands 71 and 72 in different ratios governed by the phosphine substituents (Scheme 13) [75]. When the R-substituent is more electron donating, the pyridine nitrogen ortho to the phosphine becomes more nucleophilic and intermediate 70 undergoes ring closure to give compound 71 with the phosphanyl substituent in the 7-position of the fused ring structure. On the contrary, when the substituent R is electron withdrawing the pyridine nitrogen furthest away from the phosphine is more nucleophilic and hence is attacked resulting in isomeric ligand 72. Thus triazolopyridines and quinolones can undergo ring-chain isomerism, which is dependent on the inductive and/or steric effects of the substituents present on the backbone [75,76].

The α-phosphorus methylene lithiation presents more prospects for the development of modified 1,3,5-triaza-7-phosphaadamantane (PTA) ligands [77,78]. A chiral center is also introduced adjacent to the coordinating phosphorous [79]. The PTA-PPh₂ ligand 76 is derived from the lithiated intermediate 75 (Scheme 14) [79]. The conversion of PTA (74) to the organo-

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**Scheme 12:** Synthesis of triazol-4-ylphosphine ligands.

**Scheme 13:** Synthesis of phosphanyltriazolopyridines and product selectivity depending on the substituents’ effects.
lithium intermediate (PTA-Li, 75) is almost quantitative with a 90% isolated yield. However, the yield of the desired ligand PTA-PPh$_2$ 76 was very low after trapping 75 with diphenylchlorophosphine [79]. The PTA motif is water soluble, thermally, air and moisture stable. The PTA building block can be synthesized by coupling tris(hydroxymethyl)phosphine (73) with formaldehyde and ammonia in ice water or with hexamethylenetetramine.

A selective metalation can be achieved by varying reaction conditions and reagents. α-Lithiation of the methylene bridge and pyrazole ring in compound 77 allows for the synthesis of tris- and bis(pyrazole)phosphines. Antiñollo et al. [80] and Otero et al. [81] (Scheme 15) demonstrated the effect of varying the temperature on the synthesis of ligands 80 and 81. Otero et al. [81] selectively obtained compound 80 when allowing the reaction mixture comprising compound 77 and 2.5 equiv n-BuLi in THF to warm to room temperature prior to reaction with chlorodiphenylphosphine at rt. On the other hand, when both steps, the lithiation and the introduction of the phosphine were performed at low temperature (−70 °C), compound 81 was obtained in 63% yield [80]. In both instances, the other isomer was present in minute quantities and could be separated by recrystallization.

Hybrid phosphine N-heterocyclic carbenes (NHCs) have proved to be versatile ligands in organometallic chemistry [82]. The synthesis of sterically crowded biaryl ligands is still a challenging task, especially under mild reaction conditions. The diphosphine complexes of imidazolylphosphines proved to be an alternative towards the coupling of sterically crowded biaryl ligands as they showed outstanding performances [8]. Phosphines with imidazole and imidazoline functional groups present some interesting features. The imidazolium functionality mimics active sites in biological molecules [83,84]. The ionic nature adds another dimension to the applicability of the catalysts in two-phase homogeneous catalysis because it allows easy recycling [85] and separation from the reaction mixture [8].

Carbon–halogen bonds are more activated than carbon–hydrogen bonds and hence the halogen is more labile and preferentially displaced. Brill et al. [86] took advantage of this fact by synthesizing a class of N-tethered phosphine imidazole ligands (Scheme 16, route A). The lithiation of the presynthesized chloromethylimidazolium iodide 82 and subsequent trapping with borane-protected di-tert-butylphosphine gave the imidazolium borane adduct 83a. The subsequent deprotection then furnished 83b in reasonable yields between 68 and 87%.
Bis(diphenylphosphine)-substituted imidazoles were also synthesized by Karthik et al. [87] starting from the diiodoimidazole derivative 84. The lithium chloride mediated magnesium/iodine exchange reaction of 84 followed by the addition of chlorodiphenylphosphine, afforded 1-methyl-4,5-bis(diphenylphosphino)imidazole (85). Finally, N-methylation gave the imidazolium salt derivative 86 in good yield (65%).

Preparation of N-heterocyclic phosphines via metal-catalyzed P–C/N bond formation

There is limited availability of certain N-containing precursors and hence they need to be synthesized through coupling of suitable pre-synthesized fragments. This, however, increases the number of synthetic steps making the procedure time consuming and unattractive for commercial use. The successful synthesis of configurationally stable diphenyl[(R-quinazolin-4-yl)(2-naphthyl)phosphines [R = 2-(2-pyridyl) and 2-(2-pyrazinyl)] (QUINAP) by Brown et al. [88] as ligands for asymmetric catalysis instigated the synthesis of structurally similar ligands. Flanagan et al. [89] modified the QUINAP ligand by attaching 2-(2-pyridyl) (R = CH) and 2-(2-pyrazinyl) (R = N) moieties on the quinazoline ring (Scheme 17) and the phosphine was introduced via metal-catalyzed phosphorylation. The ligands were synthesized in eight steps with relatively good yield. The reaction between substituted nitrile derivatives 87 and anthranilic acid (88) catalyzed by sodium methoxide...
formed quinazolinones 89. Subsequent chlorination of the quinazolinone resulted in the formation of 4-chloroquinazoline intermediates 90. The subsequent Pd-catalyzed coupling of 90 and arylboronic acid 91 gave the methoxy intermediates 92 in reasonable yields. The demethylation of the 2-(2-pyridyl) methoxy intermediate was effected with aluminum chloride [90] and in case of the pyrazinyl derivative, sodium ethanethiolate [91] was used. The generated compounds 93 were then converted into triflate derivatives 94 by treatment with triflic anhydride in the presence of N,N-dimethyl-4-aminopyridine (DMAP) as the catalyst. Finally, the desired ligands were obtained by palladium-catalyzed phosphorylation with triphenylphosphine in DMF [92]. Resolution with palladium amine complexes and subsequent crystallization resulted in the enantiomerically pure ligands 95.

$C_2$-Symmetric atropisomeric diphosphines are among a diverse family of privileged chiral ligands in asymmetric catalysis [12]. In these compounds, the $C_2$ axis of symmetry helps in increasing the selectivity of the formation of certain enantiomers by inhibiting other possible reaction pathways [93]. In particular, biarylphosphines and bidentate 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl (BINAP) with a greater π-density and sterically demanding groups, have been extensively used in catalytic reactions [94].

Wang et al. [95] reported a copper-catalyzed phosphorylation in the synthesis of an oxazolylindolylphosphine as shown in Scheme 18. The intermediate amide 97 was obtained by the reaction of $\text{l-valinol}$ with in situ-generated indolylacyl chloride. The latter compound was obtained through an oxalic acid-media
ated chlorination of carboxylic acid 96 with dimethylformamide as catalyst in dichloromethane. Next, oxazoline derivative 98 was obtained via a methanesulfonyl chloride mediated cyclization of amide 97 and reaction with methyl iodide or methoxymethyl chloride afforded the N-substituted indole derivatives 99 (R = Me, MOM). The desired phosphorylated compounds 102 were obtained via three routes: The dicyclopentadiene derivatives 102a and b were only accessible using the transmetalation route B and C from compound 100 and 101, respectively. The phenyl phosphine derivatives, using the metal-catalyzed phosphorylation route A, and lower yields (14%) were obtained compared to the transmetalation route C.

P–H Bond addition to unsaturated precursors

The addition of P–H to unsaturated organic compounds (hydrophosphination) presents an atom economical, efficient and green strategy for the preparation of phosphines. The process can be initiated thermally, chemically or by UV irradiation. Radicals can also be used in hydrophosphination reactions. For example, azobisobutyronitrile (AIBN) can initiate the addition of secondary phosphines to N-vinylpyrroles under heating or UV irradiation resulting in regio- and chemospecific adducts. Using the same approach Trofimov et al. [96] reported on the selective synthesis of tertiary diorganyl pyrrolylphosphines 105 and 106 in high yields starting from the corresponding N-vinylpyrroles 103 and 104 (Scheme 19). The N-isopropenylpyrrole precursor 104 gave the adducts with 100% regioselectivity. More recently a solvent and catalyst-free method has been reported for vinylpyridines [97].

Preparation of N-heterocyclic phosphines via P–N-bond formation

A P–N bond formation reaction is easier to be done than a P–C bond formation because the construction of the latter involves reaction conditions that are not suitable for multifunctionalized precursors. On the other hand, the installation of P–N bonds is usually done via a “one-pot synthesis” protocol. The quaternary salt byproduct that is formed when using an amine as the base can be easily separated by filtration. Bis(phosphine)amines with a P–N–P framework are more flexible to manipulate than diphosphines with a P–C–P framework [98]. The P–N–P cone angle and geometry on the phosphorus can be adjusted by changing the bulkiness of substituents around both, the N and P centers [99]. When reacting anilines and chlorophosphines under basic conditions they undergo P–N bond formation affording conventional aminophosphines [100,101]. A facile alternative method replaces the aniline with aminosilanes which produces trimethylchlorosilane as a byproduct which can be distilled off easily [102].

Bicyclic guanidine frameworks present an opportunity to form inflexible ligands that are inclined to exhibit a κ²,P,N-bonding mode in metal complexes. Dyer et al. [103] prepared cycloguanidine phosphate ligands (Scheme 20) using a one-pot procedure. First, the triazabicyclodecene 107 was metalated with n-butyllithium to give the intermediate 108 which was quenched with a chlorophosphine to produce the desired ligands 109 in excellent yields.

Besides substituents effects it has been reported that solvents may substantially influence reaction kinetics and product formation [102]. Bircik et al. [98] reported the preparation of polynodentate aminophosphine 111 through a condensation–elimination–aminolysis reaction (Scheme 21). Reactions performed in diethyl ether and toluene resulted in bisphosphine imines and the reaction rates were low for anilines and analogous compounds. However, using dichloromethane proved to be a more suitable solvent because of higher product solubility and the

Scheme 19: Synthesis of pyrrolylphosphine ligands.
Scheme 20: Synthesis of phosphine guanidinium ligands.

The substituents on the amine nitrogen affect the reaction conditions as well as the stability of the P–N bond. Wassenaar et al. [22] reported on a flexible click-phosphine ligand (120, Scheme 23) which could only be obtained by using a strong base such as n-BuLi for proton abstraction, probably due to a reduced acidity induced by the positive inductive effect of the substituents. The use of a weaker base such as triethylamine did not result in the targeted compounds and the authors attributed this to a stabilization of the NH proton by hydrogen bonds to the triazole nitrogen and methoxy oxygen atoms. The initial step in the synthesis of 120 is the enantioselective synthesis of the propargylamine 118 through the reaction of propargyl acetate 117 with the corresponding amine. This reaction is catalyzed by a copper(I) complex of 2,6-bis(4R,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine. The triazole amine 119 is obtained in situ by the reaction with the corresponding azide, which is catalyzed by the catalyst from the prior step. Finally,
lithiation of compound 119 and addition of the corresponding chlorophosphines gave the phosphine triazole ligands 120. Some ligands synthesized by the same route are included in Figure 2 (121–123).

P-stereogenic phosphine ligands are difficult to synthesize because of low configurational stability and less availability of P-stereogenic precursors. However, asymmetric synthesis can be used as strategy to introduce stereoactive P-atoms into the ligand’s backbone. The borane complexation approach is a unique stereoselective way for introducing a P-stereogenic center.

Benoit et al. [2] reported on the synthesis of 2-phenyl-1,3,2-oxazaphosphorine ligands with a P-center and backbone chirality (Scheme 24). Spiro-1,3-amino alcohol compounds 124 were synthesized according to a literature procedure [107]. For the synthesis of the mono-N-methylated amino alcohol ligands 125 and 127 was obtained. Treating the mixture with borane-dimethyl sulfide gave a mixture of diastereoisomers in a ratio of 2:5. The major isomer (+)-125 was crystallized from...
(-)-127 using an isopropanol/hexane mixture and confirmed to have R-configuration. The free ligand was obtained by deprotection of the P-center with 1,4-diazabicyclo[2.2.2]octane (DABCO) under refluxing in chloroform for two days at 50 °C.

Duplicating the same protocol with free amine spiro-amino alcohol derivative 124 gave compounds 125 and 127 (R = H) in low yields. An optimized procedure was used where dichlorophenylphosphine and borane-dimethyl sulfide in tetrahydrofuran were premixed at −78 °C. The temperature was then raised to 25 °C before neutralizing with triethylamine. Finally, spiro-1,3-amino alcohol was added and an equimolar mixture of compounds 125 and 127 was obtained with good yields. The dimeric ligands 126 and 128 were obtained by coupling each mono ligand in THF by first treating with potassium butoxide with subsequent addition of dibromomethane [2].

Substrate postfunctionalization and heterocycle construction

Some heterocyclic precursors can be readily obtained via accessible synthetic protocols. The nitrogen-containing compounds can be constructed and grafted on the phosphine precursor. Some available phosphines and organic precursors contain functional groups which can also be modified.

Jiang et al. [108] attached a pyridyl moiety to a [2.2]paracyclophane phosphine support via a nucleophilic substitution reaction (Scheme 25). The nucleophile was generated by the addition of n-BuLi to enantiomerically pure [2.2]paracyclophane 129. Subsequent addition of 2-pyridinecarboxaldehyde (130) afforded the hydroxy intermediate 131 with a high diastereoselectivity bias towards the (R,R)-isomer. The racemic mixture could be separated by chromatography. Dehydroxylation of intermediate (R,R)-131 by using palladium on carbon as catalyst furnished planar chiral P,N-paracyclophane phosphine ligand 132 with a relatively low yield (42%). The [2.2]paracyclophane has proved to be an important support for planar chiral phosphine ligands. The ligands are generally rigid crystalline compounds that are stable in both high and low pH media and thermally stable up to 200 °C [109,110].

In these reactions the phosphine precursor can also be functionalized with appropriate groups for postfunctionalization. Detz et al. attached an alkyne to a phosphine which could easily be transformed to triazoles using click chemistry (Scheme 26) [111]. The click-phosphine ligands of type 136 were prepared by reacting phosphoacetylene 134 with different alkyl azides to generate the borane-protected ligand 135. The protection is necessary because it prevents the formation of iminophosphorane during the click reaction. The click-phosphine ligands 136 can be liberated in excellent yields by reacting the protected ligands 135 with DABCO [111,112]. A diverse library of ligands prepared in a similar manner can be obtained by varying the phosphine and the substituents around the skeleton. Some of
the ligands prepared include compounds 137–140 shown in Figure 3 [111,112].

Phosphines with amine functional groups can easily undergo Mannich condensation reactions. Ferrocene-based Schiff base ligands containing pyridine-\(n\)-yl ring \((n = 2, 3, 4)\) (Scheme 27) were synthesized by Hu et al. [113] through the Mannich condensation of ferrocenylphosphine amine 142 and the appropriate pyridine carboxaldehyde 143 in refluxing ethanol/magnesium sulfate solution. The targeted ferrocenylphosphine imines 144 were obtained in almost quantitative yield. The \(\alpha\)-ferrocenylethyl(dimethyl)amine 141 can be synthesized from ferrocenylethanol using phosgene and subsequent treatment with dimethylamine or, by using ferrocenyl(dimethylamino)acetone. The phosphine group is introduced by \(\alpha\)-lithiation of the ferrocenylamine followed by subsequent trapping with chlorophosphine [114,115].

Preceding the groundbreaking work by Pfaltz, many P,N ligands have been prepared for asymmetric catalysis [116]. However, the majority of them exhibited good to moderate enantioselectivity. The syntheses of chiral phosphinoxazolines was reported independently by Williams et al., Pfaltz and Helmchen, and Matt and Pfaltz [48,116,117]. Pfaltz et al. reported on

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**Figure 3:** Click-phosphine ligands.

**Scheme 27:** Ferrocenyl pyridylphosphine imine ligands.
the postfunctionalization in the synthesis of phosphinoxazoline (PHOX) ligands (Scheme 28) [48,117]. The 2-bromobenzonitrile (145) was treated with an in situ-generated phosphide reagent to obtain the 2-(diphenylphosphine)benzonitrile (146). This was then reacted with zinc chloride and aminoalkyl alcohol 147 in chlorobenzene to generate a Zn-oxazole complex 148. Finally, ligand exchange with 2,2-bipyridine generated the desired 2-(diphenylphosphine)oxazole 149.

Metallocenes have been used as ligand building blocks for many catalytic transformations. Especially, ferrocene has been used due to its high electron-donating capability and because it can be easily modified [118]. Furthermore, the ferrocenyl derivatives are reasonably stable and easily crystallize which makes purification much easier [119]. Ferrocene’s distinctive attributes, like explicit geometry and conformational adaptability, can orientate donor atoms prior to coordination making it ideal for syntheses of chiral ligands [118]. In the recent decades, Ugi’s amine has been one of the major interesting chiral ferrocenyl derivatives because the configuration at the α-ferrocenylmethyl position can be retained after nucleophilic substitution [115].

Drahonovsky et al. [120] conveniently modified ferrocene to synthesize a series of ferrocenylphosphine oxazoles as depicted in Scheme 29. The ligand can be prepared from readily available ferrocene (150). The ferrocenophane 151 was prepared via a stannylferrocenyl derivative that was reacted with the phosphide. Subsequent reaction with carbon dioxide and phenyl-lithium gives the phosphine ferrocene carboxylic acid 152 as the major reagent. Oxidation of the phosphine using hydrogen peroxide generated the phosphine oxide 153. In situ chlorination of the carboxylic acid followed by addition of the chiral amino alcohols gave the phosphoryl amido alcohols 154. Cyclization in the presence of tosyl chloride/triethylamine yielded the analogous ferrocenyl phosphoryl oxazoles 155, which were
further reduced to give the corresponding phosphine oxazole ligands 156. The ferrocenylphosphine oxazole ligand 156 is a fascinating example which contains three metal-centered chiral elements which are conferred upon coordination with a metal [121].

Conclusion
In this review, the diversity of phosphine N-heterocyclic ligands and the variety of phosphate skeletons, which includes different five- and six-membered heterocycles and different coordinating sites has been reviewed. Different synthetic methods have been included which vary for different ligand systems. Some of the procedures satisfy more or less the following benchmarks, i.e., higher isolated yields and optical purity, allow variable substitution around the skeleton to adjust electronic and steric properties, use of low-priced and easily available reagents, mild and expedient reaction conditions, and few reaction steps. The motifs can also be chiral, and this is helpful in stereoselective synthesis. The introduction of different moieties can bring about enhanced properties like fluorescence, which can present possibilities for other interesting applications not only limited to organometallic catalysis. The combination of different heterocycles to make hybrid ligands can stimulate studies on their applicability in medicinal and OLEDs among other applications. In short, this review article presents the syntheses and architectures of phosphate N-heterocyclic ligands. Despite their success and many reported P,N-phosphate ligands, there is a need to designed new compounds to increase their library and to investigate other applications. It can be foreseen, that more probing and research on better synthetic protocols, which are fast, easy and greener, are needed. This is prime in the advancement of more flexible organometallic catalyst with novel applications.

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ORCID® iDs
Bernard Omondi - https://orcid.org/0000-0002-3003-6712

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