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Chapter I

Coordination Chemistry of Tris(azolyl)phosphines

An overview is given of the chemistry of tris(azolyl)phosphines with focus on their preparation and application in coordination- and organometallic chemistry and catalysis. These systems share with the more abundant tris(pyrazolyl)borates and -methanes the ability to function as tridentate nitrogen ligands with hemilabile character, but the additional phosphine donor site grants them bifunctional potential. Applications of tris(azolyl)-phosphine complexes range from enzyme models and medicinal leads to catalysts for organic transformations and polymerization reactions, which demonstrate their versatility.

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1.1 General introduction

Tris(azolyl)phosphines consist of three azoles linked together by a central phosphorus apex. Several classes with this motive have been reported, mainly as ligands in coordination chemistry. Their topology resembles that of the tris(pyrazolyl)borates, also known as scorpionates.^[1-4] These well-known ligands can bind a metal via two or three nitrogens, depending on the nature of the metal and ligands. The tris(azolyl)phosphines can play a similar role by coordinating a metal as either N₂ or N₃ donor, but they offer additional possibilities. The presence of the P-apex serves as a convenient NMR spectroscopic handle and this central phosphorus atom may also function as an alternative or additional coordination site. Moreover, these compounds are neutral instead of anionic like the scorpionates. Our interest in tris(azolyl)phosphines was sparked when working on tris(triazolyl)phosphines^[5,6] and grew when uncovering some of the potential of tris(pyrazolyl)phosphines as ligands.^[6-8] A significant number of contributions on tris(azolyl)phosphines have appeared, although the amount of literature reports stands in sharp contrast to the plethora of studies involving scorpionates. This review is intended to create an overview of the chemistry that has been reported on tris(azolyl)phosphines that function or can function as tridentate N ligands. Therefore, the focus is on any phosphorus centered compound with three planar five-membered rings directly connected to the central phosphorus atom, each with a di-substituted nitrogen atom in a beta position relative to the apex (Figure 1.1). For each azolyl substituent, the preparation of the tris(azolyl)phosphine is covered first, followed by a short description of reported applications. Publications up to and including 2016 are reviewed.

1.2 Tris(imidazolyl)phosphines

1.2.1 Preparation of tris(imidazolyl)phosphines

Preparation of imidazolylphosphines (P(Im)₃) generally starts with the reaction of PCl₃ with a deprotonated imidazole. The three methods typically used in the literature for deprotonation are (a) reaction with an organometallic base, (b) reaction with an amine, or (c) replacement of the proton with a SiMe₃ group (Scheme 1.1).

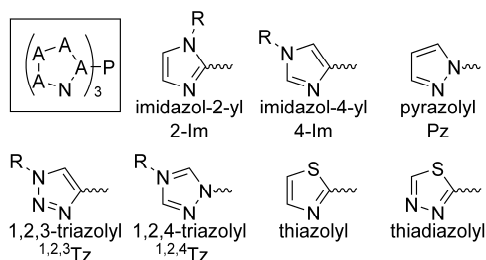
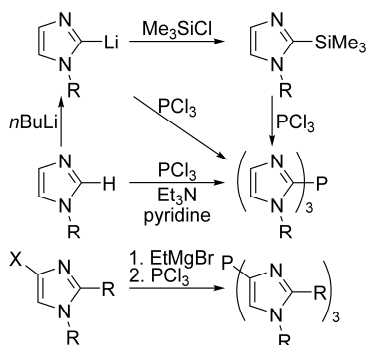


Figure 1.1. General structure of tris(azolyl)phosphine and basic structures of all azolyl substituents considered in this review, including their abbreviations.

The exchange reaction of a halo-imidazole with EtMgBr is sometimes encountered as fourth method to prepare a deprotonated imidazole (Scheme 1.1).

In the first report on imidazolylphosphines in 1980, Brown and co-workers used a dimethoxymethyl group to protect the imidazole N-1 and applied *n*BuLi as deprotonation agent.^[9] P(2-Im^{4,5-R2})₃ was obtained in moderate yields (R⁴,R⁵ = H₂: 36%; Me₂: 46%; *i*Pr₂: 55%). A crystal structure of the hemihydrate of the parent P(2-Im)₃ followed.^[10] Two years after Brown's initial study, several azolylphosphines were prepared by lithiation and subsequent silylation of the azole, followed by reaction with R_xPCl_{3-x}.^[11] This included P(2-Im^{1-Me})₃ (66%) of which a crystal structure determination was reported later.^[12] Yurchenko and co-workers have introduced the use of a pyridine/Et₃N mixture to deprotonate 1-alkylimidazoles.^[13] Subsequent reaction with PCl₃ yielded P(2-Im^{1-Me})₃ (84%) and P(2-Im^{1-Et})₃ (71%). PBr₃ was used as



Scheme 1.1. Different synthetic routes toward tris(imidazolyl)phosphines.

P precursor for tris(1-ethyl-benzimidazol-2-yl)phosphine (62%). A recent study of $^1J_{P,Se}$ coupling constants includes ample data for different imidazolylphosphines.^[14] The preparation of other $P(\text{Im})_3$ ligands will be discussed when their application is described.

1.2.2 Application as active site models of Zn enzymes: Zn and Co complexes

Following their introduction of the tris(imidazol-2-yl)phosphines,^[9] Brown and co-workers applied these compounds as ligands (Figure 1.2a) in the study of active site models for Zn containing enzymes, in particular carbonic anhydrase. First, they employed homo-imidazolyl ligands ($R^4, R^5 = \text{H}_2; \text{Me}_2; i\text{Pr}_2$) for complexation with Zn and Co^[15,16] and found the steric requirements of the ligand to be important. Coordination could only be established unambiguously for $R^4, R^5 = i\text{Pr}_2$ and its Zn complex $[\text{Zn}\{\text{P}(\text{2-Im}^{4,5-i\text{Pr}_2})_3\}](\text{ClO}_4)_2$ was the only one showing moderate catalytic activity in the hydration of CO_2 . A crystal structure of $[\text{ZnCl}\{\text{P}(\text{2-Im}^{4,5-i\text{Pr}_2})_3\}]\text{Cl}$ was reported.^[17] Brown and co-workers extended the range of ligands with $R^4, R^5 = n\text{Pr}_2$ (25%)^[18] and with mixed imidazolyl versions $\text{P}(\text{2-Im}^{4,5-i\text{Pr}_2})_2(\text{2-Im}')$ with $\text{Im}'-R^4, R^5 = \text{H}_2$ (24%) and $\text{H}_2\text{C}_2\text{H}_4\text{OH}$ (21%).^[19] These were obtained via reaction of the lithiated imidazoles with PCl_3 , using a two-step sequence for the mixed ligands. Their Co and Zn complexes were explored for catalytic activity in the dehydration of CO_3H . In a subsequent study, the rate of hydrolysis of *p*-nitrophenylpicolinate was shown to be moderately enhanced by the Co(II) and Zn(II) complexes of homo-imidazolylphosphines $\text{P}(\text{2-Im}^{4,5-R^2})_3$ with $R^4, R^5 = \text{H}_2, i\text{Pr}_2, \text{H}_2\text{C}_2\text{H}_4\text{OH}$ and those of the mixed imidazolyl ligands $\text{P}(\text{2-Im}^{4,5-i\text{Pr}_2})_2(\text{2-Im}')$ with $\text{Im}'-R^4, R^5 = \text{H}_2$ and $\text{H}_2\text{C}_2\text{H}_4\text{OH}$.^[20] The Co(II) complexes of the latter, $[\text{CoCl}\{\text{P}(\text{2-Im}^{4,5-i\text{Pr}_2})_2(\text{2-Im}')\}]\text{Cl}$, were also tested as catalysts for the hydrolysis of phosphate esters.^[21] Subsequently, Brown and co-workers found that Zn(II) can catalyze the decomposition of tris(imidazol-2-yl)phosphines.^[22] In particular, ZnCl_2 enhanced the decomposition, which was

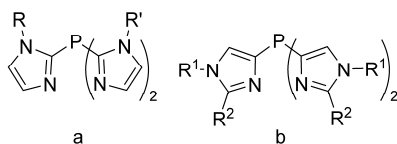


Figure 1.2. (a) Tris(imidazol-2-yl)phosphine. (b) Tris(imidazol-4-yl)phosphine.

suggested to be a reason for the observed diminishing catalytic activity in their previous studies. In contrast, Kläui et al. reported tris{2-(1-methyl-4-tolylimidazolyl)}phosphine (45%, using *n*BuLi as a base) and its $\text{Zn}(\text{NO}_3)_2$ complex as a hydrolytically stable alternative for tris(pyrazolyl)borates;^[23] no mention was made of Brown's decomposition study. It is plausible that the introduced 1-Me groups provide moderate shielding for the P-C bonds and prevent decomposition. Such a stability enhancement has been observed on introducing Me groups in the proximity of the P-apex of tris(pyrazolyl)phosphine oxides (see section 1.3.2).^[7] The group of Brown also studied the Zn(II) and Co(II) complexes $[\text{M}(\text{ClO}_4)\{\text{P}(2\text{-Im}^{4,5\text{-iPr}2})_3\}](\text{ClO}_4)$ in micellar media with the hydrolysis of *p*-nitrophenyl acetate as a catalytic model reaction, to conclude that the increased rate constant is mainly due to the increased concentration of the substrate inside the micelles.^[24]

A decade after Brown's first report on imidazolylphosphines, the group of Parkin introduced tris{2-(1-isopropyl-4-*tert*-butylimidazolyl)}phosphine as a ligand for similar applications.^[25] They reported X-ray diffraction structures of Zn complexes and concluded the monomeric Zn hydroxide complex to be an excellent model for carbonic anhydrase.^[26] A direct structural comparison of $[\text{Zn}(\text{NO}_3)\{\text{P}(2\text{-Im}^{1\text{-iPr},4\text{-tBu}})_3\}](\text{NO}_3)$ with its sterically less congested $\text{P}(2\text{-Im}^{1,4\text{-iPr}2})_3$ analogue showed that the *t*Bu substituted ligand dictates a low coordination number of the metal, separating it from many related ligands in the literature.^[27] Subsequently, tetra- ($X = \text{I}$) and pentacoordinate ($X = \text{NO}_3$) $[\text{Co}\{\text{P}(2\text{-Im}^{1\text{-iPr},4\text{-tBu}})_3\}\text{X}]\text{X}$ complexes were reported,^[28] whereas a less sterically demanding ligand resulted in octahedral $[\text{Co}(\text{ClO}_4)(\text{OH}_2)(\text{MeOH})\{\text{P}(2\text{-Im}^{1,4\text{-iPr}2})_3\}](\text{ClO}_4)$.^[29] The crystal structure of $[\text{Cd}(\text{ClO}_4)(\text{OH}_2)\{\text{P}(2\text{-Im}^{1\text{-iPr},4\text{-tBu}})_3\}](\text{ClO}_4)$ revealed the metal to be pentacoordinated, which contrasts the tetrahedral Zn analogue and may explain the significantly lower activity of carbonic anhydrase on replacing Zn for Cd.^[30] From a comparison of the crystal structures of Co, Cu, Zn, Cd, and Hg complexes, $[\text{M}(\text{NO}_3)\{\text{P}(2\text{-Im}^{1\text{-iPr},4\text{-tBu}})_3\}]^+$, it was suggested that the orientation of the nitrate ion relative to the metal is indicative for the activity of the metal in carbonic anhydrase.^[31] A computational study of four different carbonic anhydrase models included two aza-macrocycles

and a tris(benzimidazolyl)amine, together with tris(4,5-dimethyl-2-imidazolyl)-phosphine.^[32] The $P(2\text{-Im}^{4,5\text{-Me}_2})_3$ Zn(II) and Co(II) complexes were calculated to follow similar reaction profiles, with the product release being the rate determining step. Although the activation barriers for product release of all four studied ligands are close in the gas phase, they drop significantly more for both aza-macrocycles once solvation effects are considered.

The groups of Kläui and Kunz introduced tris(imidazol-4-yl)phosphine (Figure 1.2b) as an alternative ligand for Zn enzyme modeling. Because only one prototropic tautomer functions as N_3 ligand, only one apolar substituent per Im ring is required to ensure a hydrophobic pocket around the metal. The low degree of substitution enhances the solubility of the ligand and its complexes in water. The approach was first demonstrated for $[M\{P(4\text{-Im}^{2\text{-}i\text{Pr}})_3\}X]X$ with $M = \text{Ni}$ ($X = \text{NO}_3$), Co ($X = \text{Cl}, \text{NO}_3$), and Zn ($X = \text{Cl}$).^[33] The tris(2-isopropylimidazol-4-yl)phosphine ligand was prepared (35%) from 2-isopropylimidazole by N-protection with a diethoxymethyl group followed by deprotonation with *n*BuLi and reaction with PCl_3 . Also the phenyl (40%) and tert-butyl (39%) derivatives were synthesized.^[34] The UV/Vis spectra of the Co(II) complexes indicated that the differently sized substituents on the ligand influence the coordination number of the metal. After converting the P-apex to a P=O unit (95%), the oxidized ligand was shown to complex with $\text{Zn}(\text{NO}_3)_2$, $\text{Co}(\text{NO}_3)_2$, and $\text{Cu}(\text{SO}_4)$ of which the latter two showed the expected $\kappa^3\text{-N}_3$ coordination.^[35] Instead, $\kappa^2\text{-N}_2$ bonding was found for the ZnCl_2 and CoCl_2 complexes and $\kappa^2\text{-N,O}$ coordination, involving the apex P=O, for the NiCl_2 complex (Figure 1.3).^[36] The NiCl_2 complex of the non-oxidized ligand, $[\text{NiCl}\{P(4\text{-Im}^{2\text{-}i\text{Pr}})_3\}]\text{Cl}$, as well as the related Ni and Co nitrate complexes showed the common $\kappa^3\text{-N}_3$ coordination.^[37] While tris(2-isopropylimidazol-4-yl)phosphine remains bound as a tridentate ligand, the overall coordination number of these complexes is readily effected by temperature, solvent, and by N,O-bidentate ancillary ligands such as amino acids. $[\text{Co}\{2\text{-(OC(O))Py}\}\{P(4\text{-Im}^{2\text{-}i\text{Pr}})_3\}](\text{NO}_3)$, featuring an N,O bound picolinate ligand was reported.^[38] Contrasting the results of Kunz,^[37] Chavez and co-workers have shown that for $[\text{Co}\{P(2\text{-Im}^{1\text{-}Et,4\text{-}i\text{Pr}})_3\}X_2]$ the choice of counterion X can dictate the geometry also for the non-oxidized phosphine ligands.^[39] Whereas

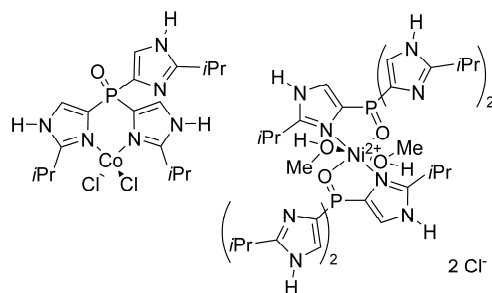


Figure 1.3. Examples of $\kappa^2\text{-N}_2$ and $\kappa^2\text{-N}_2\text{O}$ coordination complexes.

weakly coordinating OTf anions led to tridentate coordination of the ligand, more strongly coordinating Cl or Br anions gave tetrahedral complexes with bidentate coordination for the imidazolylphosphine. The geometry of these complexes was determined by X-ray crystallography and their relative stabilities were assessed with DFT calculations.

1.2.3 Application as active site models of Fe enzymes

Tris(imidazolyl)phosphines have also been applied as active site models for non-heme iron proteins. Kurtz and co-workers reported on the structural and spectroscopic properties of the (μ -oxo/hydroxy)bis(μ -carboxylato)diiron and dimanganese complexes with two capping ligands, $\text{P}(2\text{-Im})_3$ or $\text{P}(2\text{-Im}^{1\text{-Me}})_3$, the N-methyl substituted version being prepared from PCl_3 and lithiated 1-methylimidazole (40%).^[40] Figure 1.4a shows the diiron complex $[\text{Fe}_2\text{O}(\text{OAc})_2\{\text{P}(2\text{-Im}^{1\text{-Me}})_3\}_2](\text{ClO}_4)_2$, which was structurally elucidated. An isostructural complex was compared with other μ -oxo-bridged Fe dimers, where its intensive ν_s Fe-O-Fe stretch stood out, resembling Fe proteins.^[41] Complexes of both $\text{P}(2\text{-Im})_3$ and $\text{P}(2\text{-Im}^{1\text{-Me}})_3$ were included in an extensive ^1H NMR study of Fe imidazolyl compounds.^[42] 1,4-Dimethylimidazole has been used in the *n*BuLi mediated synthesis of the $\text{P}(2\text{-Im}^{1,4\text{-Me}_2})_3$ ligand from which a structurally characterized hydroxy bridged iron trimer has been generated (Figure 1.4b).^[43]

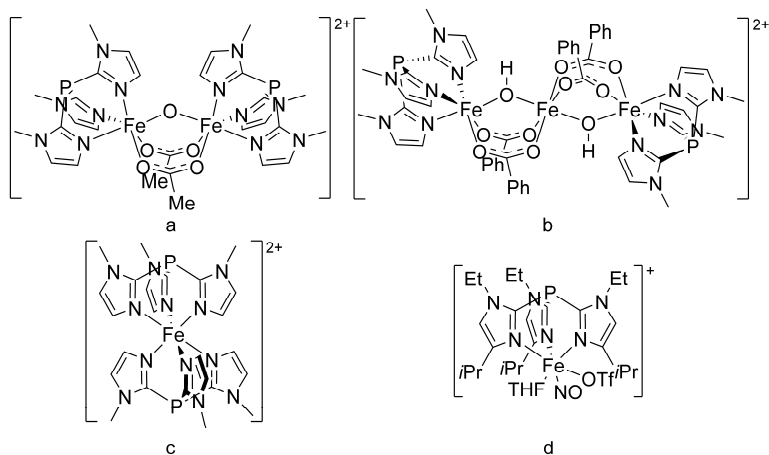


Figure 1.4. (a) Bis-iron complex. (b) Tris-iron complex. (c) Bis-ligand iron complex. (d) Mono-ligand iron complex.

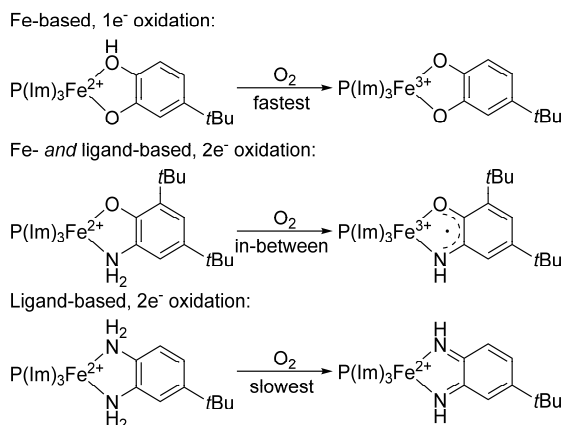
Monomeric Fe complexes have also received ample attention. The crystal structure of $[\text{Fe}\{\text{P}(2\text{-Im}^{1\text{-Me}})_3\}_2][\text{FeCl}_4]_2\text{Cl}$ (Figure 1.4c) was compared with that of the isomorphous $\text{HO}(\text{C}(2\text{-Im}^{1\text{-Me}})_3)$ complex.^[44] Reportedly, the complexes $[\text{M}\{\text{P}(2\text{-Im}^{1\text{-Et}4\text{-Me}})_3\}_2](\text{OTf})_2$ with $\text{M} = \text{Fe}$ and Mn have similar structural features and their electrochemical and magnetic properties have been studied.^[45] Mono- $\text{P}(\text{Im}^{\text{R}})_3$ Fe complexes were shown to be accessible when the alpha positions relative to the coordinated nitrogens of the ligand carry sterically more demanding groups. For instance, upon replacing the 4-Me for 4-*i*Pr groups,^[46] mono-ligand Fe(II) complex $[\text{Fe}(\text{OTf})_2\{\text{P}(2\text{-Im}^{1\text{-Et}4\text{-Me}})_3\}]$ was obtained for which the reactivity with NO was studied.^[47] Both the starting complex and the NO adduct (Figure 1.4d) were structurally characterized.

Fiedler and co-workers showed that also Ph groups in the Im-2 position, as in $\text{P}(4\text{-Im}^{2\text{-Ph}})_3$, provide sufficient steric hindrance to obtain mono-ligand complexes. This was illustrated for a series of $[\text{Fe}(\text{acac}^{\text{X}})\{\text{P}(4\text{-Im}^{2\text{-Ph}})_3\}](\text{OTf})$ complexes that were characterized by UV-Vis and NMR spectroscopy, cyclic voltammetry and DFT calculations.^[48] The complexes have been related to the enzyme acetylacetonate dioxygenase (Dke1) which features a tris-histidine Fe active center. In contrast to the enzyme, the $[\text{Fe}(\text{acac}^{\text{X}})\{\text{P}(4\text{-Im}^{2\text{-Ph}})_3\}](\text{OTf})$ complexes were stable for days on

exposure to O₂, while reacting instantaneously with NO, which indicates that reaction with O₂ should be sterically feasible.^[49] The sharp contrast between the enzyme and the model compounds in O₂ reactivity was taken to suggest that a favorable second step, supported by second-sphere effects, takes place in the enzyme. P(2-Im^{1-Me,4,5-Ph2})₃, prepared from the imidazole and PCl₃ with *n*BuLi as the base (24%), and P(4-Im^{2-Ph})₃ both have been used as suitable scaffolds for Fe enzyme modeling.^[50] The weaker ligands, like solvent molecules or carboxylates, that complete the coordination sphere in the initially formed precursor complexes are readily replaced upon addition of a β-diketonate or salicylic acid, while the P(Im)₃ remains bound to the Fe center. This contrasts other neutral N₃ ligands and demonstrates the suitability of these complexes as enzyme models. A crystallographic, spectroscopic, and computational comparison of the products of [Fe(NCMe)₃{P(2-Im^{1-Me,4,5-Ph2})₃}] (OTf)₂ and [Fe{HB(PZ^{3,5-Ph2})₃}{OC(O)Ph}] with an aminophenol showed these complexes to have different electronic structures based upon which different mechanistic pathways were suggested for extradiol catechol dioxygenases (ECDOs) and *o*-aminophenol dioxygenases.^[51] A similar comprehensive study was conducted on the reaction of the same starting complexes with 2-(1-methylbenzimidazol-2-yl)hydroquinonate to model another Fe non-heme enzyme.^[52] Related complexes with either a catechol or diaminophenylene substrate, all characterized by X-ray diffraction, have been studied for their reactivity toward O₂, showing up to a 10⁵ rate difference that contrasts with modeled enzymes, which was ascribed to a lack of control over proton transfer during the oxidation of the models (Scheme 1.2).^[53]

1.2.4 Copper complexes of tris(imidazolyl)phosphines

The study of the Cu complexes of tris(imidazolyl)phosphine has focused mainly on their reactivity toward O₂ and isolation of the oxo-products. The first reported Cu(I) complexes [Cu{P(2-Im^{1-Et,4-R})₃}]X and [Cu(NCMe){P(2-Im^{1-Et,4-*i*Pr})₃}]X (X = PF₆, ClO₄, OTf, Cl) reacted irreversibly with O₂ at ambient temperature via two intermediates to blue bis-ligand Cu(II) complexes.^[46] At low temperature, the reaction could be stopped at purple O₂-bridged Cu(I) dimers, which could be reverted to the starting complex for the 4-*i*Pr ligand derivative. [CuCl(MeOH){P(2-Im^{1-Et,4-*i*Pr})₃}]Cl has been



Scheme 1.2. Different oxidation reactions of P(2-Im)₃Fe complexes depending on the ancillary ligands.

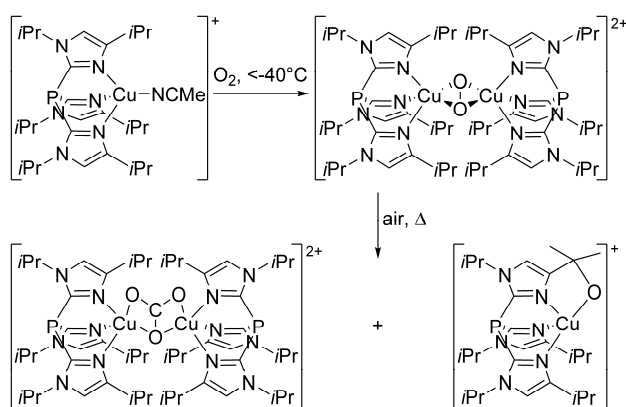
the subject of a comprehensive crystallographic, spectroscopic, and computational study.^[54]

Increasing the bulk of the ligand substituents alters the O₂ reactivity of the Cu(I) complexes. Such ligands, P(2-Im^{1-*i*Pr,4-*R*})₃ with R = *i*Pr (47%) or *t*Bu (38%), are accessible by reaction of the lithiated imidazole with PCl₃.^[25] [Cu(NCMe){P(2-Im^{1-*i*Pr,4-*t*Bu})₃}] (BF₄) appeared to be inert toward O₂, whereas the bis(*i*Pr) derivative yielded a labile dimeric peroxide complex that was unable to oxidize 1-hexene and PPh₃, but reacted with water to [(Cu{P(2-Im^{1,4-*i*Pr})₃})₂(OH)₂](BF₄)₂. This dimeric bis-hydroxide underwent intramolecular H-abstraction of one of the ligand *i*Pr groups and gave in air a structurally characterized dimeric carbonate complex (Scheme 1.3).^[55]

Severin and co-workers reported on P(Im)₃ containing polymers that, when complexed to Cu(II), act as efficient hydrolysis catalysts for phosphoesters.^[56] The monomer tris(1-vinyl-imidazol-2-yl)phosphine was obtained (29%) via the pyridine/Et₃N mediated route,^[13] and could be incorporated into a homopolymer or a co-polymer with ethyleneglycol dimethacrylate. For the latter option, [Mo(η³-allyl)(CO)₂{P(2-Im^{1-vinyl})₃}], with the Mo atom functioning as template, was also applied. The coordination geometry and the Cu(II) loading differed for the three obtained polymers and their relative activity was dependent on the substrate.

1.2.5 Gold complexes of tris(imidazolyl)phosphines

The P-apex is the primary coordination site in gold complexes of tris(imidazolyl)phosphines. The first such complex was reported in 1998 as analogue of an anti-rheumatoid arthritis drug.^[57] The P(5-Im^{1-Et,2-iPr})₃ ligand was synthesized by reacting lithiated 1-ethyl-2-isopropyl-5-bromoimidazole with PCl₃. The ethyl groups block the nitrogen atoms beta to the P-apex and thereby inhibit the ligand to act as a tridentate N donor. However, the Au complex of P(2-Im^{1-Me})₃ was shown to have additional coordination via one of its N donors to form the ligand bridged dimer [(AuC₆F₅)₂{P(2-Im^{1-Me})₃}].^[58] The same report showed that the corresponding thiazolyl based ligands coordinate only via the P apex to Au. A study on the anti-cancer behavior of several well-characterized mono-, bis-, and tris(imidazolyl)phosphine gold complexes, including [AuCl{P(2-Im^{1-Me})₃}] and [Au{P(4-Im^{2-iPr})₃}]₂Cl₂, showed some activity against selected cell lines, with mono imidazolyl [AuCl{PPh₂(2-Im^{1-Me})}] as most promising complex.^[59] The dimeric [Au{P(4-Im^{2-iPr})₃}]₂Cl₂ could be broken up with ZnCl₂ to yield heterobimetallic [AuCl{P(4-Im^{2-iPr})₃}ZnCl]Cl. The readily oxidizable tris(1-benzylimidazol-2-yl)-phosphine was obtained (66%) via deprotonation of the imidazole with *n*BuLi.^[60] Its AuCl complex reacted with NaAuCl₄ to form tetranuclear [Au₂(μ-*N,N'*-(P(2-Im^{1-CH₂Ph})₃)AuCl)₂](AuCl₂)(AuCl₄). Both Au complexes were structurally characterized and shown to display unexpected Au⋯H-C interactions with benzylic hydrogens in the solid state (Figure 1.5a).



Scheme 1.3. Reactivity of Cu(I) complex with O₂: Formation of an oxygen bridged dimer, followed by decomposition upon warming up.

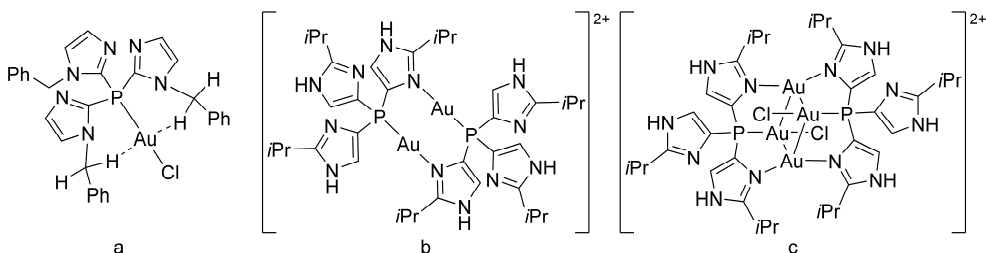


Figure 1.5. a) Gold complex featuring H-Au interactions. b) Au dimer supported by $P(\text{Im})_3$ ligands. c) Au tetramer supported by $P(\text{Im})_3$ ligands.

Besides mono- and bis-imidazolylphosphines, $P(2\text{-Im})_3$,^[13] $P(2\text{-Im}^{1\text{-Me}})_3$, and $P(4\text{-Im}^{2\text{-iPr}})_3$ were studied as potential ligands for Au(I) catalysts.^[61] The desired Au complexes were obtained from the ligands and $(\text{tht})\text{AuCl}$, but in the case of $P(4\text{-Im}^{2\text{-iPr}})_3$ also Au_2 , Au_3 , and Au_4 complexes could be obtained by varying the Au/ligand ratio (Figure 1.5b and c). All monomeric Au complexes catalyzed the reaction between phenyl acetylene, benzaldehyde, and piperidine. Under homogeneous conditions, the catalysts with the $P(2\text{-Im})_3$ ligands performed best whereas those with bis(imidazolyl) ligands gave the better performance in a biphasic mixture. Only complexes of the mono(imidazolyl) ligands were able to hydrate 1-octyne to 2-octanone. Whereas the $P(4\text{-Im})_3$ complexes proved to be stable in H_2O and MeOH , the $[\text{AuCl}\{P(2\text{-Im})_3\}]$ complexes were not. $\text{Au}(\text{NHC})_2$, imidazole and H_3PO_3 or $P(\text{OMe})_3$ were found in a decomposition akin to that observed when $P(2\text{-Im}^{4,5\text{-Me}_2})_3$ was reacted with HAuCl_4 .^[62]

1.2.6 Other applications

In 2004, Enders et al.^[63] reported on the LiCl , ScCl_3 , CuBF_4 and AgBF_4 complexes with N_3 -coordinating ligands of the type $P(2\text{-Im}^{1\text{-nBu}})_3$ and $P(2\text{-Im}^{1\text{-CH}_2\text{Ph}})_3$, which were obtained (~70%) by the method of Tolmachev,^[13] and provided molecular structures for the Li and Sc complexes (Figure 1.6a and b, respectively). Deprotonation of the parent $P(2\text{-Im})_3$ with 3 eq. of $n\text{BuLi}$ generated the tri-anion of the ligand (Figure 1.6c) that was structurally characterized as well.

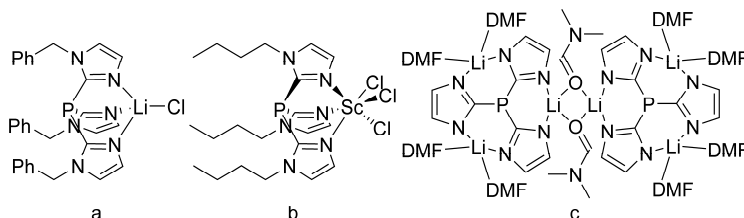


Figure 1.6. a) LiCl complex of $P(2\text{-Im}^1\text{-CH}_2\text{Ph})_3$. b) ScCl_3 complex of $P(2\text{-Im}^1\text{-}n\text{Bu})_3$. c) Dimer of trilitiated $P(2\text{-Im})_3$, supported by ten eq. of dimethylformamide.

As polymerization catalyst, complex $[\text{CrCl}_3\{P(2\text{-Im}^1\text{-}i\text{Pr},4\text{-}t\text{Bu})_3\}]$ was found to give low activity, but high selectivity, which was attributed to the steric protection of its metal center that hampers beta-hydride elimination.^[64] The ligands $P(2\text{-Im})_3$, $P(2\text{-Im}^1\text{-Me})_3$, and $P(4\text{-Im}^2\text{-}i\text{Pr})_3$, together with the oxide and sulfide of the latter, have also been complexed to $\text{Mn}(\text{CO})_3$ and $\text{Re}(\text{CO})_3$ of which the Mn complexes were evaluated as CO-releasing agents for medical applications (Figure 1.7).^[65]

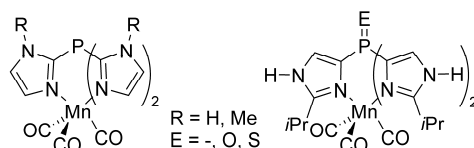
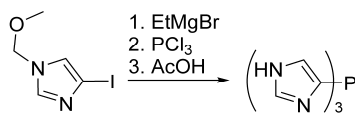


Figure 1.7. $\text{Mn}(\text{CO})_3$ complexes that were evaluated as CO-releasing agents.

In this study, Kunz et al. showed that the imidazol-2-ylphosphine complexes release nearly 2 eq. of CO under UV irradiation and the imidazol-4-yl complex half of that, which was subsequently ascribed to the steric bulk of the ligands.^[66] The ligand of the used $[\text{Mn}(\text{CO})_3\{P(4\text{-Im})_3\}]$ was generated (33%) from the reaction of the Grignard reagent of 4-iodo-1-(methoxymethyl)imidazole with PCl_3 , followed by acidic workup that also removed the N-methoxymethyl protecting group (Scheme 1.4).

Ru complexes of $P(2\text{-Im})_3$ have been explored as alkyne hydration catalysts.^[67] In the reaction with $\text{CpRuCl}(\text{PPh}_3)_2$ at 70 °C one PPh_3 ligand remained attached to the metal. Upon heating to 110 °C the final products $[\text{RuCp}\{P(2\text{-Im})_3\}]$ and $[\text{RuCp}\{P(2\text{-Im}^1\text{-Me})_3\}]$ were obtained with the $P(2\text{-Im})_3$ ligands binding as tridentate N donors (Figure 1.8a). The lack of catalytic activity in the hydration of 1-octyne was attributed



Scheme 1.4. Preparation of unsubstituted tris(imidazol-4-yl)phosphine.

to the fact that the complexes are coordinatively saturated. Kunz and co-workers also synthesized Ru(II) piano-stool ($\kappa^3\text{-N}_3$)-complexes based on $\text{P}(2\text{-Im})_3$ or $\text{P}(2\text{-Im}^{1\text{-Me}})_3$ (Figure 1.8b) as potential anti-cancer drugs, with neither showing cytotoxic activity against selected cell lines.^[68]

The well-characterized 3d-transition metal sandwich complexes $[\text{M}\{\text{P}(2\text{-Im}^{1\text{-Me}})_3\}_2](\text{ClO}_4)_2$ with $\text{M} = \text{Co}, \text{Ni}, \text{Cu}$ and Zn (Figure 1.9) have been reported as potential templates for building polymetallic species, but the steric crowding around the phosphorus atoms appeared to be prohibitive.^[69]

In their early report on the synthesis of tris(azolyl)phosphines, Moore and Whitesides described the *cis*- $[\text{PtMe}_2\{\text{P}(2\text{-Im}^{1\text{-Me}})_3\}_2]$ complex in which the imidazolyl phosphine ligands act as monodentate P donors.^[11] In 2015, the same ligand was applied in a study on in situ generated Pd-complexes of $(2\text{-Im}^{1\text{-Me}})_n\text{PPh}_{3-n}$ ($n = 1\text{-}3$) for Suzuki coupling.^[70]

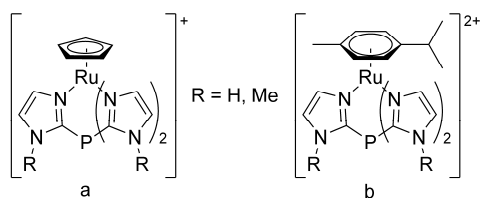


Figure 1.8. a) Ru complexes for alkyne hydration. b) Ru complexes tested as potential anti-cancer drugs.

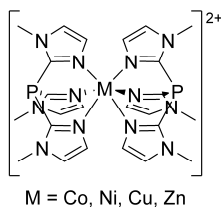


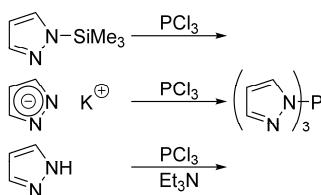
Figure 1.9. Transition metal sandwich complexes supported by $\text{P}(2\text{-Im}^{1\text{-Me}})_3$.

1.3 Tris(pyrazolyl)phosphines

1.3.1 Preparation and initial coordination complexes of tris(pyrazolyl)phosphines

In a pioneering study on azoles N-bound to phosphorus, the group of Peterson reported on the synthesis of the first tris(pyrazolyl)phosphines, $P(\text{Pz})_3$ (98%) and $P(\text{Pz}^{3,5\text{-Me}_2})_3$ (98%), by reacting PCl_3 with an excess of Pz^xSiMe_3 (Scheme 1.5);^[71] a crystal structure of $P(\text{Pz})_3$ has been reported separately.^[72] $P(\text{Pz})_3$ was also shown to result (85%) from the reaction of potassium pyrazolide with PCl_3 , but $P(\text{Pz}^{3,5\text{-Me}_2})_3$ could not be generated in this fashion. Combining POCl_3 with potassium pyrazolide gave both phosphine oxide analogues $\text{OP}(\text{Pz})_3$ (91%) and $\text{OP}(\text{Pz}^{3,5\text{-Me}_2})_3$ (65%)^[73] and using SPCl_3 provided $\text{SP}(\text{Pz})_3$ (75%), which is not accessible via PzSiMe_3 . In a study on the reaction with small molecules, $P(\text{Pz})_3$ was found to form an adduct with BF_3 , give chloride-pyrazolyl exchange with BCl_3 , and proved to be inert toward MeI and CS_2 . The transition metal complexes containing the ligand system: $[\text{Mn}(\text{CO})_3\{\text{P}(\text{Pz}^{3,5\text{-Me}_2})_3\}]\text{Cl}$, $[\text{Re}(\text{CO})_3\{\text{P}(\text{Pz})_3\}]\text{Br}$, $[\text{Re}(\text{CO})_3\{\text{P}(\text{Pz}^{3,5\text{-Me}_2})_3\}]\text{Br}$, $[\text{Mo}(\text{CO})_3\{\text{P}(\text{Pz}^{3,5\text{-Me}_2})_3\}]$, and $[\text{W}(\text{CO})_3\{\text{P}(\text{Pz}^{3,5\text{-Me}_2})_3\}]$, were all shown to have $\kappa^3\text{-N}_3$ coordination, based on analysis of IR, NMR, and mass spectra.^[74,75]

In a study on catalytic allylation, $[\text{Mo}(\text{CO})_3\{\text{OP}(\text{Pz}^{3,5\text{-Me}_2})_3\}]$ (Figure 1.10a) proved inert toward allyl halides.^[76] The phosphine oxide ligand was synthesized (59%) from $\text{Pz}^{3,5\text{-Me}_2}\text{H}$ and PCl_3 with Et_3N as a base. When the allyl functionality was introduced via allyl substituted Mo precursors, $\text{OP}(\text{Pz}^{3,5\text{-Me}_2})_3$ hydrolyzed partly to the anionic $[\text{O}_2\text{P}(\text{Pz}^{3,5\text{-Me}_2})_2]^-$ ligand (Figure 1.10b). The same result was obtained with Mo precursors carrying different allyl ligands^[77] and the same ligand decomposition was reported for the reaction with $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$.^[78,79]



Scheme 1.5. Different routes for the preparation of tris(pyrazolyl)phosphines.

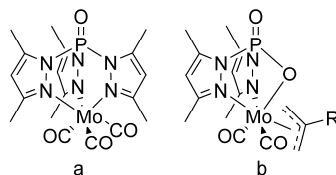


Figure 1.10. (a) Molybdenum carbonyl complexes supported by $P(Pz)_3$ and (b) partly hydrolyzed $P(Pz)_3$.

The attempted formation of lead complexes by reacting $HB(Pz^{3,5-Me_2})_3$ and $OP(Pz^{3,5-Me_2})_3$ with $Pb(NO_3)_2$ resulted in decomposition of $OP(Pz^{3,5-Me_2})_3$ to give $[Pb\{HB(Pz^{3,5-Me_2})_3\}(Pz^{3,5-Me_2}H)_2](NO_3)$ where the pyrazoles stem from the phosphine oxide ligand.^[80] More successful was the formation of Mg complexes of $P(Pz)_3$ by interaction with $MgI_2(Et_2O)_2$ in acetonitrile to generate $[Mg(NCMe)_3\{P(Pz)_3\}]I_2$ or homoleptic $[Mg\{P(Pz)_3\}_2]I_2$, depending on whether a 1 : 1 or 2 : 1 ratio of the ligand was used, respectively; X-ray structures of both compounds were provided.^[81]

1.3.2 Copper complexes of tris(pyrazolyl)phosphines

The group of Tolman explored the use of chiral derivatives of the pyrazolyl group (Figure 1.11) to obtain chiral ligands, including C_3 symmetric tris(pyrazolyl)-phosphine oxides.^[82-86] The OP centered ligands were all prepared (~60%) in refluxing benzene using stoichiometric amounts of Pz and $POCl_3$ and an excess of Et_3N as base. Camphor-pyrazole was used in this manner to generate $OP(\text{Camphpz})_3$ that was complexed to copper ($Cu(NCMe)(BF_4)$, $CuOTf$, $CuCl$).^[82,83] $[ZnCl_2\{OP(\text{Camphpz})_3\}]$ was structurally elucidated to display κ^2-N_2 coordination. Catalytic cyclopropanations using $[Cu(NCMe)\{OP(\text{Camphpz})_3\}](BF_4)$ gave products with ee's of 30 to 60%; $[Cu(NCMe)\{OP(Pz^{3-tBu})_3\}](BF_4)$ was found to be an efficient achiral catalyst for this reaction. The analogous syntheses and spectroscopic details

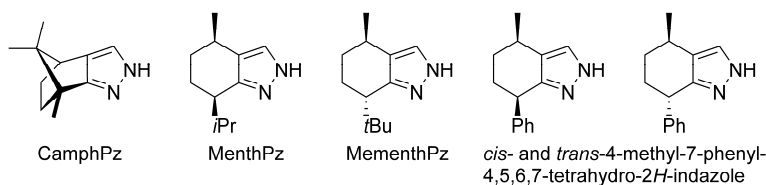


Figure 1.11. Pyrazoles used for C_3 chiral ligands.

of tris(menthyl-pyrazolyl)phosphine oxide^[84] (62%) and tris(mementhyl-pyrazolyl)phosphine oxide^[85] (60%, see Figure 1.11) were also reported. The scope of chiral tris(pyrazolyl)phosphines was further extended with methyl and phenyl substituted 4,5,6,7-tetrahydro-2H-indazoles.^[86] Catalytic cyclopropanations using in situ generated Cu(I) complexes showed as best result a disappointing ee of 36%, whereas the analogous borate centered ligand gave an ee of 85%.

Tris(pyrazolyl)phosphine sulfide with pyridyl substituted pyrazoles has been synthesized (82%) from 3-(2-pyridyl)pyrazole and SPCl_3 with Et_3N as a base,^[87] but complexation to either Cu(I) or Cu(II) proceeded with partial hydrolysis, resulting in bis(pyridyl pyrazolyl)thiophosphinate complexes, e.g. $[(\text{Cu}\{\text{O}(\text{S})\text{P}(\text{Pz}^{2-\text{Py}})_2\})_2(\text{Pz}^{2-\text{Py}})_2]$.

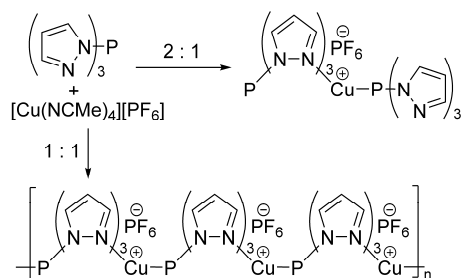
The group of Lammertsma reported a set of tris(pyrazolyl)phosphine oxides with different steric demand.^[7] All ligands were prepared by reacting PCl_3 with 3 equivalents of the corresponding pyrazole in the presence of a slight excess of base; Et_3N was used for $\text{Pz}^{3,5-\text{Me}_2}$ (90%), $\text{Pz}^{3-\text{Ph}}$ (86%) and $\text{Pz}^{3-t\text{Bu}}$ (93%), while the stronger base KO^tBu was required for $\text{Pz}^{3-\text{Ph}-5-\text{Me}}$ (30%) and $\text{Pz}^{3-t\text{Bu}-5-\text{Me}}$ (53%). The ligands with a single substituent per pyrazolyl group showed immediate decomposition upon exposure to water, but an additional Me group at the 5-position inhibited hydrolysis. Cu(I)(NCMe) complexes could be formed from all ligands and the acetonitrile in the resulting Cu complexes could be exchanged for PPh_3 or CO. The ligands were shown to have stronger electron withdrawing properties than the homologous tris(pyrazolyl)methanes. A computational analysis suggested similar Cu(I) ligating properties for tris(pyrazolyl)phosphine oxide, tris(triazolyl)phosphine oxide (section 1.4.2), and their CH centered analogues.^[6] Lammertsma and co-workers also synthesized the (non-oxidized) tris(pyrazolyl)phosphines $\text{P}(\text{Pz})_3$ (42%) and its 3,5-Me₂ (96%), 3-Ph (52%), and 3-*t*Bu (81%) substituted derivatives by reaction of the corresponding pyrazoles with PCl_3 in the presence of Et_3N as a base.^[8] Reaction of the ligands with $[\text{Cu}(\text{NCMe})_4](\text{PF}_6)$ gave $[\text{Cu}(\text{NCMe})\{\text{P}(\text{Pz}^X)_3\}](\text{PF}_6)$ complexes, except for unsubstituted $\text{P}(\text{Pz})_3$. When a 2 : 1 ratio was used, $\text{P}(\text{Pz})_3$ gave $[\text{Cu}\{\text{P}(\text{Pz})_3\}_2](\text{PF}_6)$ with one $\text{P}(\text{Pz})_3$ acting as a N₃ donor and the other coordinating via its P-apex. With a 1 : 1 ligand to Cu ratio, a one-dimensional coordination

polymer was formed in which each ligand acts as both N₃ donor to one Cu atom and as P donor to the next (Scheme 1.6). X-ray structures of both complexes were reported.

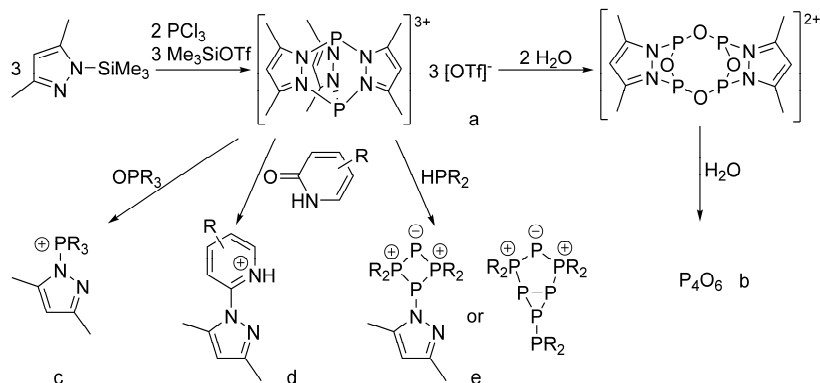
1.3.3 Application of tris(pyrazolyl)phosphines as synthon

In a comparative study, the tris(pyrazolyl) derivative P(Pz)₃ was found to be the least effective of various tris(azolyl)phosphines in forming oligoribonucleotides from their constituents,^[88] while tris(3,5-dimethylpyrazolyl)phosphite has been used effectively as a phosphorylating agent to obtain the 1,2,4-phosphite of D-xylose.^[89]

Weigand and co-workers used tris(pyrazolyl)phosphines as a building block in their phosphorus chemistry.^[90-95] They synthesized on large scale (60 g, 97%) P₂(Pz^{3,5-Me2})₃(OTf)₃ (Scheme 1.7a), which can be viewed as a P³⁺ cation supported by a N₃ coordinated tris(pyrazolyl)phosphine.^[90] This P-building block hydrolyzed to a P₄O₄ dication or a P₄O₆ neutral species depending on the amount of water added (Scheme 1.7b). It converted R₃PO into [R₃PPz^{3,5-Me2}]⁺ that could be further derivatized (Scheme 1.7c).^[91] The carbonyl oxygens in 2- and 4-pyridones and cyclic urea were also replaced by a pyrazolyl group upon exposure to the stabilized P trication, further demonstrating its use as a deoxygenation agent (Scheme 1.7d).^[92] Furthermore, P₂(Pz^{3,5-Me2})₃(OTf)₃ proved useful as a P₁-source to obtain polyphosphorus cations, giving access to different P frameworks with secondary phosphines (Cy₂PH and Ph₂PH; Scheme 1.7e).^[93]



Scheme 1.6. Formation of monomeric and polymeric Cu(I) complexes.



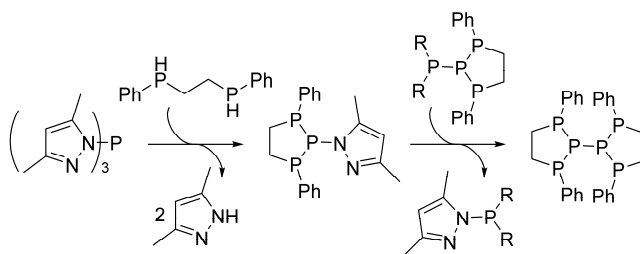
Scheme 1.7. Preparation of the trication $P_2(Pz^{3,5-Me_2})_3^{3+}$ (a) and follow-up chemistry.

$P(Pz^{3,5-Me_2})_3$ was also shown to react with Cy_2PH via protolysis and exchange of P-H for P-P bonds to form, depending on the ratio used, P_3 or P_4 frameworks that can be used as ligands for $Fe(CO)_4$.^[94] When treating $P(Pz^{3,5-Me_2})_3$ with 1,2-bis(phenylphosphanyl)ethane, protolytic P-P bond formations and P-N/P-P bond metatheses occurred to form a hexaphosphane with two linked C_2P_3 rings (Scheme 1.8) that can serve as a bridging ligand for two $Fe(CO)_4$ fragments.^[95]

1.4 Tris(1,2,3-triazoly)phosphines

1.4.1 Preparation of tris(1,2,3-triazoly)phosphines

In 2008, the group of Lammertsma reported on tris(triazoly)phosphine and its oxide and their first transition metal complexes.^[5] They synthesized $OP^{(1,2,3Tz^{1-Ph})}_3$ by means of a triple Cu catalyzed Huisgen [2+3]-cycloaddition of PhN_3 to $OP(C_2H)_3$ and

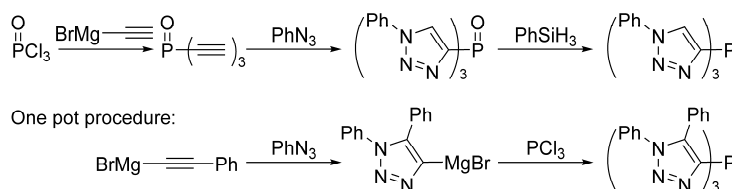


Scheme 1.8. Protolysis and P-N/P-P bond metathesis involving $P(Pz^{3,5-Me_2})_3$.

the reduced form $P(1,2,3Tz^{1-Ph})_3$ by treatment with $PhSiH_3$ (40%; Scheme 1.9). Subsequently, Bräse and co-workers reported an alternative route toward $P(1,2,3Tz)_3$, starting with the [2+3] azide cycloaddition to alkynyl Grignard reagents, followed by reaction of the formed triazolyl Grignard with PCl_3 (Scheme 1.9).^[96] This one-pot procedure has the advantage that a broader range of alkynes can be used to introduce different substituents at the 5-position, as exemplified by $P(1,2,3Tz^{1-Ph,5-Ph})_3$ (64%) and $P(1,2,3Tz^{1-Ph,5-nBu})_3$ (63%). A similar methodology was also used to prepare two diastereomers of a [2,2]-para-cyclophane substituted tris(triazolyl)phosphine.^[97] In this case a neutral triazole was prepared first, which was deprotonated with $LiNiPr_2$ prior to reaction with PCl_3 .

1.4.2 Coordination complexes of tris(1,2,3-triazolyl)phosphines

In their study of $P(1,2,3Tz^{1-Ph})_3$, the group of Lammertsma showed the P apex being the donor in $[W(CO)_5\{P(1,2,3Tz^{1-Ph})_3\}]$, while the oxide ligand functioned as a tridentate N ligand in $[RhCl_3\{OP(1,2,3Tz^{1-Ph})_3\}]$.^[5] Both coordination modes were combined by reacting the W complex with $C_7H_8Mo(CO)_3$ to obtain bimetallic $[(OC)_5W\{P(1,2,3Tz^{1-Ph})_3\}Mo(CO)_3]$ (Figure 1.12a). Crystal structures were reported for all metal complexes. The group compared computationally the ligating properties of tris(triazolyl)phosphine oxide with the more abundant tris(pyrazolyl)phosphine oxide (section 1.3.2) and both CH centered analogues.^[6] They found the Cu(I) complexation energetics to be slightly more favorable for the triazolyl containing ligands, whereas the effect of the apex seemed negligible. Experimentally, complexation of $OP(1,2,3Tz^{1-Ph})_3$ to Cu(I) yielded dimeric $[Cu\{OP(1,2,3Tz^{1-Ph})_3\}]_2X_2$ ($X = PF_6, B\{C_6H_3(CF_3)_2\}_4$) in which the N-2 nitrogen of one of the triazolyl rings of each ligand coordinates to the opposite Cu center (Figure 1.12b).



Scheme 1.9. Preparation of tris(1,2,3-triazolyl)phosphines.

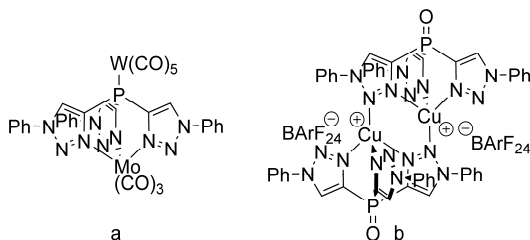


Figure 1.12. a) A bimetallic complex of $P(1,2,3Tz^1-Ph)_3$. b) $OP(1,2,3Tz^1-Ph)_3$ supported Cu-dimer.

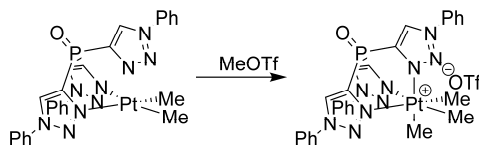
Bräse and co-workers have shown $[Zn\{P(1,2,3Tz^1-Ph,5-nBu)_3\}_2](Zn_2Br_6)$ to be a bis(κ^3-N_3)-ligand complex, whereas the ligand coordinates in a κ^2-N_2 fashion in $[ZnI_2\{P(1,2,3Tz^1-Ph,5-Ph)_3\}]$.^[96]

In their studies on the reactivity of unsaturated complexes, Templeton and co-workers applied tris(triazolyl)phosphine oxides as hemilabile nitrogen ligands for Pt dimethyl and diphenyl complexes $[PtR_2\{OP(1,2,3Tz^1-X)_3\}]$ ($R = Me, Ph; X = Ph, Cy$).^[98] They showed interconversions to take place at lower energy relative to the well-studied tris(pyrazolyl)borate ligand, due to facile $\kappa^2-N_2/\kappa^3-N_3$ isomerization of the complexes (Scheme 1.10). This hemilabile nature of the ancillary ligand was further explored in platinum phenyl olefin complexes, like $[PtPh(C_2H_4)\{OP(1,2,3Tz^1-X)_3\}](BF_4)$.^[99]

1.5 Tris(1,2,4-triazolyl)phosphines

1.5.1 Preparation of tris(1,2,4-triazolyl)phosphines

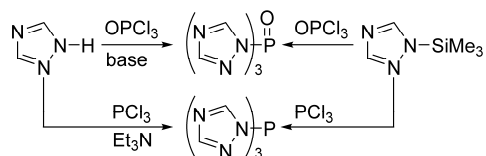
Tris(1,2,4-triazolyl)phosphine and its derivatives have hardly been applied as coordinating ligand and instead have been used mostly as synthons to introduce either a phosphorus or triazolyl group. The first syntheses of



Scheme 1.10. κ^2 / κ^3 isomerization of Pt complexes.

tris(triazolyl)phosphines $P^{(1,2,4Tz)_3}$ (81%) and $OP^{(1,2,4Tz)_3}$ (66%) employed the reaction of $^{1,2,4Tz}SiMe_3$ with PCl_3 and $POCl_3$, respectively (Scheme 1.11).^[100] Both tend to decompose in air into the bis(triazolium)phosphite and -phosphonate. $OP^{(1,2,4Tz)_3}$ (47%) has also been prepared from $POCl_3$ and $^{1,2,4Tz}H$ in MeCN with an excess of the triazole functioning as base.^[101] The use of Et_3N as base is more common (see below) and, starting from PCl_3 , has also yielded (in situ) $P^{(1,2,4Tz)_3}$.^[88]

1.5.2 Complexation of tris(1,2,4-triazolyl)phosphines



Scheme 1.11. Different routes toward tris(1,2,4-triazolyl)phosphine (oxide).

$OP^{(1,2,4Tz)_3}$ was used as an O-donor ligand for Sn(IV) complexation using $SnMe_2Cl_2$ to give cis- and trans- $[SnCl_2Me_2\{OP^{(1,2,4Tz)_3}\}_2]$ (Figure 1.13),^[102] which have been characterized by NMR, IR and DFT studies.

1.5.3 Phosphorylation by tris(1,2,4-triazolyl)phosphines

Kraszewski and Stawiński used $OP^{(1,2,4Tz)_3}$ in a phosphorylating reaction of a nucleoside with addition of two different alcohols to obtain phosphate tri-esters (60-70%; Scheme 1.12) in a far more effective manner than on using $POCl_3$ (5-10%).^[103] This procedure was adopted in several other studies,^[104-106] including a change in solvent from dioxane to CH_2Cl_2 ,^[107,108] using N-methylmorpholine as base, and to THF^[109] and MeCN.^[110-112] A triphosphate was obtained upon treatment of the phosphorylated product with pyrophosphate.^[113]

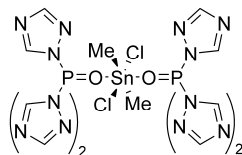
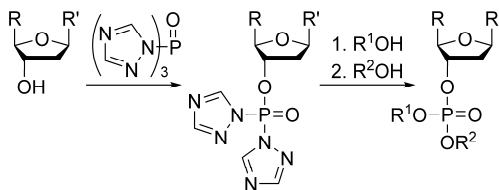


Figure 1.13. Trans complex of $SnMe_2Cl_2$ and $OP^{(1,2,4Tz)_3}$.



Scheme 1.12. Phosphorylation employing tris(1,2,4-triazolyl)phosphine oxide.

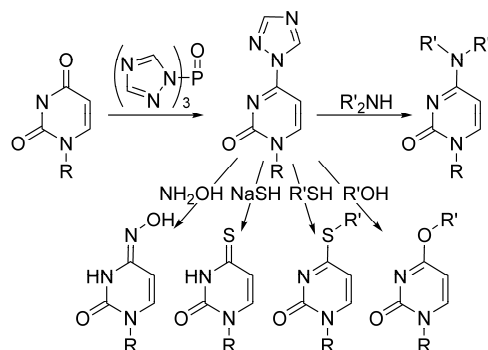
Reacting $OP^{(1,2,4Tz)}_3$ with 4-aminopyridine afforded di(1,2,4-triazol-1-yl)-[N-(pyridin-4-yl)]phosphoramidate, which is also a phosphorylating agent.^[114] The method has the advantage that pyridyl-amines with $pK_a > 7$ can be used where other phosphorylation reactions fail. The products have been applied in the synthesis of potential anti-viral drugs.^[115] With appropriate precursors, the phosphorylation can also give access to cyclic products. Reaction of $OP^{(1,2,4Tz)}_3$ with ethanolamine in the presence of DMAP formed 2-triazolyl-1,3,2-oxazaphospholane, which is a synthon for the introduction of a phosphatidylethanolamine group.^[116] $OP^{(1,2,4Tz)}_3$ has also been used to convert N-acetylated beta-amino alcohols into 2-oxazolines.^[117] Whereas most studies employed $OP^{(1,2,4Tz)}_3$ for phosphorylations, the corresponding sulfide can also be used.^[118,119] $SP^{(1,2,4Tz)}_3$ has been prepared in THF, using either Et_3N ^[118] or pyridine^[119] as a base. Reportedly, this sulfide gave higher yields than the oxide, but phosphorylation agents with P substituents other than 1,2,4-triazoles led to products that were easier to purify.^[118]

Contrasting the broad applicability of $OP^{(1,2,4Tz)}_3$, the reduced form, $P^{(1,2,4Tz)}_3$, is not as effective in forming phosphate bridges as was illustrated by the reaction with uridine (low temperature, followed by I₂-oxidation) that gave monomers instead of the desired oligoribonucleosides, supposedly due to the lability of the ligand.^[88] Finally, penta(1,2,4-triazolyl)phosphine has been explored as P precursor to generate a tricyclic tetra(amino)phosphonium salt, but with disappointing results.^[120]

1.5.4 Triazolylolation by tris(1,2,4-triazolyl)phosphines

In 1982, in situ generated $OP(1,2,4Tz)_3$ in acetonitrile with Et_3N as base was used for the first time to replace a carbonyl oxygen in uracil derivatives for a triazolyl group.^[121] Subsequent treatment with a nucleophile enabled substitution of the triazolyl group. This methodology has been applied to convert uracil rings into cytosine (using ammonia)^[121-129] or substituted cytosines (using organic amines).^[121,130-132] Reactions with hydroxylamines,^[133] alcohols,^[134-137] or thiols,^[121] introduced oxime, alkoxy or thiol functionality, respectively. Sulfur precursors like thioacetic acid,^[138-140] H_2S ,^[137] or $NaSH$ ^[140] have been used to generate a thioamide group (Scheme 1.13).

The triazolylolation also worked in dichloromethane with N-methyl morpholine as base.^[141] There are several reports on the use of pyridine as solvent and base.^[142-145] In one case only a pyridinium salt was isolated, presumed to result from a secondary reaction with pyridine.^[142] In other instances, the triazolyl-substituted products were successfully used in situ^[143,144] or isolated in up to 60% yield.^[145]

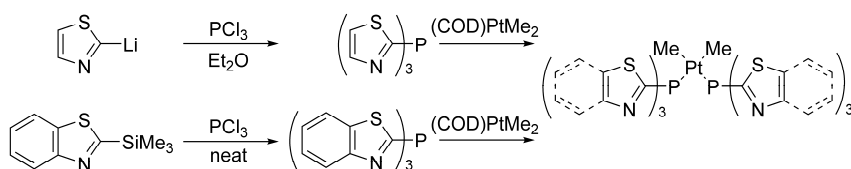


Scheme 1.13. The “triazolylolation” reaction that is used to replace a carbonyl site by other functional groups.

1.6 Tris(thiazolyl)phosphines and tris(thiadiazolyl)phosphines

1.6.1 Tris(thiazolyl)phosphines

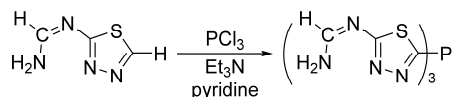
Moore and Whitesides connected besides imidazoles also thiazoles to phosphorus by reacting PCl_3 with the lithiated heterocycles (47-64%).^[111] The parent and the benzannulated derivative, accessible only from (benzothiazol-2-yl)trimethylsilane and PCl_3 (83%), both formed bis-ligand dimethyl platinum complexes, with metal bonding at the P-apex, as derived from NMR spectra (Scheme 1.14). Reaction of the tris(thiazolyl)phosphines with aryl lithium or heteroaryl lithium reagents resulted in P-substituent exchange, whereas coupling reactions dominated for the benzothiazolyl derivative.^[146] Abstraction of one benzothiazolyl group from tris(benzothiazolyl)phosphine gave access to the corresponding phosphanide ligand.^[147] In a study previously mentioned in section 1.2.5, AuCl complexes of tris(4,5- R_2 -thiazol-2-yl)phosphines (with $\text{R}_2 = \text{H,H}; \text{Me,H}; \text{Me,Me}$) were studied.^[58] Crystal structure determinations showed the tris(thiazolyl)phosphines to bind to the metal exclusively via the phosphine apex, while a variety of Au-Au and Au-Cl interactions was found in the solid state.



Scheme 1.14. Preparation of tris(-benzo-thiazolyl)phosphines and their reaction with dimethyl(cyclooctadiene)platinum.

1.6.2 Tris(thiadiazolyl)phosphines

The only reported tris(thiadiazolyl)phosphine was obtained from the reaction of N,N -dimethyl- N' -(2-thiadiazolyl)formamidine and PCl_3 with Et_3N in pyridine (72%; Scheme 1.15).^[148] It was shown for the related mono-thiadiazolyl-diphenylphosphine that the formamidine group can be removed, leaving an amino group.



Scheme 1.15. Preparation of a tris(thiadiazolyl)phosphine.

1.7 Concluding remarks

The literature on tris(azolyl)phosphines has been dominated by tris(imidazolyl)phosphines, which have been used mainly to model enzymes with histidine residues at the active site. In recent years, also more non-enzyme inspired metal complexes have been studied. For the other tris(azolyl)phosphines, no biomimetic applications have been reported, while they do display interesting coordination chemistry, with some complexes being applied in catalysis. Tris(1,2,4-triazolyl)phosphine forms an exception as it has almost exclusively been applied as synthon in heterocyclic chemistry.

The tris(imidazolyl)phosphines have their azolyl substituents connected to the phosphorus apex via carbon-phosphorus bonds, making them more stable than most other tris(azolyl)phosphines under diverse conditions. However, they typically suffer from more complex and lower yielding syntheses that often involve functional group protection schemes.

Whereas all tris(azolyl)phosphines have the potential to serve as multi-site ligands, there are very few examples in which both coordination sites are used at the same time, despite their potentially interesting applications. An avenue to explore is to tune the electronic influence on one metal by varying the opposite one, whereas the second binding site might also be used for ligand fixation on a metal surface.

1.8 References

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