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Azaphosphinines and their derivatives

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Six-membered heterocycles containing one phosphorus and one nitrogen atom, known as azaphosphinines, have existed in the shadows of their single heteroatom-containing analogues for almost 150 years. Despite this, recent chemistry has seen a rapid increase in publications concerning this uncommon scaffold. Azaphosphinines exist in one of six isomers—there are three possible orientations of the pnictogen atoms and in each of these, the phosphorus is in one of two valences (P^{III} vs. P^V). This review aims to outline and inform on the synthesis and applications of all six isomers. P^V -oxo azaphosphinines are of particular interest to this review as many of the discussed heterocycles either form as the pentavalent species directly or oxidize to this over time. In very recent years the published applications of azaphosphinines have blossomed into subjects spanning several fields of chemistry such as asymmetric catalysis, supramolecular association, cellular imaging, and medicinal chemistry.

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Introduction

Historically, heterocycle chemistry is inseparable from organic chemistry. The first isolated heterocyclic species, alloxan, discovered by Gaspard Brugnatelli in 1818,¹ predates the Kekulé

model of benzene by roughly 50 years. These humble beginnings of a small nitrogenous poison isolated from uric acid kicked off an intense interest that has yet to subside. In the last 200 years, heterocycles have spread and flourished into every facet of chemistry—organic, medicinal, metal coordination, and otherwise. Much of the heavy lifting done in the field of heterocycles is done by pnictogen-based species. Simple five- and six-membered nitrogen-containing ring systems such as pyrrole, piperidine, and pyridine commonly act as solvents and/or bases in synthetic processes as well as fundamental building blocks to all manner of pharmaceuticals, dyes, ligands, and

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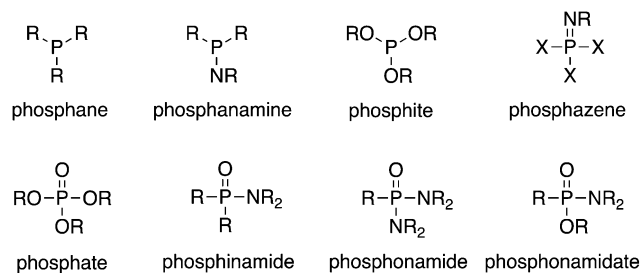


Fig. 1 Phosphorus nomenclature commonly referred to in this article.

pesticides.^{2–12} In comparison to their 2nd row counterparts, phosphorus heterocycles are considerably less common in the literature. However, this is not to say that these molecules do not find important uses in the modern world. A few specific examples include the use of phospholes in optoelectronic applications and phosphinines in catalysis and photophysical applications.^{13–21} Nitrogen and phosphorus together serve as an interesting pair in heterocycles as well. In particular, the nature of the $P^V=N$ bond has been a hotly researched phenomenon.

This review will reference phosphorus-specific nomenclature extensively. Many of the functional groups have alternative common names that have risen and fallen out of popularity in the last few decades or even centuries. For the sake of consistency, the nomenclature applied in the review will adhere to the following guide (Fig. 1). This is not an exhaustive list of phosphorus nomenclature but rather establishes the naming for the functional groups referred to frequently in this review. More elaborate descriptions of azaphosphinine nomenclature are found below (Fig. 3 and 4). It should be noted that the term phosphine is generally used interchangeably with phosphane in the current literature; however, over a decade ago IUPAC decided that phosphane is the preferential term for the PR_3 functional group. For the sake of standardizing phosphorus

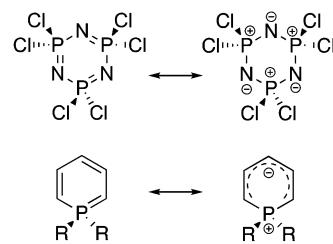


Fig. 2 Examples of (top) ionic nature in hexachlorophosphazene and (bottom) ylidic nature in P^V phosphinine.

nomenclature in this review, phosphane naming is used exclusively. This also extends to the pentavalent $P(O)R_3$, dubbed phosphane oxides.

An intriguing example of what makes the $P^V=N$ bond so unique are cyclophosphazenes.^{22–24} They are cyclic species with the chemical formula $(X_2PN)_n$ (Fig. 2, top), that at first glance, present the qualities one would expect in an aromatic ring. Prepared by Liebig *et al.* in 1834, hexachlorophosphazene is one of the best examples, with the ring being totally planar, containing 6π electrons, and all ring bond-lengths being uniform.²⁵ For many years following its discovery, it was assumed that these qualities resulted from true delocalization of π -electrons from the nitrogen atoms into the participating 3d orbitals of the adjacent phosphorus atoms. However, it has become well understood in recent decades that a pentavalent phosphorus species has little-to-no participation of the 3d orbitals in its bonding. Instead, the nature of the $P^V=N$ bond can be better described as highly polarized, bordering on ionic. The electronegativity difference in nitrogen and phosphorus atoms results in a transfer of the π electron to the nitrogen atom which can then participate in negative hyperconjugation. Popularized by Schleyer and Kos in 1983, negative hyperconjugation is the donation of π orbitals into adjacent σ^* orbitals. This ultimately results in a stabilizing effect for the π -bond and



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Michael M. Haley

Michael M. Haley received his Bachelor's (1987) and PhD (1991) degrees from Rice University working with Prof. Ed Billups. Haley then pursued his postdoctoral studies with Prof. Peter Vollhardt at the University of California-Berkeley from 1991 to 1993. He joined the faculty at the University of Oregon in 1993 where he is currently the Richard M. and Patricia H. Noyes Professor of Chemistry. He also served as Head of the Department from 2008 to 2014. Haley is an expert in aromatic and carbon-rich molecules. He was recognized for his innovative hydrocarbon research with the 2021 American Chemical Society George A. Olah Award in Hydrocarbon or Petroleum Chemistry.

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a weakening of the σ -bond.²⁶ In the context of cyclophosphazenes, the lone pair orbitals of the nitrogen donate back into the $\sigma^*_{\text{P-N}}$ and $\sigma^*_{\text{P-X}}$. In total, this ionic character of each $\text{P}^{\text{V}}=\text{N}$ bond and the consistent negative hyperconjugation from each nitrogen into each adjacent σ^* creates a facsimile of aromaticity despite there being no delocalization through the phosphorus center (Fig. 2, top). However, the heterocycles discussed in this review are not the inorganic cyclophosphazenes but are rather azaphosphinines containing just one nitrogen and phosphorus atom each. This difference adds two levels of complexity that must be addressed. While it would be appropriate to translate the cyclophosphazene example to 1,2 λ^5 -azaphosphinines with a $\text{P}^{\text{V}}=\text{N}$ bond, we must also consider the other isomers.

It is commonly recognized that P^{III} phosphinines are aromatic heterocycles in the same vein as pyridine. However, P^{V} phosphinines are just as commonly understood to be nonaromatic. Several publications^{27–29} have addressed the cyclophosphonium ylide nature of P^{V} phosphinines (Fig. 2, bottom), describing the partial negative charge buildup on the 2-, 4-, and 6-carbons with corresponding positive charge on the phosphorus. The result is a nonaromatic system that does not delocalize through the phosphorus like cyclophosphazenes. This situation would apply directly to the 1,4 λ^5 -azaphosphinines discussed in this review as there is no direct bond between the phosphorus and nitrogen in these cases, yet the electronegative nitrogen atom would be even more accepting of the negative character of the ylide. In this case it would be appropriate to conclude that the isolated 1,4 λ^5 -azaphosphinine ring could not be aromatic.

The last consideration to address is the phosphoryl ($\text{P}^{\text{V}}=\text{O}$) bond found in many of the heterocycles discussed in this review. Like the $\text{P}^{\text{V}}=\text{N}$ bond, the phosphoryl bond is known to be extremely polarized³⁰ and exhibits negative hyperconjugation from the oxygen lone pairs back into the adjacent σ^* of the other phosphorus bonds. While there are no thorough computational investigations into the electronics of azaphosphinines with exocyclic $\text{P}^{\text{V}}=\text{O}$ bonds, we can imagine the resultant heterocycle shares the combined properties of phosphinines and phosphane oxides in which all the bonds to the phosphorus exhibit a high degree of ionic character while simultaneously being stabilized by negative hyperconjugation from not only the oxygen but also the nitrogen atom. The conclusion of

these considerations being that ultimately no P^{V} azaphosphinine ring of any form could truly be considered aromatic because of the consistent lack of π -delocalization through the phosphorus atom. Despite this, many of the species discussed in this review have aromatic rings fused to the azaphosphinine rings, which result in an overall aromatic structure.

Azaphosphinines have a history that spans back 135 years, yet for much of their existence they have remained little more than a synthetic curiosity.³¹ Early work on these molecules was generally fueled by a desire to explore the definition of aromaticity and its existence in unusual heteroaromatic environments. However, the initial synthetic pathways that were developed by the likes of Campbell, Dewar, Märkl, and more provided the necessary groundwork for translating azaphosphinines into modern heterocyclic chemistry.^{32–36} Since the start of the 21st century, azaphosphinines have begun to find increasingly diverse uses in the fields of asymmetric catalysis, supramolecular association, cellular imaging, and even medicinal chemistry.^{37–39}

The primary goal of this review is to shed light on where the science of azaphosphinines originated, illustrate both older fundamental studies and numerous recent advances, and offer insights of what is yet to come. Most of the research done on this class of molecules comes from the last 25–30 years. The compounds surveyed in this review will contain at least one six-membered ring with no more than one endocyclic phosphorus and nitrogen atom. Only compounds with high degrees of unsaturation in the PN ring will be considered. Heterocycles with partial saturation will be included as necessary to give useful counterpoints and context when discussing reactivities or properties of the heterocycles such as aromaticity. Despite the propensity for P^{V} -azaphosphinines to be *P*-stereogenic, stereochemistry will typically only be shown for chiral centers (*i.e.*, non-identical *P*-substituents) generated by asymmetric reactions where the enantiomeric or diastereomeric excess can be determined.

A secondary goal of this review is to provide a standardized nomenclature for azaphosphinines. While several names have been used to describe the same general system, it is the opinion of the authors that the terminology of azaphosphinine should be used to describe any six-membered ring containing one phosphorus and one nitrogen atom. This can be further divided into the isomers of 1,2-, 1,3-, and 1,4-azaphosphinine **1a–c** (Fig. 3, top), where the “1-” is in reference to the position of the nitrogen atom and the second number refers to the position of the phosphorus atom. The commonly observed *benzo* fusion aptly results in the name benzo[*x*]azaphosphinines **2a–b** (Fig. 3, bottom). The bracketed letter refers to the bond (Fig. 3, top) on which ring fusion occurs, with the N–X bond being “a”, where *x* is either the phosphorus atom or the closest carbon to it. In the case of naming fused ring systems, Hantzsch–Widman nomenclature rules should be used.⁴⁰ Further π -extension *via* ring fusion will continue appropriately. The phosphorus atom in every compound discussed will exist in one of two valences, either P^{III} or P^{V} . This is denoted by the superscript number on the λ inserted into the chemical name. Examples of this

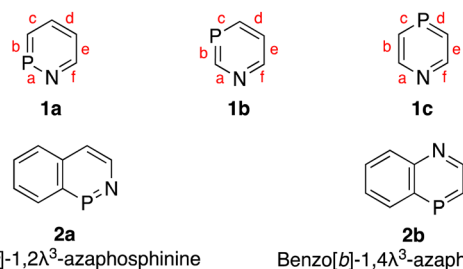


Fig. 3 Examples of (top) 1,2- (**1a**), 1,3- (**1b**) and 1,4-azaphosphinines (**1c**) and (bottom) benzo[*c*]- (**2a**) and benzo[*b*]azaphosphinine (**2b**) isomers.

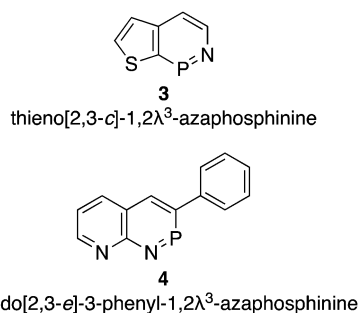


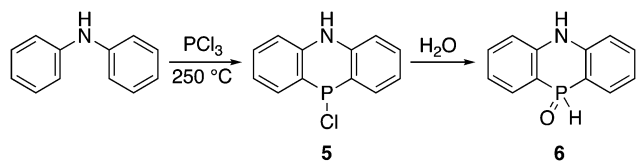
Fig. 4 Examples of nomenclature rules applied to more complex azaphosphinine derivatives such as **3** and **4**.

nomenclature system are given for compounds **3** and **4** (Fig. 4). As apparent, while these naming conventions are accurate, they rapidly become encumbered with substituents and substitution patterns. As such, when referring to libraries of synthesized azaphosphinines, the authors of this review will typically refer to them as azaphosphinines or benzo[*x*]azaphosphinines with key substituents as appropriate.

This review is divided primarily into three sections concerned with the three isomeric forms of azaphosphinine. The 1,2-isomer is by far the most studied of the three, likely because of the wealth of reactions that have been developed to afford this scaffold. The inherent difference in electronegativities between the phosphorus and nitrogen atoms increases their electrophilicity and nucleophilicity, respectively. This increased reactivity aids reactions such as heteroannulation and C–H activation. These factors could help explain why there are several more publications for the 1,4-isomer than 1,3-isomers, with the latter being quite rare in the current literature. For the purposes of organization, each isomer's section will be divided into subcategories to distinguish between the different methods of synthesis applied to form the azaphosphinine ring.

Azaphosphinine origins

The first published example of a six-membered PN-heterocycle dates to 1888 with the work of Schenk and Michaelis on what are commonly referred to as dihydrophenophosphazines (Scheme 1).³¹ This heterocyclic scaffold could also be classified as dibenzo[*b,e*]-1,4-dihydro-1,4λ⁵-azaphosphinine under the naming scheme used in this review. The synthesis proceeds through an addition of PCl₃ to diphenylamine at elevated

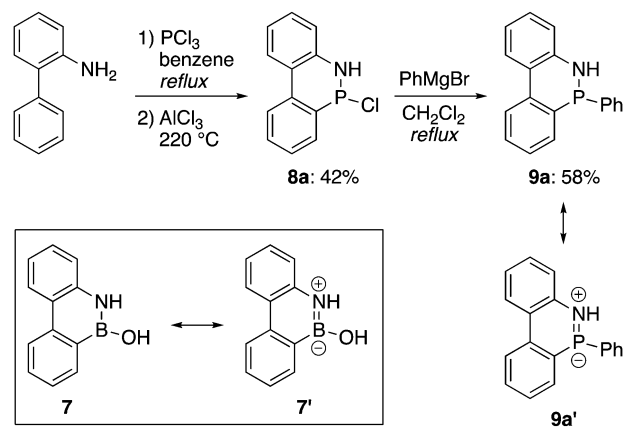


Scheme 1 Schenk and Michaelis' first reported synthesis of a PN-heterocycle scaffold, dibenzo[*b,e*]-1,4-dihydro-1,4λ⁵-azaphosphinine 4-oxide.

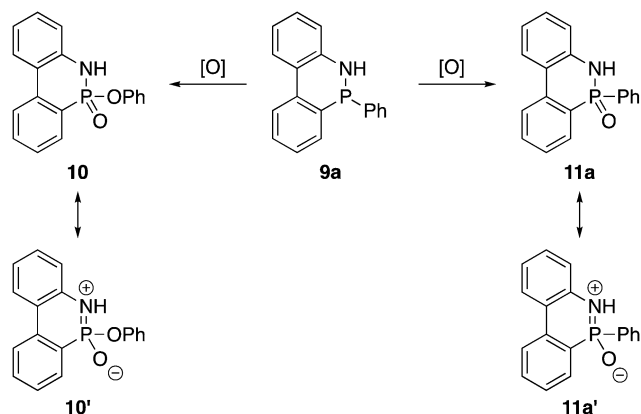
temperatures. This reaction yields the *P*-chloro species **5**, which can be subsequently hydrolyzed/oxidized into the corresponding 1,4λ⁵-azaphosphinine 4-oxide **6**. Due to technological constraints, the structure of **6** was not definitively confirmed until nearly a century later thanks to the work of Häring.⁴¹ The dihydrophenophosphazine scaffold stands somewhat alone among azaphosphinine derivatives, as the 1970s and 1980s saw three excellent review articles detailing the chemistry of these species, which we encourage those with further interest to read.^{42–44} Since then, the literature has been extremely sparse on publications concerning these chemicals.^{45,46} Due to the wealth of previously compiled research and a dearth of recent studies, dihydrophenophosphazines will be excluded from the remainder of this review.

The oldest example of a 1,2-azaphosphinine comes from Dewar and Kubba in 1960.⁴⁷ Their synthesis follows a similar pathway to that laid out by Schenk and Michaelis nearly a century before.³¹ This team had released a publication two years earlier describing aromatic resonance forms in boron-containing **7** and were interested in developing analogous PN species.⁴⁸ The work was aimed at trying to develop a phenanthrene-like dibenzo[*c,e*]-1,2-dihydro-1,2λ³-azaphosphinine **9a** with hypothetical resonance structure **9a'**, in which the lone pair of the nitrogen atom would resonate through phosphorus to give some additional π -delocalization through the hyper-valent P resonance structure **9a'** (Scheme 2). Starting from 2-aminobiphenyl, the authors generated an acyclic intermediate by reacting with phosphorus trichloride in benzene. This was then cyclized crude with AlCl₃ at elevated temperatures to furnish **8a**. Finally, replacement of the chlorine with PhMgBr resulted in the desired compound **9a**.

Comparison of UV-Vis spectra of **7** and **9a** indicated that while the electronic structures of the two species were similar, they were not identical. However, the authors noted that when left exposed to air for extended periods of time, two oxidation products (**10** and **11a**) were generated from **9a** (Scheme 3). Interestingly, the spectra of these oxidation products were nearly identical when compared to that of **7**. This emergent



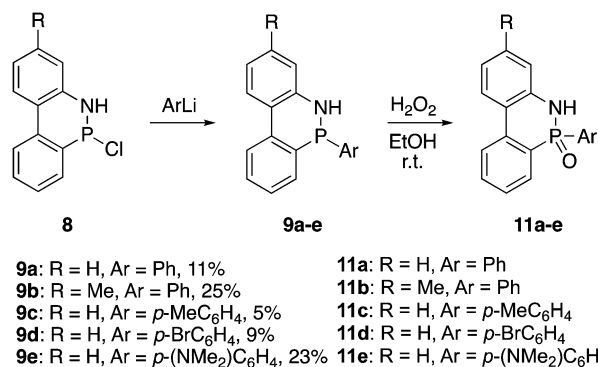
Scheme 2 Synthesis of Dewar and Kubba's early dibenzo[*c,e*]-1,2-dihydro-1,2λ³-azaphosphinine **9** and comparison to the previously prepared boron-containing species **7**.



Scheme 3 Oxidation products of Dewar and Kubba's azaphosphinine **9** with aromatic resonance structures.

electron delocalization was rationalized by Dewar and Kubba through proposed resonance structures **10'** and **11a'**. By convention, P^V -oxo compounds are represented as $P=O$ double bonds; however, due to the nature of the hypervalent bonding of these atoms, it can be argued that the phosphonyl moiety exists as P^+-O^- in most cases. As discussed previously, it is unlikely any true aromaticity is occurring in these P^V heterocycles, but rather electron delocalization from the lone pairs of the oxygen and nitrogen to adjacent bonds *via* negative hyperconjugation. Further consideration of aromaticity in different azaphosphinine isomers is discussed at the end of the review. A majority of the azaphosphinines discussed in this review will feature this negative hyperconjugation phenomenon.

That same year, Campbell and Way significantly expanded upon the previous work laid out by Dewar and Kubba.⁴⁹ Starting from one of two *P*-chloro species **8** ($R = H$ or Me), they arylated the system directly with several different aryl lithiates to furnish a family of corresponding azaphosphinines **9**. The authors found that they could induce the oxidation observed by Dewar and Kubba by exposing the heterocycles to a mixture of H_2O_2 and $EtOH$ at room temperature (Scheme 4). No yields were reported for the final oxidation to furnish **11**.



Scheme 4 Campbell and Way's synthesis of early azaphosphinines **9** and oxidation to **11**.

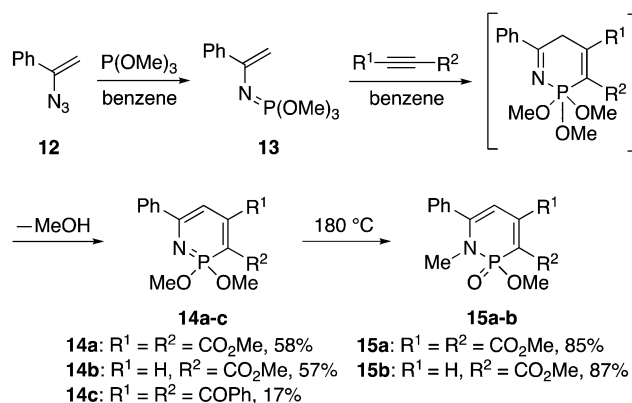
1,2-Azaphosphinines

Reactivity with alkynes

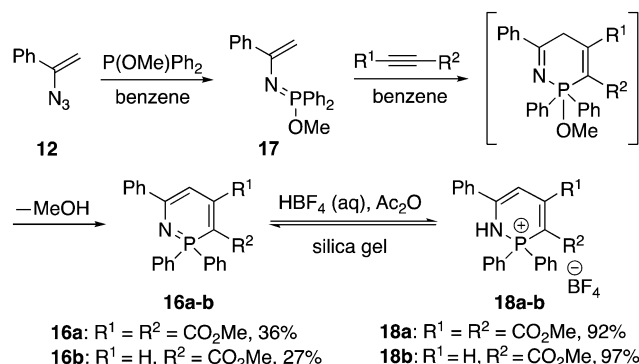
Pericyclic/cycloadditions. When considering the different synthetic approaches used in the development of 1,2-azaphosphinines, few are as prevalent in the early literature as the $[4+2]$ cycloaddition, more commonly known as the Diels–Alder reaction. The earliest example of this reaction being applied to the 1,2-isomer of azaphosphinine is from Kobayashi and Nitta in 1985 to furnish three 1,2λ⁵-azaphosphinine derivatives.³⁴ While not the first reported synthesis of this family of heterocycle, it did lay the groundwork for what would become a very typical method. The researchers used an *N*-vinylphosphazene (**13**) as their diene (Scheme 5), which was generated through the Staudinger reaction of azidostyrene **12** and trimethyl phosphite. The Diels–Alder reaction was then carried out using various substituted alkynes to yield 2,2-dimethoxy-1,2λ⁵-azaphosphinines **14** in modest to good yields. The observed regioselectivity of **14b** is ascribed to the ylidic nature of the phosphazene diene and the comparatively electrophilic β-carbon of the ester dienophiles. When heated to high temperatures, azaphosphinines **14a–b** underwent a methyl shift to yield the corresponding dihydro derivatives **15** in excellent yields.

Over a decade later, Nitta and coworkers returned to their work on the cycloadditions of *N*-vinyl-phosphazenes and substituted alkynes to explore further modifications.⁵⁰ They synthesized a similar series of 2,2-diphenyl-1,2λ⁵-azaphosphinines **16** in modest yields by using phosphazene **17** as the phosphorus source for diene preparation (Scheme 6). Besides the new azaphosphinines, this paper also served to demonstrate potential post-synthetic modifications to these heterocycles. Unlike **14**, azaphosphinines **16** did not rearrange but instead could be reversibly protonated to give the corresponding azaphosphininium tetrafluoroborate salts **18**.

In 1996, López-Ortiz and coworkers published an interesting alternative pathway to the 2,2-diphenyl-1,2λ⁵-azaphosphinine scaffold by using *N*-methoxycarbonyl alkylidiphenylphosphazenes **19** as the pnictogen source in the cycloaddition.⁵¹ The key difference in this procedure from previous work was the



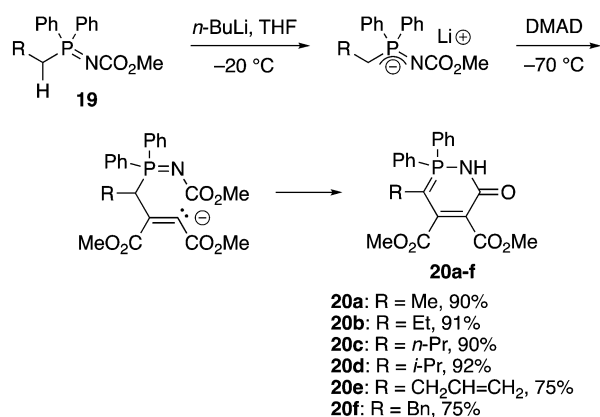
Scheme 5 Synthesis of 1,2-azaphosphinine **14** using the Staudinger reaction and subsequent Diels–Alder cycloaddition.



Scheme 6 Preparation of heterocycles **16** using phosphazene **17** and formation of azaphosphininium salts **18**.

generation of a stable ylide by deprotonation of the phosphazene with *n*-BuLi. The ylide then cyclized with dimethyl acetylenedicarboxylate (DMAD) to form the corresponding 2,2-diphenyl-1,2 λ^5 -azaphosphinin-6-one **20** in very good to excellent yields (Scheme 7). The authors concluded that only alkylidiphenylphosphazenes will react accordingly, as the substitution of a hydrogen inhibits the process. The authors noted that they had no explanation for the lack of reactivity in their system when $\text{R} = \text{H}$.

Following this work from López-Ortiz, the chemistry of 1,2 λ^3 -azaphosphinines began to flourish with the seminal 1996 publication from Mathey and coworkers in which 1,3,2-diazatitanacyclohexa-3,6-dienes **21** were reacted with an equivalent of PCl_3 at low temperature to furnish the corresponding 1,3,2-diazaphosphinines **22** (Scheme 8, top).⁵² These diazaphosphinines can then be subjected to [4+2] cycloaddition conditions to yield a diazaphosphabarrelene intermediate **23**, which undergoes a subsequent [4+2] cycloreversion to extrude an equivalent of *t*-BuCN to yield 1,2 λ^3 -azaphosphinines **24**. Interestingly, this reaction can be repeated through the same conditions and extrude another equivalent of *t*-BuCN and furnish the corresponding phosphinine. This finding was similar to that of Märkl several years earlier who observed similar nitrile-extrusion properties in 1,3 λ^3 -azaphosphinines, as will be

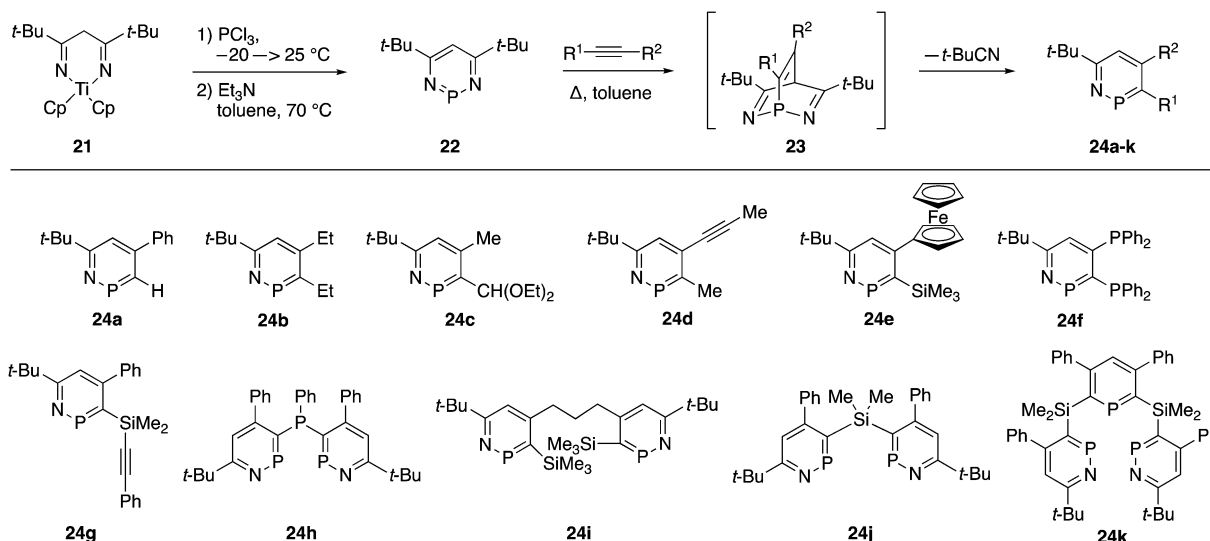


Scheme 7 Synthesis of 2,2-diphenyl-1,2 λ^5 -azaphosphinin-6-ones **20** through cycloaddition with DMAD.

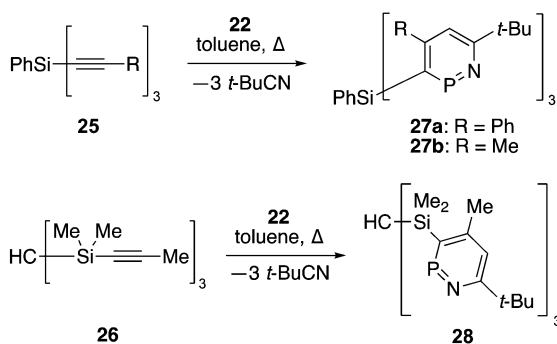
discussed in a later section of this review.⁵³ This mild synthesis offered several distinct advantages in the forms of regioselectivity, functional group tolerance, and high yields.

In 1997, Mathey and coworkers released a follow-up publication that dramatically expanded the substrate scope.⁵⁴ Despite demonstrating how titanocenes with either diphenyl or di-*t*-butyl substitution could be applied to the initial cycloaddition–cycloreversion reaction, the authors only used the di-*t*-butyl substituted derivative for the sake of purification. This resulted in a library of diverse 6-*t*-butyl-1,2 λ^3 -azaphosphinine derivatives **24**, highlighting the benefits of this synthetic approach (Scheme 8, bottom). The previously inaccessible derivatives include ferrocene, exocyclic phosphane, and silane-containing species. An interesting facet of the synthesis was discovered when comparing conjugated *vs.* nonconjugated diynes in the reaction. The authors found that use of conjugated diynes such as 2,4-butadiyne only facilitated a reaction from one of the triple bonds, leading to a 4-ethynyl azaphosphinine. Conversely, by using nonconjugated diynes, the reaction occurs at both alkyne sites resulting in bisazaphosphinines (**24h–k**). It should be noted that every azaphosphinine generated through this method can be further transformed into the corresponding phosphinine as described above. Unfortunately, only the yields of the terminal phosphinines are reported. Application of this cycloaddition–cycloreversion strategy with nonconjugated diynes to generate more complex bisazaphosphinine heterocycles begged the question as to whether it could be extended to higher order systems. In 2000, Le Floch and coworkers provided the answer by performing the same reaction on tripodal species **25** and **26** to generate 1,2 λ^3 -azaphosphinine heterocycles **27** and **28** (Scheme 9).⁵⁵

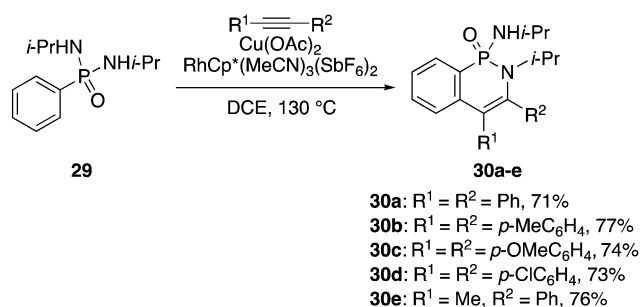
Transition metal-catalyzed C–H activation. While the preparation of azaphosphinines *via* cycloaddition reactions was the most popular method in the 1980s and 1990s, this route has been supplanted by more modern techniques in recent years. One of the biggest synthetic advances across all of organic chemistry has been the advent and popularization of transition metal-mediated reactions stemming from pioneering works of Heck, Suzuki, Sonogashira, and more. One popular recent advance is transition-metal based C–H activation. A common technique for such reactions is the use of *ortho*-directing groups in aryl systems. By having an appropriate functional handle, specific aryl C–H bonds can be selected and reacted upon. In 2013, Glorius and coworkers published their work using phosphoryl-related directing groups in Rh^{III} -catalyzed C–H activation.⁵⁶ They reasoned that because there was a plethora of carbonyl-based directing groups for C–H activation, phosphonyl-based systems may work as well. After screening conditions, the authors found that the catalyst $\text{RhCp}^*(\text{MeCN})_3(\text{SbF}_6)_2$ was able to effect C–H activation reactions directed by different aryl phosphonamides. Within the scope of this review, when this reaction was performed on phosphonamide **29** and various bis-functionalized alkynes, the corresponding benzo[*c*]-1,2-dihydro-1,2 λ^5 -azaphosphinines **30** were furnished in good yields (Scheme 10). There was no apparent preference in electronic character of the alkyne. While



Scheme 8 (top) Synthesis of 1,2-azaphosphinines **24** through the formation and cycloaddition of a 1,3,2-diazaphosphinine. (bottom) Substrate scope of the heterocycles prepared in this way.



Scheme 9 Preparation of tripodal 1,2λ³-azaphosphinine heterocycles (top) **27** and (bottom) **28**.

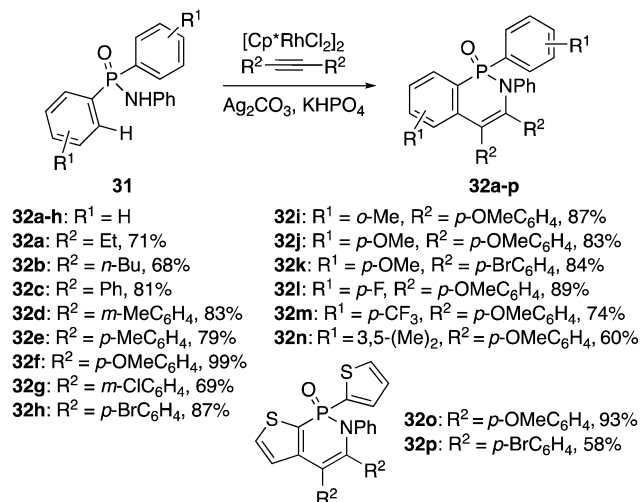


Scheme 10 Aryl phosphonamide directed C–H activation to furnish **30**.

the authors note that the desire to synthesize **30** was fueled by the biological relevance of the analogous isoquinolinone, this paper served more as a foray into phosphonyl-directed C–H activation and was not focused on the azaphosphinines outside of their application in reaction scope.

In the same year as the work from Glorius, Lee and co-workers sought to use phosphinamides for C–H activation and

heteroannulation using a different Rh catalyst.⁵⁷ Unlike the work from Glorius and coworkers, this publication was entirely focused on the construction of azaphosphinines. The goal was to use the lone pair of the phosphinamide as a directing group for the heteroannulated benzo[*c*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxides. After optimizing the reaction conditions, Lee and coworkers examined a variety of phosphinamide substrates **31** (Scheme 11) and generated several derivatives of azaphosphinine **32** in good to excellent yields. There was no apparent preference for electron density or steric bulk in the alkyne coupling partner, and they observed excellent functional group tolerance. In several instances, they obtained heterocycles containing aryl chlorides and bromides that are available for further manipulation. They also proceeded to show how more complex, heterocyclic



Scheme 11 Formation of [c]-fused 1,2-dihydro-1,2λ⁵-azaphosphinine-2-oxide **32**.

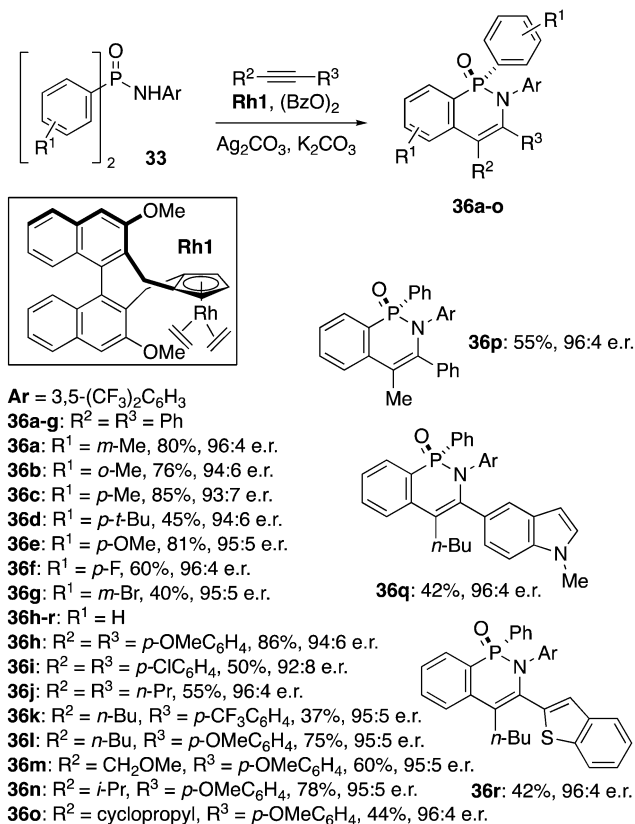
phosphinamides tolerate the reaction as with *P*-thiophene derivatives **32o** and **32p**.

Electron lone pairs, particularly those on pnictogen atom centers, are commonly used to effect ligation. However, while many pnictogen-based ligands exist, the phosphinamide motif is rarely accessed for this purpose. Despite underutilization, the propensity of P^V to form chiral centers combines well with an adjacent directing lone pair. In 2017, Cramer and coworkers aimed to take the previous work from Lee and use it to develop a new class of benzo[*c*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxide based *P*-stereogenic ligands.⁵⁸ To accomplish this, Cramer took advantage of prochiral molecule **33** to carry out the transition metal-catalyzed heteroannulation reaction. By using the nitrogen to direct the chiral catalyst to one of the two ortho aryl C–H bonds **34**, chiral intermediate **35** is formed, which is then carried through the reaction to give chiral benzo[*c*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxide **36** (Scheme 12).

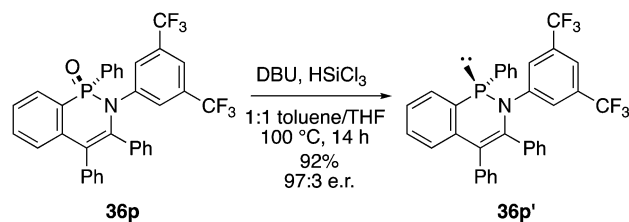
Optimization experiments determined that **Rh1** was the most appropriate catalyst for good enantioselectivity of the products, and thus a wide substrate scope was examined (Scheme 13). From the results of the synthetic trials, there does not seem to be a large electronic preference of substrate. Regardless, the high enantioselectivity of the reaction is undeniable, with enantiomeric excess being greater than 10 : 1 (*S* : *R*) for every derivative of **36** synthesized.

Because the primary aim of the Cramer paper was to generate useful chiral phosphinamide ligands for further chemistry, they also reported reducing the benzo[*c*]azaphosphinine from P^V to P^{III} . Although the authors found that the heterocycles were prone to racemization under certain conditions, the optimal method (Scheme 14) used 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and trichlorosilane, resulting in 92% yield of P^{III} product and 97% retention of the initial configuration. The authors concluded this is a feasible pathway to enantiospecific benzo[*c*]-1,2-dihydro-1,2λ³-azaphosphinines ligands **36'**; however, they have not reported additional studies on this system to date.

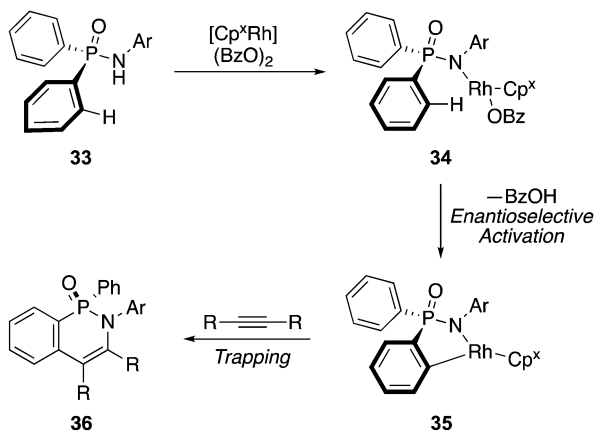
In 2018, Cramer and Sun published a follow-up study that revealed a promising application for their system.³⁸ Previously,



Scheme 13 Chiral C–H activation heteroannulation to afford **36**. For every entry, Ar = 3,5-(CF₃)₂C₆H₃.



Scheme 14 Enantiospecific reduction to chiral azaphosphinine **36p'**.



Scheme 12 Proposed mechanism for chiral C–H activation heteroannulation of achiral phosphinamide.

the syntheses of chiral azaphosphinines **36** via this method were limited to the desymmetrization of achiral phosphinamides with two identical aryl *P*-substituents **33**. The authors hypothesized that if the selectivity for the reactive enantiomer could be great enough, then one would be able to take a racemic mixture of chiral phosphinamide and generate two enantiomerically-pure materials, the heteroannulated reactive enantiomer **37** and the purified unreactive enantiomer of the starting racemate **38** (Table 1). In this study the chiral catalyst **Rh1** did not give sufficient selectivity, so Rh complexes with bulky trisubstituted Cp^x ligands (to deactivate reactivity on the mismatched substrate) were screened, with **Rh2** proving to be the most effective.

Much like their previous publication, this 2018 Cramer paper featured a large library of derivatives to emphasize the efficacy of their system. Varying the electronic and steric

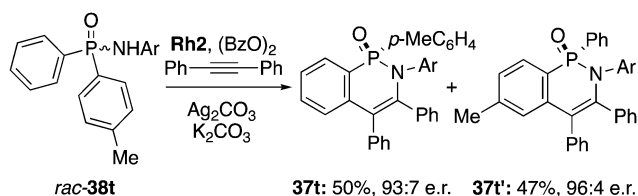
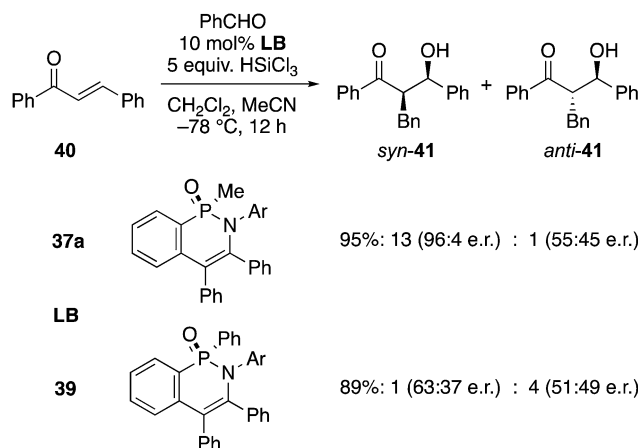
Table 1 Experimental details for reactions of *rac*-**36** with various internal alkynes. Ar = 3,5-(CF₃)₂C₆H₃

<i>rac</i> - 38	R ¹	R ²	R ³	R ⁴	Time [h]	Conv. [%]	E.r. 37 (% yield)	E.r. 38 (% yield)
<i>rac</i> - 38a	H	Me	Ph	Ph	8.5	51	93 : 7 (46)	95 : 5 (46)
<i>rac</i> - 38b	<i>p</i> -Me	Me	Ph	Ph	10.5	55	89 : 11 (50)	98 : 2 (42)
<i>rac</i> - 38c	<i>p</i> -F	Me	Ph	Ph	10.5	55	90 : 10 (48)	98 : 2 (40)
<i>rac</i> - 38d	<i>p</i> -Cl	Me	Ph	Ph	10.5	55	89 : 11 (45)	97 : 3 (40)
<i>rac</i> - 38e	<i>p</i> -OMe	Me	Ph	Ph	8.5	54	91 : 9 (48)	99 : 1 (42)
<i>rac</i> - 38f	<i>p</i> -NMe ₂	Me	Ph	Ph	9.5	42	95 : 5 (36)	83 : 17 (50)
<i>rac</i> - 38g	<i>m</i> -Me	Me	Ph	Ph	10.5	58	85 : 15 (53)	99 : 1 (38)
<i>rac</i> - 38h	<i>m</i> -Br	Me	Ph	Ph	14	55	91 : 9 (42)	99 : 1 (38)
<i>rac</i> - 38i	<i>o</i> -Me	Me	Ph	Ph	10	53	77 : 23 (42)	79 : 21 (44)
<i>rac</i> - 38j	H	Bn	Ph	Ph	4	59	84 : 16 (53)	99.5 : 0.5 (37)
<i>rac</i> - 38k	H	(CH ₂) ₂ OBn	Ph	Ph	6.5	51	93 : 7 (47)	93 : 7 (44)
<i>rac</i> - 38l	H	<i>N</i> -Pyrrolidiny	Ph	Ph	5	57	79 : 21 (52)	89 : 11 (40)
<i>rac</i> - 38m	H	<i>N</i> -Morpholiny	Ph	Ph	3.5	61	79 : 21 (55)	95 : 5 (37)
<i>rac</i> - 38n	H	OMe	Ph	Ph	24	60	81 : 19 (55)	97 : 3 (37)
<i>rac</i> - 38o	H	OPh	Ph	Ph	14	53	86 : 14 (48)	91 : 9 (44)
<i>rac</i> - 38p	H	Me	<i>p</i> -OMeC ₆ H ₄	<i>p</i> -OMeC ₆ H ₄	8.5	51	89 : 11 (46)	95 : 5 (46)
<i>rac</i> - 38q	H	Me	<i>n</i> -Bu	<i>p</i> -OMeC ₆ H ₄	8.5	50	95 : 5 (46)	90 : 10 (46)
<i>rac</i> - 38r	H	Me	<i>i</i> -Pr	<i>p</i> -OMeC ₆ H ₄	8.5	43	94 : 6 (37)	82 : 18 (52)
<i>rac</i> - 38s	H	Me	<i>n</i> -Bu	5-Indolo	8.5	54	96 : 4 (48)	98 : 2 (43)

properties of both the alkyne and chiral phosphinamide led to moderate but consistent yields (36–55%) and enantioselectivities, in some cases exceeding 99:1. This included the use of various heterocycles and alkyl chains on both starting materials. The reaction was also performed on achiral diaryl phosphinamide **38t** to explore any possible regioselectivity for which ring results in the benzo fusion (Scheme 15). The authors found that there was an almost 1:1 distribution between the two possible products with an excellent overall yield for the transformation.

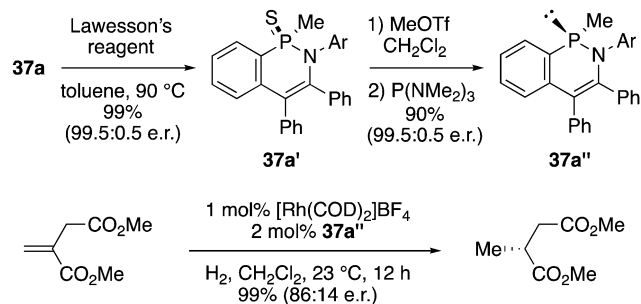
To investigate the application of this newly synthesized series as chiral phosphorus-based reagents for asymmetric catalysis, **37a** and **39** were added as a Lewis base (LB) to a reductive aldol condensation of chalcone **40** and benzaldehyde to furnish **41** (Scheme 16). Interestingly, the methyl-bearing **37a** gave not only a higher overall yield (95%) of product but also a dramatically improved enantioselectivity (96:4 e.r. of major diastereomer) compared to less selective **39**.

Continuing their investigation into asymmetric applications of their materials, the authors reduced **37a** from the P^V to P^{III} valence *via* thionation to **37a'** and reduction to **37a''**, which was

**Scheme 15** Reactivity of bis-aryl functionalized chiral phosphinamide. Ar = 3,5-(CF₃)₂C₆H₃.**Scheme 16** Asymmetric reductive aldol condensation of enone **40** and benzaldehyde using chiral benzo[*c*]-1,2-dihydro-1,2λ³-azaphosphinine additives as Lewis base (LB). Ar = 3,5-(CF₃)₂C₆H₃.

then used as a ligand for asymmetric hydrogenation (Scheme 17). This hydrogenation reaction proceeded with quantitative yield and decent enantioselectivity, suggesting promising future applications for azaphosphinines in the field of organic catalysis.

While these studies generated a large body of work that furthered the science of azaphosphinines considerably, the one potential drawback was the reliance on expensive Rh^I catalysts. In 2022, Shi and coworkers reported the design and application of a *in situ*-generated Co^{III} catalyst for the asymmetric heteroannulation of achiral phosphinamides **42** to benzo[*c*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxides **43**.⁵⁹ Similar to Cramer's initial work, the early substrates are diphenylphosphinamides



Scheme 17 Enantioselective reduction of **37a** and its use as a chiral ligand in an asymmetric hydrogenation reaction. Ar = 3,5-(CF₃)₂C₆H₃.

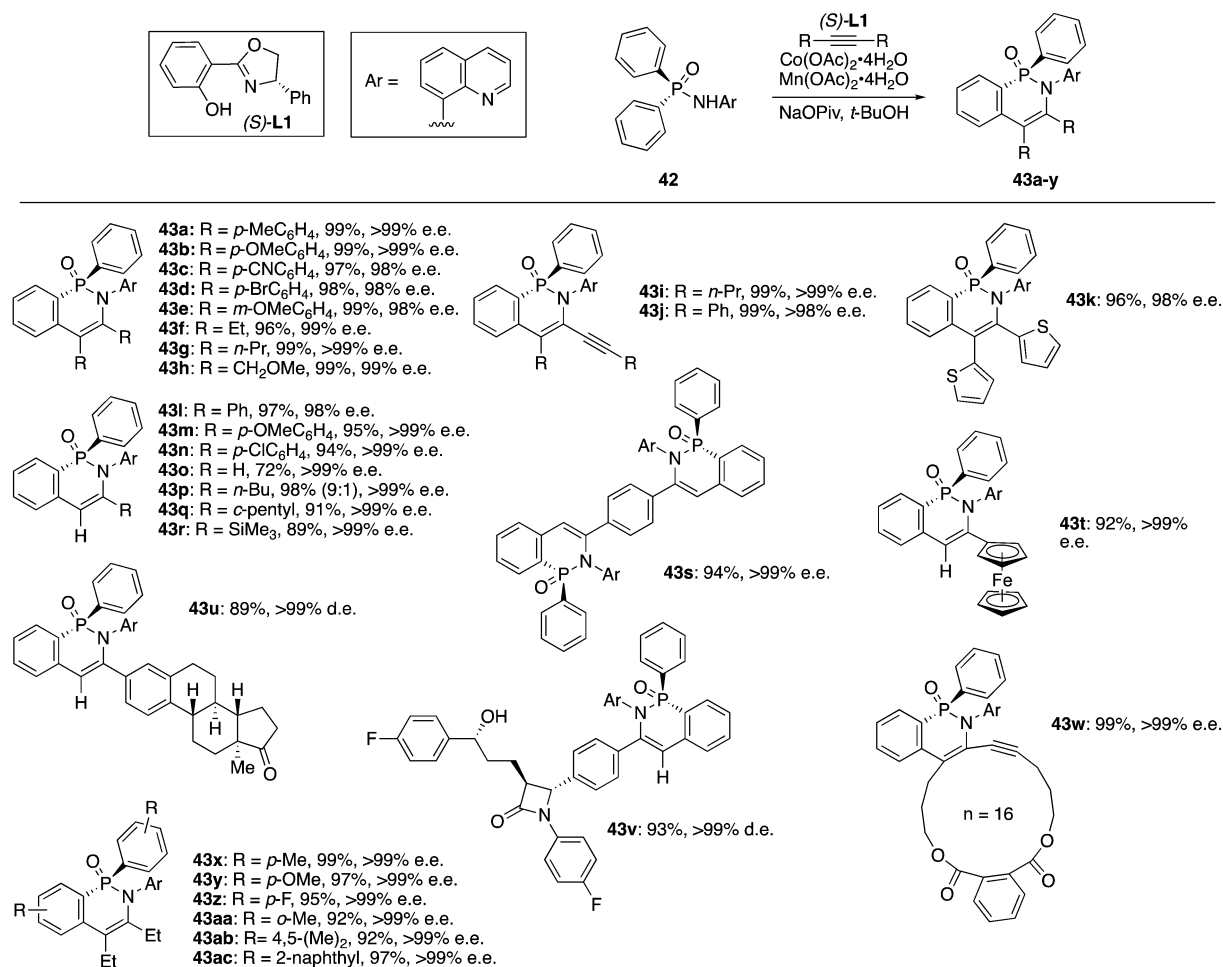
that rely on the enantiotopic aryl C–H bonds to generate a chiral intermediate.⁵⁷ Much of this work is dedicated to the logical design of an appropriate chiral ligand. Previous research suggested that monoanionic bidentate ligands were necessary for the *in situ*-generation of chiral Co^{III} active species.^{60,61} After screening a number of ligands, the authors eventually decided upon salicyloxazoline (Salox) (*S*)-**L1**. This ligand, along with the Co(OAc)₂·4H₂O precatalyst and Mn(OAc)₂·4H₂O oxidant, were applied to many

substrates where both the achiral phosphinamide and alkyne were varied to form **43** (Scheme 18). In the case of every substrate, the aryl substituent is an 8-quinolynyl motif.

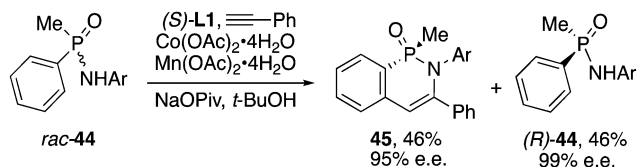
Shi and coworkers then performed a kinetic resolution experiment like Cramer, reacting a racemic mixture of compound **44** with phenylacetylene under conditions identical to the above trials (Scheme 19). The experimental results were excellent, with a near-quantitative overall yield and high enantioselectivity in forming just the (*S*)-enantiomer of the product **45** while ignoring the unreactive enantiomer of the starting phosphinamide (*R*)-**44**.

Shi and coworkers also showed that the heteroannulation would proceed when the alkyne was replaced with a variety of allene coupling partners **46** (Scheme 20), affording **47** in good to excellent yields with high e.e. values.

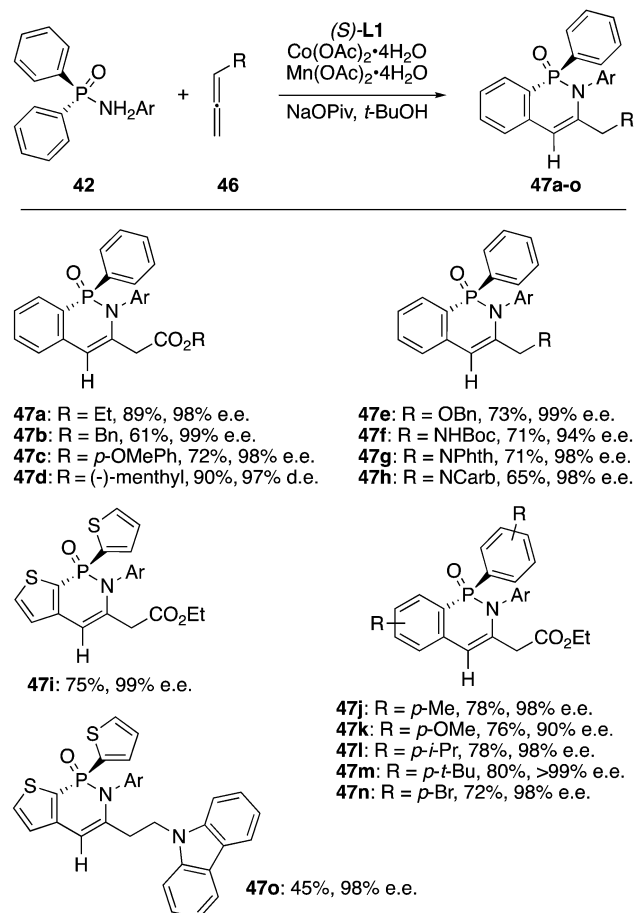
Very recently in 2023, Shi and coworkers reported similar transition-metal catalyzed [4+2] heteroannulation reactions on phosphanamines **48** and functionalized alkynes.⁶² There are several important distinctions that separate this work from earlier publications. The design of the starting material is quite different, notably that the phosphorus atom of the phosphanamines is trivalent and is oxidized to pentavalence during the



Scheme 18 Chiral C–H activation and heteroannulation using Co^{III} to afford **43**.

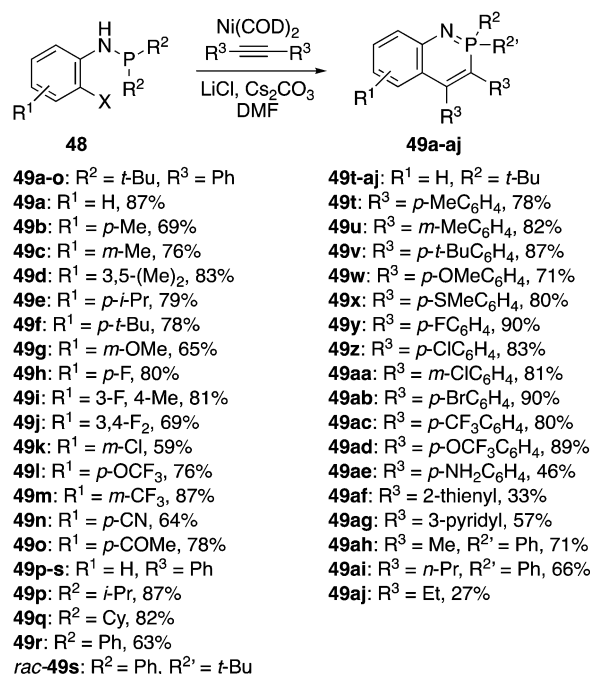


Scheme 19 Chiral resolution of phosphinamide **44** under standard reaction conditions. Ar = 8-quinoliny.



Scheme 20 Heteroannulation with allene coupling partners. Ar = 8-quinoliny.

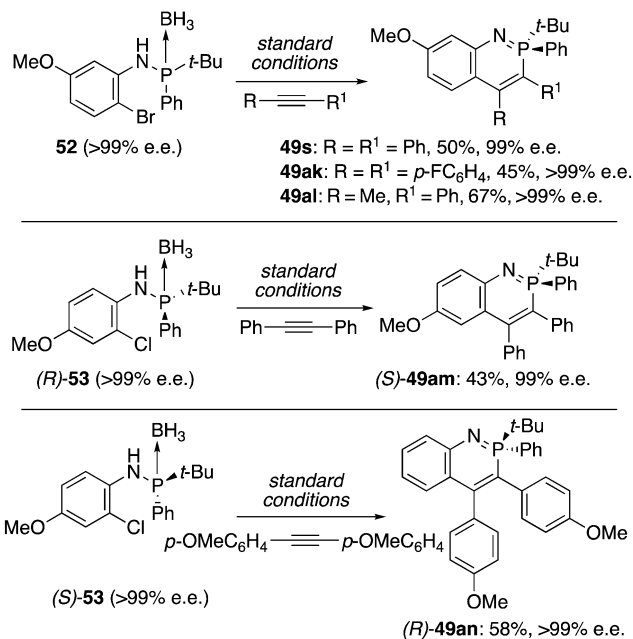
reaction. Secondly, the heteroannulation is conducted on *ortho*-halo-phosphanamines where the reactive bond is adjacent to the nitrogen instead of the phosphorus. This results in an inversion of the product atom geometry relative to the other species in similar publications. Although initially probed using tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) as the catalyst, screening studies revealed that $\text{Ni}(\text{COD})_2$ gave dramatically improved yields. Further optimization of conditions showed that stoichiometric amounts of LiCl aided in the reduction of the Ni catalyst, and that elevated temperatures were required for optimal yield. The main body of explored substrates comprised of achiral phosphanamines with two identical alkyl or aryl substituents to furnish benzo[*e*]-1,2λ⁵-azaphosphinines **49** (Scheme 21, top). The scope of



Scheme 21 Ni⁰-mediated heteroannulation to afford azaphosphinines **49** and **51**.

functionalized alkynes includes not only aryl but also heteroaryl and alkyl substituents, indicating the wide degree of functional group tolerance. A dual heteroannulation was also conducted on **50** to furnish **51** with good to excellent yields (Scheme 21, bottom).

Shi and coworkers continued to explore the heteroannulation of *P*-stereogenic phosphanamines as well by protecting the P^{III} as borane complexes **52** and **53**. The starting materials were deprotected *in situ* and proceeded with moderate yields but excellent enantioselectivities for retention of the geometry of the chiral center in heterocycles **49s** and **49ak-an** (Scheme 22). Unlike most of the azaphosphinines covered in this review, this paper does provide analysis of the photophysical properties of the molecules. Density functional theory (DFT) provided the computed HOMO and LUMO energy levels of **49a**, which showed a clear distinction between HOMO and LUMO localization, with the HOMO predominantly on the benzo[*c*]azaphosphinine core while the LUMO is distributed across all the aromatic rings. This reasoning led to the conclusion that the LUMO and subsequent photophysical properties could be modulated through the identity of the aryl-substituent. Six heterocycles with varied aryl-substituents were measured for their emission in both solution and the solid state (Table 2).



Scheme 22 Asymmetric [4+2] heteroannulation starting from chiral phosphanamines. Standard conditions of phosphanamine (1 equiv.), alkyne (2 equiv.), Ni(COD)₂ (10 mol%), LiCl (1 equiv.), Cs₂CO₃ (3 equiv.), DMF, 130 °C.

Table 2 Emission data for measured heterocycles **49**

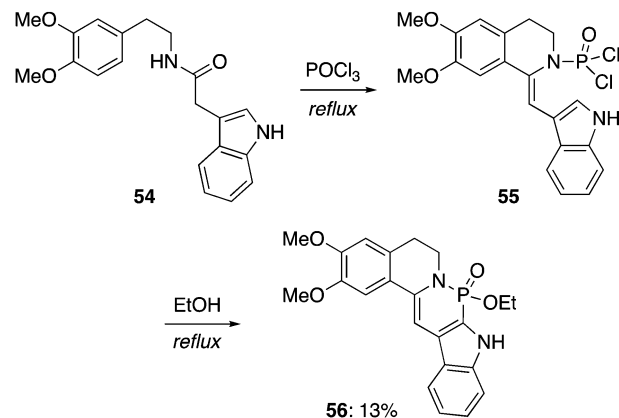
Substrate	Aryl group	λ_{em}^{ab} (nm)	ϕ^b (%)	λ_{em}^{ac} (nm)	ϕ^c (%)
49a	Ph	514	40	547	5
49t	<i>p</i> -MeC ₆ H ₄	530	30	539	4
49w	<i>p</i> -OMeC ₆ H ₄	518	11	536	4
49y	<i>p</i> -FC ₆ H ₄	515	90	543	13
49ab	<i>p</i> -BrC ₆ H ₄	561	66	560	7
49ac	<i>p</i> -CF ₃ C ₆ H ₄	551	24	582	6

^a Emission maxima upon excitation at maximum absorption wavelength. ^b Measured in solid state. ^c Measured in CH₂Cl₂.

While the solution-state quantum yields of the analyzed species were rather low (4–13%), the solid-state quantum yields were comparatively quite high with **49y** reaching 90%.

Intramolecular cyclization reactions

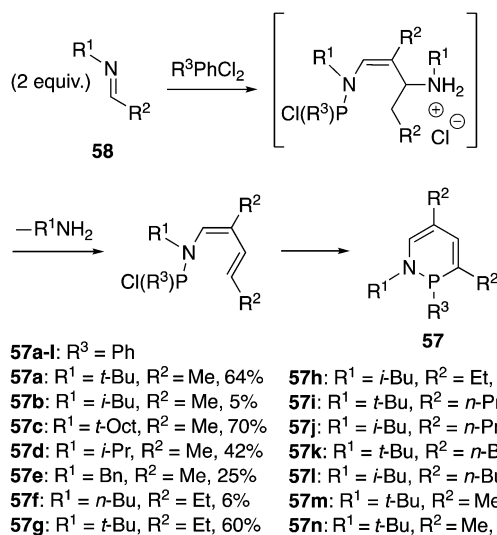
Intermolecular heteroannulation reactions, particularly those catalyzed by transition metals, have the decided benefit of extremely varied substrate scopes and in many cases enantioselectivity. However, in terms of published methods, intramolecular cyclization reactions to form benzo[*x*]azaphosphinine systems remains the most popular. Like cycloaddition reactions, these intramolecular cyclizations are generally transition-metal free. Besides this, lack of reliance on an added alkyne allows for different substitutions made directly on the PN-heterocycle such as *O*- and *N*-substitutions, as well as fusion to larger conjugated systems. In 1966, a very early example of an azaphosphinine synthesis from Shavel and coworkers was the intramolecular Bischler–Napieralski cyclization of indole derivative **54** via dichloro intermediate **55**, ultimately furnishing



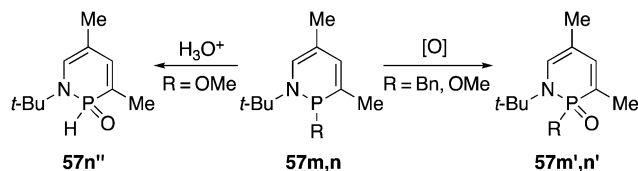
Scheme 23 Synthesis of indole-fused azaphosphinine 2-oxide **56**.

1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxide **56** (Scheme 23).⁶³ Due to the time period, there is little analytical data for **56**, but it is one of the earliest examples of a PN-heterocycle prepared by an intramolecular route.

Twenty years later, Bourdieu and Foucaud reported in 1986 a concise synthesis to several 1,2-dihydro-1,2λ³-azaphosphinines **57**.³³ This pathway was influenced by an earlier study from Nurtdinov *et al.* that prepared 2-oxo-1,2-azaphospholenes using dichlorophosphanes and *N*-butylimines.⁶⁴ In their adaption, Foucaud combined dichlorophenylphosphane with two equivalents of various alkyl imines **58** to furnish 1,2-dihydro-1,2λ³-azaphosphinines **57** (Scheme 24). Several of these compounds featuring different alkyl substituents were synthesized in low to very good yields, with the corresponding azaphosphole generated as a side product. In a follow-up study the authors incorporated much larger number of *N*-alkylimines.⁶⁵ Overall, variation of chain length led to little discernable trend in the yields of the products.



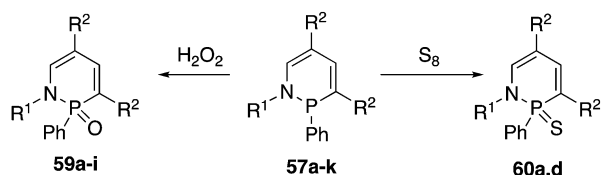
Scheme 24 Proposed pathway to 1,2-dihydro-1,2λ³-azaphosphinines **57**. No yield reported (*n.y.r.*).

Scheme 25 Oxidation and hydrolysis of heterocycles **57m** and **57n**.

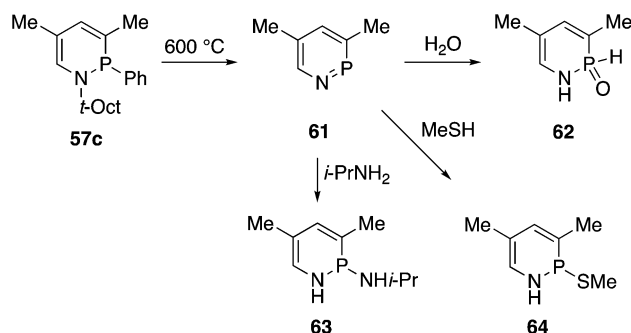
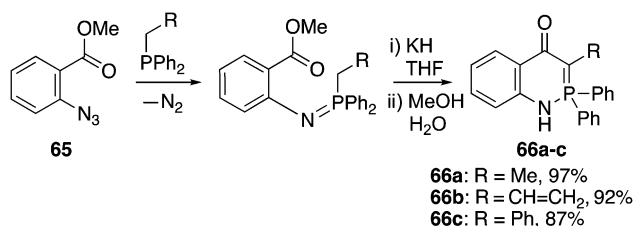
Bourdieu and Foucaud also performed several experiments with alternative phosphane and phosphinite reagents, namely $\text{P}(\text{CH}_2\text{Ph})\text{Cl}_2$ and $\text{P}(\text{OMe})\text{Cl}_2$, respectively; however, neither of the desired P^{III} heterocycles (**57m** and **57n**) were stable enough to be isolated and instead underwent oxidation in air to furnish the corresponding P^{V} oxo-compounds **57m'** and **57n'** (Scheme 25). Compound **57n** would also hydrolyze in the presence of acid to give **57n''**. Finally, the authors also showed how the P^{III} heterocycles could be intentionally oxidized to P^{V} using either H_2O_2 or S_8 to form the corresponding oxide **59** or sulfide **60** (Scheme 26).

A third paper from Bourdieu and Foucaud in 1987 rounded out the story by briefly describing a protocol for the conversion of the dihydro heterocycles to the corresponding fully conjugated azaphosphinine **61** (Scheme 27).⁶⁶ Pyrolysis of 1,2-dihydro-1,2λ³-azaphosphinine **57c** at 600 °C thermolytically cleaved the substituents on both the 1 and 2 positions; however, product **61** was highly electrophilic and added a variety nucleophiles (water, isopropylamine, or methylmercaptan) across the reactive $\text{P}=\text{N}$ bond, affording heterocycles **62–64**. Interestingly, both *P*-amino **63** and *P*-thio **64** also hydrolyzed to furnish **62** when exposed to water. No yields were reported for the reactions.

Also in 1987, Barluenga *et al.* published their work on the first example of benzo[*e*]-1,4-dihydro-1,2λ⁵-azaphosphinin-4-ones, which was achieved *via* intramolecular cyclization of *N*-aryl phosphazene (Scheme 28).⁶⁷ These imides were prepared *via* Staudinger reaction of methyl *o*-azidobenzoate **65** with various alkylidiphenylphosphanes. The phosphazenes were then cyclized with KH under mild temperatures to furnish the final heterocycles **66**. The authors found that the benzo[*e*]azaphosphinine resulting from a *P*-methylphosphazene was unstable and could not be isolated. Similar to previously discussed early works, this brief publication provides little-to-no subsequent analysis of the new compounds besides NMR chemical shifts. Despite that, the Barluenga study proved to be a key publication

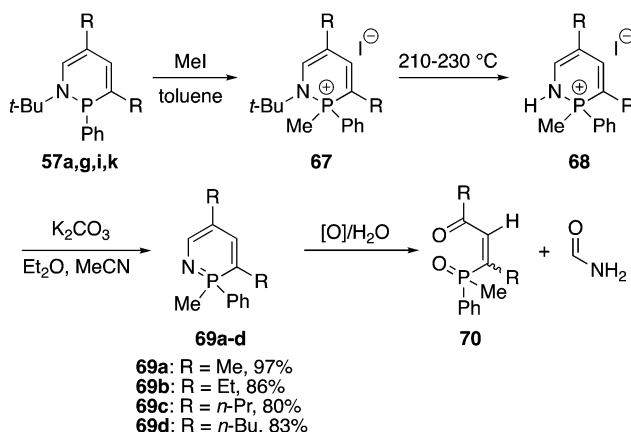


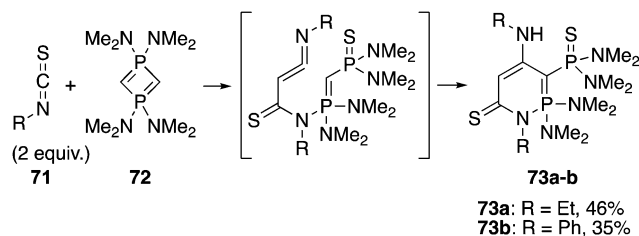
59a: $\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{Me}$, 83%
59b: $\text{R}^1 = i\text{-Bu}$, $\text{R}^2 = \text{Me}$, 78%
59c: $\text{R}^1 = t\text{-Oct}$, $\text{R}^2 = \text{Me}$, 86%
59d: $\text{R}^1 = i\text{-Pr}$, $\text{R}^2 = \text{Me}$, 75%
59e: $\text{R}^1 = \text{Bn}$, $\text{R}^2 = \text{Me}$, 70%
59f: $\text{R}^1 = n\text{-Bu}$, $\text{R}^2 = \text{Et}$, *n.y.r.*
59g: $\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{Et}$, *n.y.r.*
59h: $\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = n\text{-Pr}$, *n.y.r.*
59i: $\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = n\text{-Bu}$, *n.y.r.*
60a: $\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{Me}$, 49%
60d: $\text{R}^1 = i\text{-Pr}$, $\text{R}^2 = \text{Me}$, 44%

Scheme 26 H_2O_2 and S_8 oxidations of azaphosphinines **57**.Scheme 27 Thermolytic synthesis of 1,2λ³-azaphosphinine **61** and its dihydro products **62–64** from attack of various nucleophiles.Scheme 28 Synthesis of benzo[*e*]-1,4-dihydro-1,2λ⁵-azaphosphinin-4-ones **66**.

that opened the door for several additional reports to further develop the scaffold.

In 1991, Bedel and Foucaud published the oxidation of their previously prepared 1,2-dihydro-1,2λ³-azaphosphinines from P^{III} to P^{V} ,⁶⁸ building upon the knowledge gained from their thermolysis of these heterocycles.⁶⁶ Methylation of azaphosphinines **57** generated *P*-methyl azaphosphininium salts **67**, which afforded **68** after thermolysis at 210–230 °C (Scheme 29). This system was deprotonated under mildly basic conditions to furnish 1,2λ⁵-azaphosphinines **69** in good-to-excellent yields. Upon exposure to air and/or water, the azaphosphinines slowly decomposed to give one equivalent of formamide and the corresponding phosphane oxide **70**.

Scheme 29 Synthesis of 1,2λ³-azaphosphinine **69** and subsequent hydrolysis/oxidation.



Scheme 30 Phosphite and isothiocyanate cyclization into azaphosphinine **73**.

Fluck *et al.* published an entirely novel approach to the synthesis of 1,2λ⁵-azaphosphinines in 1995, exploring the reactions between isothiocyanates **71** and 1,1,3,3-tetrakis(dimethylamino)-1λ⁵,3λ⁵-diphosphite **72** (Scheme 30).⁶⁹ Depending on the molar ratio of starting materials used, exotic azaphosphinine derivatives **73** are furnished. Despite not having an apparent application, this synthesis stands as a unique example of reactivity to obtain the typical azaphosphinine core. The resultant heavily substituted 1,2λ⁵-azaphosphinines are notably stable with melting points near or at 200 °C.

The first example of benzo[*c*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxides were published by Tang and Ding in 2006.³⁷ Their goal was to explore the azaphosphinine analogues of isoquinolin-1-ones, which they termed phosphaisoquinolin-1-ones. To generate these species, the authors first synthesized a library of *o*-(1-alkynyl)phenylphosphonamidate **74**. These were prepared in two steps by chlorinating the starting *o*-(1-alkynyl)phosphonic acid monoester with thionyl chloride and subsequently aminating with various primary amines. The phosphonamidates were then cyclized in a Pd-catalyzed reaction to yield **75** (Table 3). Because this was the first reported instance of the P^V-NH intramolecular heteroannulation, a variety of transition metals and temperatures were investigated, revealing the use of PdCl₂(MeCN)₂ at 80 °C as optimal. Although, the reaction times varied from entry to entry, there was little notable effect on yield resulting from the R group

Table 3 Substrate scope of cyclization of **74** to afford **75**

R ¹	R ²	R ³	Product	Yield [%]
H	Ph	Bn	75a	80
H	Ph	H	75b	68
H	Ph	<i>n</i> -Pr	75c	72
H	<i>n</i> -Bu	Bn	75d	87
Cl	Ph	Bn	75e	85
Cl	Ph	<i>n</i> -Pr	75f	67
Cl	<i>n</i> -Bu	Bn	75g	85
Cl	<i>p</i> -EtC ₆ H ₄	Bn	75h	72
Cl	<i>p</i> -EtC ₆ H ₄	<i>n</i> -Pr	75i	70
Cl	<i>c</i> -propyl	Bn	75j	90
Cl	CH ₂ OMe	<i>n</i> -Pr	75k	65
OMe	Ph	Bn	75l	79

identities. One noted exception was for **75k** where only 15% yield was isolated under normal optimized conditions, but the addition of a few drops of AcOH led to the dramatically improved yield of 65%. The authors proposed that this was a result of an external proton source aiding the cleavage of the vinylpalladium intermediate and regeneration of the PdCl₂(MeCN)₂. For these reactions only the six-membered product was generated, which is consistent with a 6-*endo-dig* cyclization. A potential explanation for the regioselectivity of cyclization is that the long C-P and P-N bonds would favor the transition state that leads into the six-membered product. The authors studied the antitumor properties of **75** *in vitro*, noting at high concentrations these species had very high inhibition ratios of A-549 lung cells in SRB (sulforhodamine B) assay; however, this inhibition fell off dramatically at lower concentrations, so further analysis is warranted.

In 2008, Ding and coworkers published a follow-up study that now included added allyl halide **76** in stoichiometric excess.⁷⁰ This reaction yielded the same benzo[*c*]-1,2-dihydro-1,2λ⁵-azaphosphinine scaffold as previously observed but with a 4-allyl substitution leading to series **77** (Table 4). A screen of reaction conditions showed that with excess methyloxirane the desired product **77** was formed in very good yield, with **75** generated in small amounts. Increasing the equivalents of both methyloxirane and allyl halide improved the yield of **77** and decreased formation of **75**. The reaction is decidedly robust with a large functional group tolerance and good yields. Much like the previous entry from Ding, it appears that the electron density of the phosphonamidate starting material has little bearing on the yield of the product. This reaction also tolerates *N*-unsubstituted phosphonamidates, as is the case with **77b**.

Table 4 Cyclization and subsequent allylation of give azaphosphinines **77**

R ¹	R ²	R ³	R ⁴	X	Product	Yield [%]
H	Ph	Bn	H	Br	77a	90
H	Ph	H	H	Br	77b	69
Cl	Ph	Bn	H	Br	77c	92
Cl	Ph	<i>n</i> -Pr	H	Br	77d	87
Cl	<i>p</i> -EtC ₆ H ₄	Bn	H	Br	77e	88
Cl	<i>n</i> -Bu	Bn	H	Br	77f	82
OMe	Ph	Bn	H	Br	77g	85
H	Ph	Bn	Me	Cl	77h	85 ^a
H	<i>n</i> -Bu	Bn	Me	Cl	77i	78 ^a
Cl	Ph	Bn	Me	Cl	77j	86 ^a
Cl	Ph	<i>n</i> -Pr	Me	Cl	77k	81 ^a
Cl	<i>p</i> -EtC ₆ H ₄	<i>n</i> -Pr	Me	Cl	77l	83 ^a
H	Ph	Ph	H	Br	77m	83
Cl	Ph	Ph	H	Br	77n	80
OMe	Ph	Ph	H	Br	77o	78
H	Ph	CH ₂ CO ₂ Et	H	Br	77p	82
Cl	Ph	CH ₂ CO ₂ Et	H	Br	77q	85

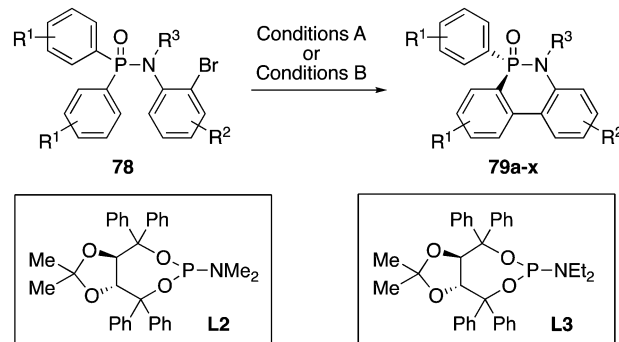
^a Products isolated as (*E/Z* = 77:23).

It is also worth noting that the reactivity of the system is selective for the allyl halide over the aryl halide even when both are the same (e.g., **77i-l**). The authors do note that the use of the substituted allyl chlorides (e.g., 3-chloro-1-butene) leads to an internal alkene in the final heterocycle with a consistent 77:23 distribution of *E* to *Z* isomers across all such products.

As with their previous work, the authors also tested the biological properties of nine derivatives of **77**. At a concentration of 20 $\mu\text{g mL}^{-1}$, the enzyme Src homology 2-containing phosphatase-1 (SHP-1) inhibition ratios varied from 20.2% (**77a**) to 54.3% (**77i**). The heterocycles were then tested against melanin-concentrating hormone receptor-1 (MCH-1R) with IC_{50} values varying from 3.78 (**77d**) to 10.23 μmol (**77e**). The benzo[*c*]-4-allyl-1,2-dihydro-1,2 λ^5 -azaphosphinine 2-oxides showed no MCH-1R activities and are reported in the publication as the first example of using phosphorus analogues of heterocyclic natural products as MCH-1R inhibitors. An in-depth screen of a variety of antagonists of MCH-1R by Wang and coworkers in 2008⁷¹ showed that of the derivatives of **75** and **77** tested, only **75a'** (Cl on C(4)) showed significant binding affinity ($K_i = 115.7 \text{ nmol L}^{-1}$) and potent antagonism ($K_B = 23.8 \text{ nmol L}^{-1}$). The authors note that the benzo[*c*]-2-ethoxy-1,2 λ^5 -azaphosphinine 2-oxide core may prove to be a powerful motif in MCH-1R binding in the future despite being structurally quite different from previously found MCH-1R modulators.

In 2015, Duan and coworkers and Ma and coworkers kicked off what would become a period of great activity for azaphosphinine chemistry.^{72,73} The two groups submitted and published their papers within a week of one another and the content of both is very similar, with some identical derivatives being prepared. These works were conceptual continuations of the studies of not only Lee⁵⁷ and Cramer^{38,58} but also the very early systems from Dewar⁴⁷ and Campbell,⁴⁹ with the aim being the generation of chiral, dibenzo[*c,e*]-1,2-dihydro-1,2 λ^5 -azaphosphinine 2-oxide species *via* transition-metal catalyzed C–H activation. Starting from achiral phosphinamide **78** (Scheme 31), one of the identical *P*-aryl substituents would be converted to a biphenyl derivative, generating a stereogenic phosphorus center. Interestingly, the two groups of authors screened the same exact pool of chiral phosphorus ligands and decided upon a ligand that only differed in chain length of the dialkylamino group. Whereas Duan used *N,N*-dimethyl ligand **L2**, Ma chose *N,N*-diethyl ligand **L3** and that their choices likely arise from the different reaction conditions, *i.e.*, Conditions A (Duan) *vs.* Conditions B (Ma) in Scheme 31. Cyclization of a variety of achiral phosphinamide **78** furnished the corresponding dibenzo[*c,e*]-1,2-dihydro-1,2 λ^5 -azaphosphinine **79** with both reactions showing excellent yields across the substrates studied. While the results suggest the conditions of Duan and coworkers were more consistent, Ma and coworkers used a wider substrate scope particularly in terms of *N*-substituents. Heterocycles **79b**, **79d**, **79e**, and **79f** were synthesized by both groups with Conditions B performing slightly better in the identical transformation.

Duan and coworkers also explored the generation of chiral phosphane oxides **80** from the P–N bond cleavage of **79** using



Conditions A (Duan)

79a-l: $\text{R}^3 = \text{Me}$

79a: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, 94%, 90% e.e.

79b: $\text{R}^1 = \text{H}$, $\text{R}^2 = p\text{-Me}$, 88%, 93% e.e.

79c: $\text{R}^1 = \text{H}$, $\text{R}^2 = p\text{-OMe}$, 80%, 91% e.e.

79d: $\text{R}^1 = \text{H}$, $\text{R}^2 = m\text{-F}$, 94%, 90% e.e.

79e: $\text{R}^1 = \text{H}$, $\text{R}^2 = m\text{-CF}_3$, 92%, 92% e.e.

79f: $\text{R}^1 = \text{H}$, $\text{R}^2 = p\text{-Cl}$, 88%, 93% e.e.

79g: $\text{R}^1 = p\text{-OMe}$, $\text{R}^2 = \text{H}$, 88%, 89% e.e.

79h: $\text{R}^1 = p\text{-Cl}$, $\text{R}^2 = \text{H}$, 87%, 91% e.e.^[a]

79i: $\text{R}^1 = p\text{-CF}_3$, $\text{R}^2 = \text{H}$, 91%, 91% e.e.^[a]

79j: $\text{R}^1 = o\text{-Me}$, $\text{R}^2 = \text{H}$, 62%, 85% e.e.

79k: $\text{R}^1 = 3,5\text{-(CF}_3)_2$, $\text{R}^2 = \text{H}$, 79%, 83% e.e.

79l: $\text{R}^1 = 3,5\text{-(CF}_3)_2$, $\text{R}^2 = m\text{-Me}$, 58%, 86% e.e.

79m: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = p\text{-OMeC}_6\text{H}_4$, 81%, 91% e.e.

Conditions B (Ma)

79b: $\text{R}^1 = \text{H}$, $\text{R}^2 = p\text{-Me}$, 99%, 95% e.e.

79d: $\text{R}^1 = \text{H}$, $\text{R}^2 = m\text{-F}$, 99%, 95% e.e.

79e: $\text{R}^1 = \text{H}$, $\text{R}^2 = m\text{-CF}_3$, 99%, 95% e.e.

79f: $\text{R}^1 = \text{H}$, $\text{R}^2 = p\text{-Cl}$, 98%, 95% e.e.

79n-u: $\text{R}^1 = \text{H}$

79n: $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Et}$, 94%, 89% e.e.

79o: $\text{R}^2 = \text{H}$, $\text{R}^3 = n\text{-Bu}$, 61%, 88% e.e.

79p: $\text{R}^2 = m\text{-Me}$, $\text{R}^3 = \text{Me}$, 72%, 92% e.e.

79q: $\text{R}^2 = p\text{-t-Bu}$, $\text{R}^3 = \text{Me}$, 99%, 97% e.e.

79r: $\text{R}^2 = p\text{-Ph}$, $\text{R}^3 = \text{Me}$, 68%, 93% e.e.

79s: $\text{R}^2 = p\text{-CN}$, $\text{R}^3 = \text{Me}$, 64%, 96% e.e.

79t: $\text{R}^2 = p\text{-CF}_3$, $\text{R}^3 = \text{Me}$, 83%, 96% e.e.

79u: $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Bn}$, 12%, 92% e.e.

79v: $\text{R}^1 = p\text{-Ph}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$, 90%, 95% e.e.

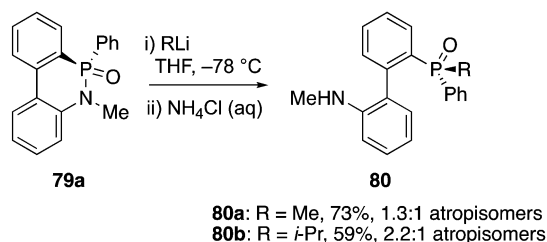
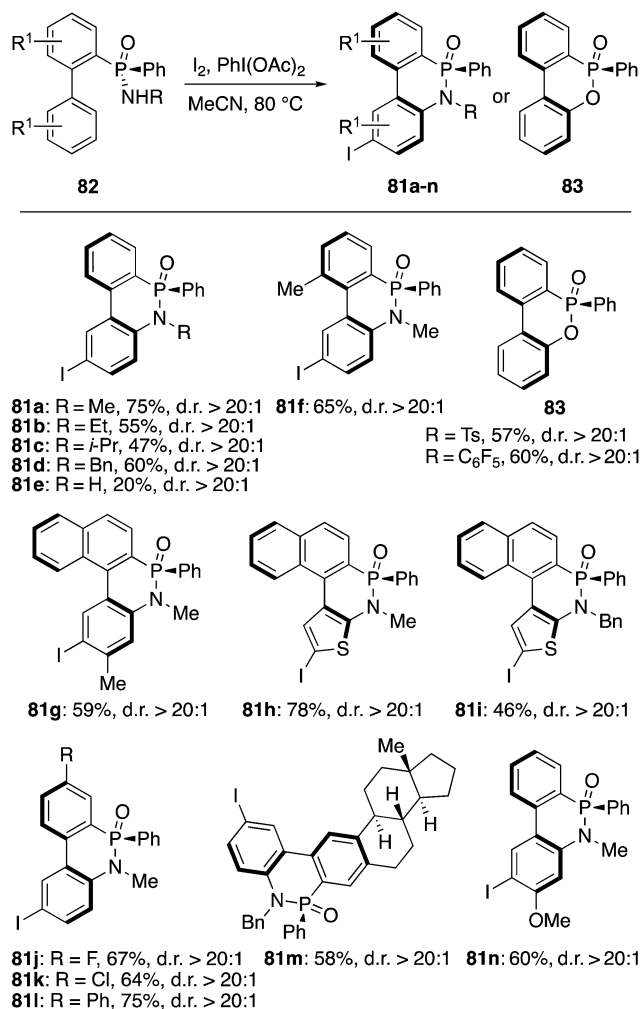
79w: $\text{R}^1 = p\text{-Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$, 92%, 96% e.e.

79x: $\text{R}^1 = m\text{-OMe}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$, 54%, 91% e.e.

Scheme 31 Palladium catalyzed C–H activated heteroannulation to furnish chiral azaphosphinines **79**. Conditions A: $\text{Pd}(\text{OAc})_2$ (5 mol%), **L2** (10 mol%), K_3PO_4 (1.5 equiv.), PivOH (30 mol%), toluene, 80 °C. Conditions B: $\text{Pd}(\text{dba})_2$ (8 mol%), **L3** (10 mol%), Cs_2CO_3 (1.5 equiv.), PivOH , (40 mol%), hexanes, 60 °C. ^a Reaction performed at room temperature.

MeLi , $i\text{-PrLi}$, and $t\text{-BuLi}$ (Scheme 32). The former two yielded nearly racemic mixtures of the alkyl addition product, whereas the $t\text{-BuLi}$ reaction resulted in a complex mixture of products that was not identified. This is a convenient route to chiral phosphane oxides that may find further use in catalysis.

In early 2017, Yang and coworkers published their work on the transition-metal free *P*-stereogenic dibenzo[*c,e*]-1,2-dihydro-1,2 λ^5 -azaphosphinine derivatives **81** (Scheme 33).⁷⁴ In the aim of making the cyclization more economical, the authors decided to investigate the potential for transition-metal free oxidative C–H activation instead. An added benefit of this system would be stability under ambient atmosphere. After screening a variety of oxidants, the authors settled on

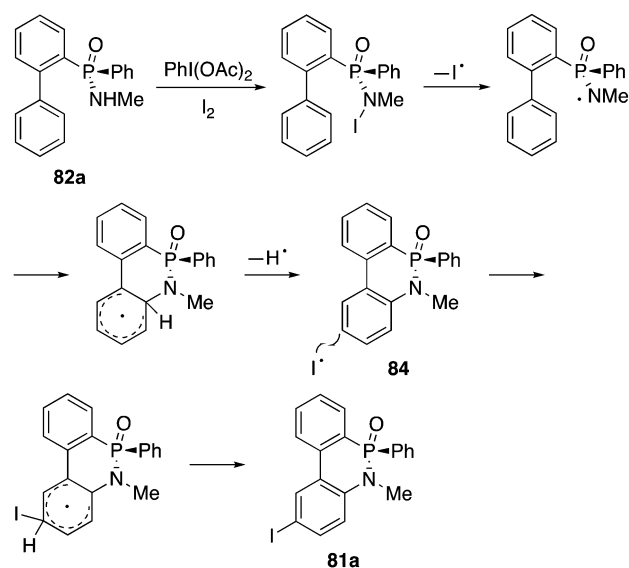
Scheme 32 P–N bond cleavage to furnish chiral phosphane oxides **80**.Scheme 33 Transition-metal free heteroannulation reaction to give aza-phosphinines **81**.

hypervalent iodine species PhI(OAc)_2 with added I_2 in MeCN at 80°C as the optimal conditions, which were applied to a library of phosphinamides **82** with various aryl and *N*-alkyl functional groups, giving the dibenzo[*c,e*]-8-iodo-1,2λ⁵-azaphosphinine 2-oxides **81**. They found that the reaction proceeded better with less sterically demanding *N*-substituents, but having any *N*-alkyl group (46–78% yield) worked better than a hydrogen (20% yield). Electron-withdrawing R-groups (e.g., tosyl or pentafluorobenzene) resulted in C–H hydroxylation and instead

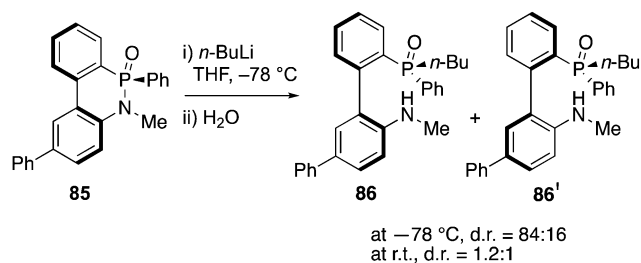
gave **83** as product in moderate yields. In every case, excellent diastereoselectivities for the *P*-stereogenic center and the axial chirality of the aryl linking unit were obtained for **81** and **83**. It was also observed that substitution of KBr for I_2 in the reaction furnished the corresponding 5'-bromo heterocycle but did not work with NaCl to yield the corresponding 5'-chloro species.

To probe the mechanism of their hypervalent iodine-mediated heteroannulation, Yang and coworkers attempted the reaction in the presence of radical scavengers 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and butylated hydroxytoluene (BHT). The addition of either inhibited the reaction. Next, a noniodinated analogue **84** was reacted with PhI(OAc)_2 and I_2 under standard conditions and the corresponding product **81a** was isolated. This led the researchers to conclude that the iodination step occurs after the annulation. Their proposed radical mechanism for the transformation is shown in Scheme 34. The reaction is initiated by the homolytic cleavage of a weak N–I bond to generate a radical species, which is subsequently trapped by the nearby arene. This is rearomatized *via* PhI(OAc)_2 to give electron-rich **84**, which can rapidly iodinate to furnish the final heterocycle **81a**.

Yang and coworkers showed that the aryl iodide generated during the heteroannulation could undergo typical cross-coupling reactions, providing examples of **81a** acting as a substrate in Heck, Suzuki–Miyaura, azidation, phosphination, and Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) ‘click’ reactions in moderate to excellent yields and the typical high degree of diastereoselectivity. Finally, to prove the existence of the axial chirality component in their system, the P–N bond of **85** was selectively cleaved *via* addition of *n*-BuLi at -78°C (Scheme 35). Once the rigidity of the aryl system was severed, racemization began, but at low temperatures the diastereomers **86** and **86'** were still detected, indicating axial chirality was



Scheme 34 Proposed mechanism for radical C–H activation heteroannulation and subsequent iodination.



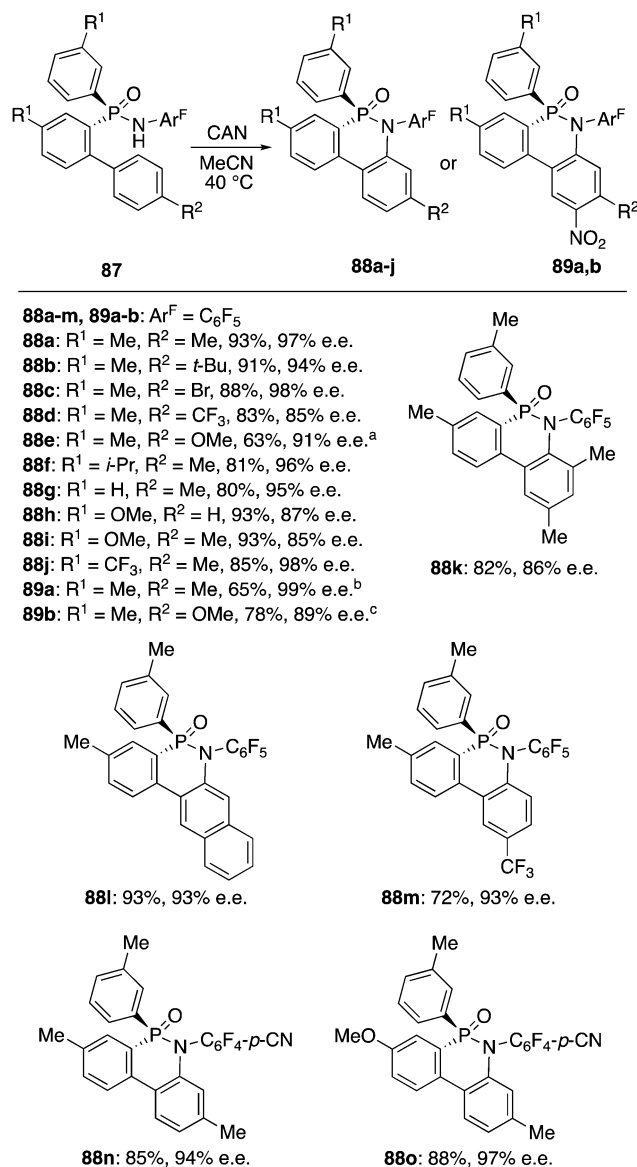
Scheme 35 Cleavage of P–N bond and racemization at different temperatures.

preserved with a persistent *P*-stereogenic center. It was proposed that the inflexibility of the fully cyclized heterocycle retains the axial chirality under ambient conditions.

Han and coworkers published in 2017 a study that took a somewhat different approach to the dibenzo[*c,e*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxide core.⁷⁵ As noted previously, the heteroannulation developed by Yang and coworkers did not tolerate electron-deficient *N*-protecting groups, the use of which resulted in oxygen substitution into the heterocycle. The authors proposed this lack of desired reactivity to be a result of difficulty in generating the necessary nitrogen radical. The Han study focused exclusively on the heteroannulation of *P*-stereogenic phosphinamide **87** with a strongly electron-deficient *N*-pentafluorophenyl group (Scheme 36). To circumvent the issues found by Yang, the authors found an alternative method of radical oxidative heteroannulation using 2.2 equivalents of Ce(NH₄)₂(NO₃)₆ (CAN) at 40 °C to generate the desired heterocycles **88** in excellent yield with high enantiomeric excess, with several examples being prepared on the gram scale. At increased temperature and additional equivalents of CAN, they could also generate a nitrated analogue **89**, much in the same way Yang and coworkers iodinated their molecules. Both electron-rich and electron-deficient substituents were tolerated in the R¹ position; however, incorporating an electron-donating methoxy group into the R² position resulted in a high yield of the nitrated byproduct. This side reaction could be inhibited by addition of 10 equivalents of water to the reaction.

Further experiments were conducted examining the post-synthetic modifications available to the azaphosphinine core. In the interest of making *P*-stereogenic bidentate ligands (**90**, **91**) for asymmetric catalysis, the P–N bond of **88a** could be cleaved by either LiMe or NaOMe (Scheme 37). Alternatively, conversion of **88a** to the sulfide **92** followed by treatment with MeOTf and then finally P(NMe₂)₃ gave the corresponding dibenzo[*c,e*]-1,2-dihydro-1,2λ³-azaphosphinine, namely the P^{III} species **93**, in high overall yield.

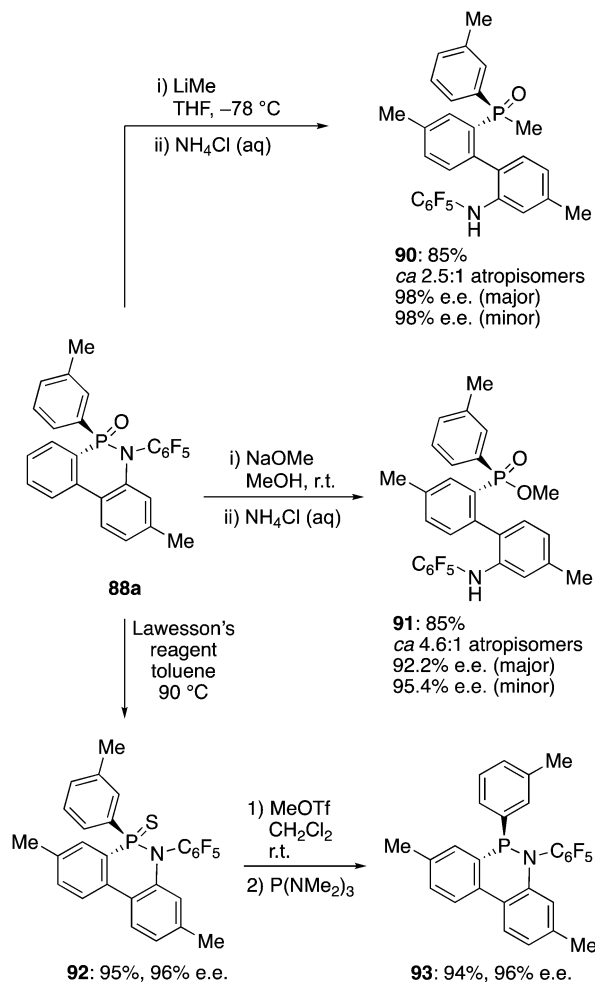
Heterocycle **88a** could be used as a chiral LB catalyst in the condensation of enone **94** and benzaldehyde to furnish **95** (Scheme 38), similar to the reaction effected by Cramer in Scheme 16.³⁸ While the reaction proceeded in excellent yield, the diastereoselectivity and enantioselectivity were considerably lower than what was previously reported. Regardless, these experimental results in concert with those of Cramer heavily



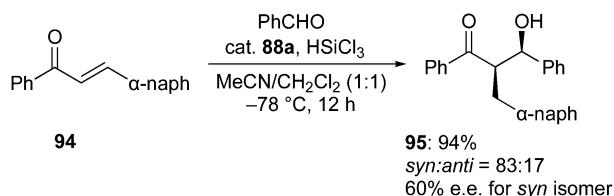
Scheme 36 CAN-mediated heteroannulation to afford **88**. ^a10 equiv. of water added. ^b5 equiv. of CAN added and conducted at 60 °C. ^cRun for 2 h.

suggest such *P*-stereogenic species could find excellent application in asymmetric catalysis upon proper optimization.

In 2015, our lab published the first of over a dozen research articles on benzo[*e*]-1,2λ⁵-azaphosphinines, benzo[*e*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxides, and related fused systems. The team had been studying arylethynyl scaffolds as anion receptors when they serendipitously discovered⁷⁶ that *ortho*-ethynylanilines react with P(OPh)₃ in the presence of pyridine at elevated temperatures to affect a heteroannulation incorporating an equivalent of the phosphite (Table 5). This was an attractive discovery as it proved to be a robust and comparatively mild route to the benzo[*e*]-1,2λ⁵-azaphosphinine core without the use of transition metals. The aniline starting materials **96** were also quite easy to diversify, with most being either commercially available or the products of one- or



Scheme 37 Post-synthetic modification of **88a** to furnish chiral acyclic species **90** and **91**, and P^{III} species **93**.



Scheme 38 Asymmetric catalyst **88a** used in condensation reaction.

two-step Sonogashira cross-couplings. The direct result of the cyclization was the *P*-diphenoxy species **97**; however, these in general rapidly hydrolyzed to the corresponding dihydro molecules **98** either intentionally or during purification, depending on the derivative.

Both azaphosphinines **97** and **98** display notable photophysical properties (Table 6). The authors comment that the emissive behavior is like that of the analogous carbostyryl scaffold, with the key differences being an overall redder emission, stronger solvatochromism, and more acidic N–H bond. Deprotonating **98** with DBU resulted in a strong bathochromic shift in emission of 22–124 nm. Following this initial

Table 5 Phosphite cyclization of *ortho*-ethynylanilines

R	Product	Yield 97 (%)	Yield 98 (%)
3,5-(CF ₃) ₂ C ₆ H ₃	a	— ^a	39
<i>p</i> -CNC ₆ H ₄	b	54	79
<i>p</i> -(CO ₂ Et) ₂ C ₆ H ₃	c	54	74
<i>p</i> -ClC ₆ H ₄	d	— ^a	80
Ph	e	45	72
<i>p</i> -MeC ₆ H ₄	f	63	82
<i>p</i> -OMeC ₆ H ₄	g	56	66
<i>p</i> -(NMe ₂)C ₆ H ₄	h	68	— ^a
<i>n</i> -Pen	i	— ^a	73
2-Pyridyl	j	71	31

^a Not isolated.

Table 6 Fluorescence properties of selected **97**, **98**, and deprotonated **98** in CHCl₃

Cmpd	97 λ _{em} (nm), Stokes shift (nm)	98 λ _{em} (nm), Stokes shift (nm)	98 + DBU λ _{em} (nm), Stokes shift (nm)
b	483, 83	430, 81, 4% ^a	554, 137, 41% ^a
c	473, 90	432, 81, 5% ^a	553, 151, 31% ^a
e	453, 80	418, 76	491, 127
f	450, 81	413, 72	482, 114
g	447, 78	410, 71	473, 107
j	467, 79	442, 79	514, 102

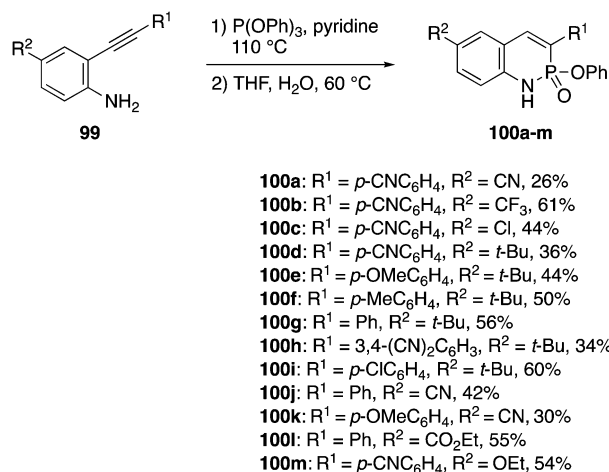
^a Photoluminescent quantum yield; other molecules not measured.

publication, several more papers were published on the benzo[*e*]-fused scaffolds,^{77–83} work that was summarized in an account in 2020.³⁹

The emissive data in Table 6 suggested that the photophysical properties of the resultant heterocycles are highly dependent on the electronic properties of the R-group. Knowing this, we broadened the substrate scope to include species with the group R² located para to the aniline nitrogen **99**, in turn yielding the more substituted series **100** (Scheme 39).⁸³ This facilitated a second handle with which to tune absorption and emission. It should be noted for nearly all subsequent studies that the pre-hydrolysis diphenoxy ‘imide’ form **97** was not isolated, but rather all yields reflect both the cyclization and hydrolysis steps. There is no recognizable preference between R-groups in the yields, as both electron-rich and -deficient substituents result in modest to good yields (26–61%).

Compared to the series **98**, the addition of the second R-group added a new dimension to the understanding of how the electronic groups modulate the photophysics (Table 7), as donor and acceptor pairs typically resulted in redder absorption and emission. This effect was more prominent when the electron-withdrawing group was in the R¹-position and the electron-donating group was at R² (e.g., **100k** vs. **100m**).

Given the sensitivity of the photophysical properties to simple functional group substitutions, we next investigated

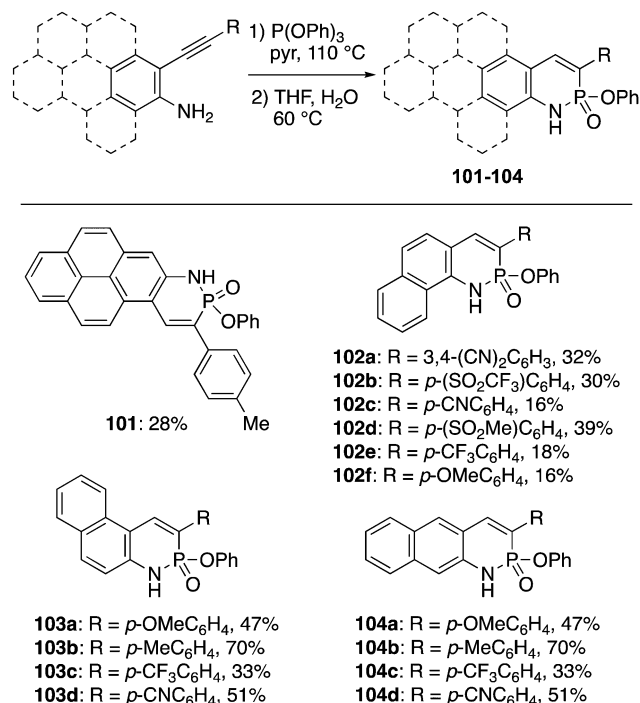
Scheme 39 Difunctionalized azaphosphinines **100**.

the effect of arene backbone extension as well. These included heterocycles featuring pyreno[2,1-*e*]-**101**, naphtho[1,2-*e*]-**102**, naphtho[2,1-*e*]-**103**, and naphtho[2,3-*e*]-**104** fusion patterns (Scheme 40).^{39,78–81}

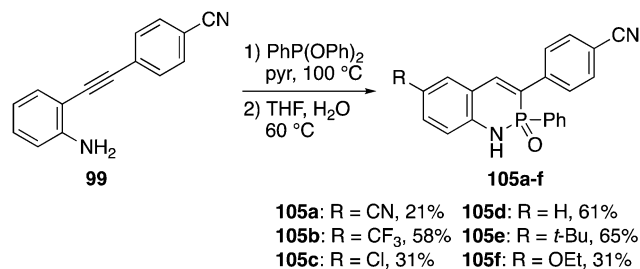
While simple modification of the aniline starting material could dramatically alter the final azaphosphinine topology, this did beg the question as to what impact, if any, would arise from alteration of the phosphorus substituent. By substituting PhP(OPh)_2 for P(OPh)_3 , running the cyclization under the same conditions generated the analogous benzo[*e*]-1,2-dihydro-2-phenyl-1,2λ⁵-azaphosphinine 2-oxides **105** (Scheme 41).⁷⁷

In addition to P substitution, we explored the inclusion of the N atom in another ring to furnish heterocycles **106** (Scheme 42).⁷⁹ Ethynylpyrene **107**, the precursor of **101**, was cyclized using PhP(OPh)_2 . The crude mixture was hydrolyzed and then iodinated under acidic conditions to give **108**, a *P*-phenyl analogue to **101**. Finally, Sonogashira cross-coupling followed by intramolecular cyclization of the alkyne with the NH group afforded π-extended and rigid **106** in good yields (63–87%).

Comparison of the photophysical properties of the extended fused-arene core heterocycles (**101–104**) and the *P*-phenyl heterocycles **105** and **106** (Table 8) with those of **100** showed that the different families cover a wide range of values in all tabulated categories. As a result of the large linearly fused core, the naphtho[2,3-*e*]-fused **104** exhibit comparatively large absorption coefficients and red-shifted emissions; however, they also display quite low quantum yields, and as a result,



Scheme 40 Scope of arene-core extended azaphosphinines.

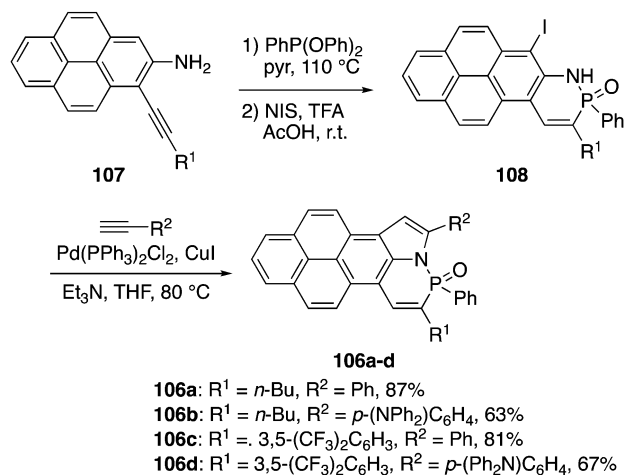
Scheme 41 *P*-phenyl substitution to afford azaphosphinines **105**.

possess consistently low brightness values. The two isomeric families of **102** and **103** display predictably similar absorption, emission, and Stokes shift values but deviate in terms of quantum yield. The ‘bent-down’ naphtho[1,2-*e*]-fused **102** family overall has a comparably high quantum yield with **102a** standing out dramatically at 93%. Conversely, the ‘bent-up’ naphtho[2,1-*e*]-fused **103** have significantly diminished quantum yield values that are comparable to the benzo-fused analogues **100**. Lastly, the *P*-phenyl derivatives **105** across the

Table 7 Photophysical properties of selected **100**^a

Cmpd	R^1	R^2	λ_{abs} (nm), ϵ ($\text{M}^{-1} \text{cm}^{-1}$)	λ_{em} (nm), ϕ^b (%)	Stokes shift (nm cm^{-1})	Brightness ($\epsilon \cdot \phi$)
100a	$p\text{-CNC}_6\text{H}_4$	CN	346, 12 000	430, 18	84/5600	2160
100e	$p\text{-OMeC}_6\text{H}_4$	$t\text{-Bu}$	344, 16 000	421, 6	77/5300	960
100f	$p\text{-MeC}_6\text{H}_4$	$t\text{-Bu}$	343, 14 000	424, 8	81/5600	1120
100k	$p\text{-OMeC}_6\text{H}_4$	CN	345, 15 000	471, 28	126/7800	4200
100m	$p\text{-CNC}_6\text{H}_4$	OEt	379, 25 000	490, 24	111/6000	6000

^a All values collected in CHCl_3 at room temperature. ^b Excited at 365 nm and collected using quinine sulfate (0.1 M H_2SO_4) standard.

Scheme 42 *P*-phenyl substituted PN-fused pyrenes **106**.Table 8 Photophysical properties of selected heterocycles **101–106**^a

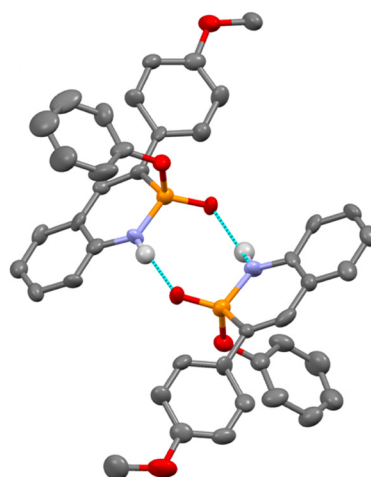
Cmpd	λ_{abs} (nm), ϵ (M ⁻¹ cm ⁻¹)	λ_{em} (nm), ϕ^b (%)	Stokes shift (nm cm ⁻¹)	Brightness ($\epsilon \cdot \phi$)
101	395, 26 000	465, 70	70/3800	18 000
102a	404, 12 000	493, 93	89/4500	11 000
102b	397, 5200	490, 80	93/4800	4100
103a	384, 13 000	461, 12	77/4300	1600
103b	375, 9800	450, 10	75/4400	980
104a	339, 27 000	464, 7	125/7900	1900
105a	348, 15 000	447, 76	99/6400	11 400
106b	431, 32 000	551, 62	120/5100	20 000
106d	437, 42 000	622, 23	185/6800	9700

^a Values collected in CHCl₃ at room temperature. ^b Excited at 365 nm and collected using a quinine sulfate (in 0.1 M H₂SO₄) standard.

board are improvements over their *P*-phenoxy counterparts **100**. It is proposed that the enhancement of their quantum yield and Stokes shift, as well as the overall red-shifting of emission, are all a result of the rigidification/reduced degrees of freedom of the scaffold and increased planarity of the aryl rings.

The pyreno[2,1-*c*]-heterocycle **101** enjoys both a large quantum yield and absorption coefficient, resulting in one of the highest brightnesses of the data set. Despite this, the small Stokes shift value presents a potential issue with self-quenching and could be modulated with further functional group tuning, *i.e.*, the **106** series. Among the azaphosphinines synthesized from our lab, compounds **106** stand in a league of their own for photophysical properties. While all of them exhibit comparatively high brightness and quantum yields, **106a** and **106d** exhibit the highest brightness value and most red-shifted emission tabulated, respectively. Fascinatingly, it was found that there was little-to-no charge transfer between excited pyrene units in mixtures of **106**, and the authors were able to show near-perfect solution-state white light emission in a mixture of **106a**, **106b**, and **106d**.⁷⁹

One of the unique benefits of the heteroannulation reaction studied by our lab is the hydrogen-bond donating N–H motif resulting from the hydrolysis. Up until this point, nearly all azaphosphinine systems discussed contain either *N*-alkyl or

Fig. 5 Representative *meso*-dimer of **98g**. Blue dashed lines represent hydrogen bonds between phosphonamide moieties. Nonparticipating hydrogen atoms omitted for clarity.

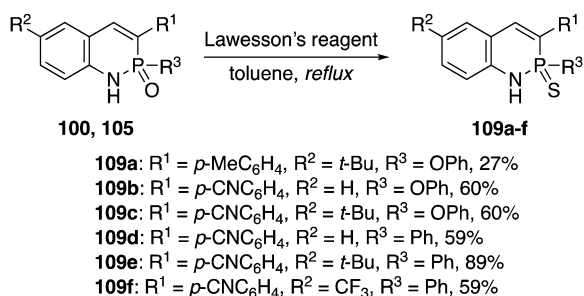
N-aryl groups (*e.g.*, **43**, **57**) or are sp² nitrogen centers with no possible proton (*e.g.*, **49**, **97**). As previously noted, **98** can be deprotonated to dramatic effect in terms of heterocycle emission. However, we also performed extensive studies in using that site as a hydrogen-bond donor as generally the molecules form homodimers that are oriented in a head-to-tail fashion (Fig. 5), as the highly polarized phosphonyl acts as hydrogen bond acceptor to complement the N–H bond donor.

With exception of the **104** and **106**, we have assessed all their azaphosphinines for homodimerization strength (K_{dim}). The experiments are conducted *via* variable concentration (VC) ¹H and ³¹P NMR experiments in water-saturated CDCl₃ at room temperature (Table 9). From the compiled data, it is noted that electron-deficient ring systems result in a higher dimerization constant (*e.g.*, **100j**), as the N–H bond is being further polarized, which in turn generates a stronger hydrogen bond donor. For series **100**, the identity of the R² group on the fused benzene

Table 9 VC ¹H and ³¹P NMR-measured dimerization constant for select azaphosphinines

Heterocycle	K_{dim}^a (M ⁻¹)	Heterocycle	K_{dim}^a (M ⁻¹)
98e	62	102b	306
98g	56	102e	84
100b	293	102f	77
100j	525	103a	206
100l	200	103b	150
101	179	105b	82

^a Values collected at room temperature in water saturated CDCl₃.

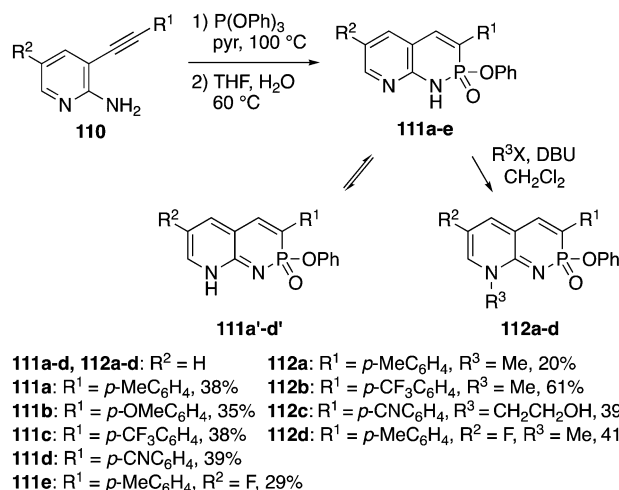


Scheme 43 Lawesson's reagent-mediated thionation.

core has a greater impact than the identity of the R¹ aryl substituent, which is thought to be a result of closer proximity to the hydrogen-bonding face. Lastly, the *P*-phenyl derivatives **105** consistently show lower dimerization values compared to their *P*-phenoxy **100** counterparts due to greater steric repulsion from proximity of the Ph group at the hydrogen-bonding face. Interestingly, X-ray crystallographic analysis of several dimers in the solid state mirror the solution data—those with the largest K_{dim} values exhibit the shortest intermolecular N...O distances (e.g., 2.768(2) Å for **100j**), and those with small K_{dim} values exhibit the longest N...O distances (e.g., 2.856(11) Å for **98g**) (Fig. 5).⁸³ In the solid state, nearly every heterocycle dimerizes as the *meso*-dimer with one *R*- and one *S*-enantiomer, although a few solid-state structures possess a polymeric zigzag ribbon structure (e.g., **100b**), likely due to steric issues within the structure.

In 2020, our lab outlined a protocol for the thionation of the benzo[*e*]-fused systems using Lawesson's reagent (Scheme 43).⁸⁴ The reaction was conducted on both *P*-phenoxy **100** and *P*-phenyl **105**. Comparison of the photophysical properties of the thionated heterocycles **109** to the previously synthesized oxo-analogues (Table 10) showed that there was no apparent change to the absorption profiles upon thionation; however, it was noted that there was a substantial reduction in brightness values and a consistent ~20 nm redshift of emission, which was attributed to a lower S₁ excited state level resulting from the weaker P–S bond.

Later entries on azaphosphinine chemistry from our lab focused primarily on the introduction of a second nitrogen atom in the fused ring. The pyrido[*e*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxides were synthesized in a similar manner using aminopyridine substrates **110** in place of anilines (Scheme 44). The first of these reports focused on a family of

Scheme 44 Pyrido-fused azaphosphinines **111** and their trapped tautomeric forms **112**.

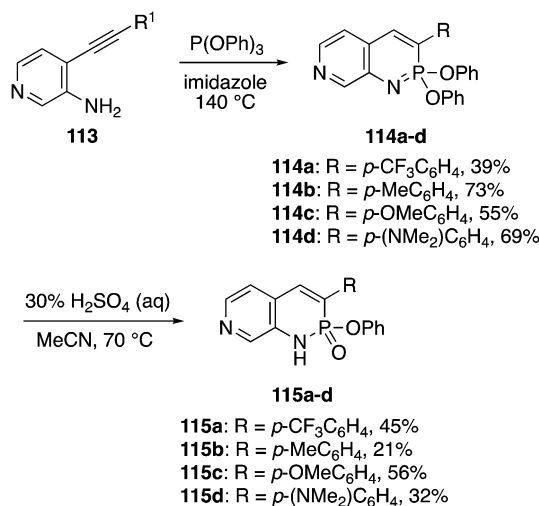
pyrido[2,3-*e*]-fused heterocycles **111** that displayed unexpected tautomerization capabilities,⁸⁵ as X-ray crystallography revealed that **111a-d** underwent a prototropic tautomerization in the solid state to assume the corresponding non-aromatic form **111'**. Only fluorinated **111e** did not undergo tautomerization in the solid state, which was attributed to the diminished basicity of the pyridyl nitrogen. Because of the regioselectivity of the alkylation from **111** to **112**, the quinoidal orientation of the core could be trapped, leading to stable samples that could be further analyzed in solution. A combination of photophysical, computational, and NMR experiments revealed that the tautomer only existed in the solid state, leading the authors to conclude that the heterocycles remained in their aromatic form in solution, regardless of environment, and tautomerized as a packing effect. Greater intermolecular forces resulting from solidification promoted the tautomerization to **111'** to allow the heterocycles to arrange in long coordination polymer-like chain of head-to-tail self-association. Computed relative free energies indicated that there is a 6.3 kcal mol^{−1} stabilizing effect for the observed tautomerization when the azaphosphinines is protonated, indicating how a close-knit hydrogen-bonding network may shift the tautomeric preference.

The second publication on pyrido[*e*]-1,2λ⁵-azaphosphinine 2-oxides focused on cyclization of 3-aminopyridines **113** to furnish pyrido[3,4-*e*]-1,2λ⁵-azaphosphinine **114** and corresponding dihydro **115** (Scheme 45), molecules that possessed a donor-acceptor conjugated system through the azaphosphinine scaffold.⁸⁶ By orienting the pyridyl nitrogen *via* this fusion pattern, a linear conjugation network was established from the electron-withdrawing pyridine to the aryl substituent of the azaphosphinine ring. After preparing several derivatives of **114** and **115** with varying degrees of electron donation from group R, assessment of the optoelectronic properties (Table 11) showed the presence of a low energy absorption band. The absorption coefficient of this peak increased linearly with electron donation and was attributed to an internal charge transfer (ICT) band, which became the dominant transition in

Table 10 Photophysical properties of selected **109**^a

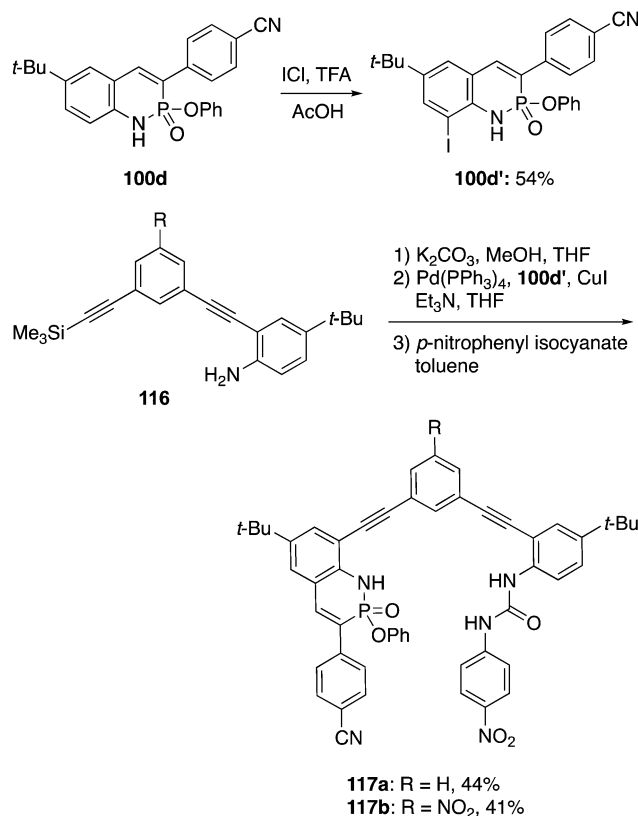
Cmpd	λ _{abs} (nm), ε (M ^{−1} cm ^{−1})	λ _{em} (nm), φ ^b (%)	Stokes shift (nm, cm ^{−1})	Brightness (ε·φ)
109a	348, 7180	444, 2	96, 6200	140
109b	352, 8600	462, 6	110, 6800	520
109c	373, 7950	492, 8	119, 6500	640
109f	357, 6840	466, 2	109, 6600	140

^a Values collected in CHCl₃ at room temperature. ^b Excited at 365 nm and collected using a quinine sulfate (in 0.1 M H₂SO₄) standard.

Scheme 45 Pyrido[3,4-*e*]-fused azaphosphinines.

the strong donor–acceptor pairs **114d** and **115d**. As a result of this intense conjugation, these heterocycles became the model system for the azaphosphinine scaffold as a charge transfer system. The emission spectra of **114d** and **115d** exhibited intense solvatochromism of 63 and 52 nm, respectively, in solvents ranging from toluene to DMSO. The pair also displayed comparatively high quantum yields with **115d** reaching 90%, likely due to the rigidity of the scaffold in the quinoidal ICT state.

In 2019, our lab took advantage of the hydrogen-bond donating and accepting ability of **100** by incorporating an azaphosphinine group into a supramolecular receptor for binding hydrogen sulfate (HSO₄[−]).⁸² HSO₄[−] is typically seen as a contaminant in agricultural and industrial fields.⁸⁷ Oxoanions in general make poor guests in anion host–guest complexes because of their mix of hydrogen-bond acceptors and donors as well as relatively oblong or tetrahedral geometries when compared to more spherical guests like halides. The nonplanar alignment of the hydrogen-bond accepting P=O and hydrogen bond donating N–H provides a unique and complementary pocket for the non-spherical HSO₄[−] anion. In this instance a stronger host–guest interaction results when compared to a more planar receptor such as an analogous bis-urea species.^{88–91} To prepare this new host, **100d** was iodinated to yield **100d'** (Scheme 46). This was attached to one of two aryl-ethynyl arms (**116**) *via* Sonogashira cross-coupling followed by urea formation to ultimately generate receptors **117**. This receptor class

Scheme 46 Synthesis of azaphosphinine-based anion receptors **117**.

not only recognized HSO₄[−] selectively over all other competing anions (Table 12) but could also be recycled for further use by washing the host–guest complex in aqueous media. This high level of selectivity for the HSO₄[−] anion (~40 : 1 for **117b**) results not only from the tetrahedral phosphorus center but also the mix of hydrogen bond donors and acceptors in the azaphosphinine core that maps ideally to the mix of donors and acceptors in HSO₄[−] (Scheme 46).

Very recently, our lab published work describing the application of benzo[*e*]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxides for cellular imaging.⁹² Use in cellular imaging is often a long-term goal for small molecule fluorophores. While this field is typically dominated by more traditional dyes (*e.g.*, coumarins, xanthenes, cyanines *etc.*),^{93–95} we envisioned the easily functionalized and emissive azaphosphinines our lab has developed as promising candidates as well. Initial studies proved that **118** (Fig. 6) was not only cell permeable at 0.5% DMSO in water but

Table 11 Photophysical properties of selected **114** and **115**^a

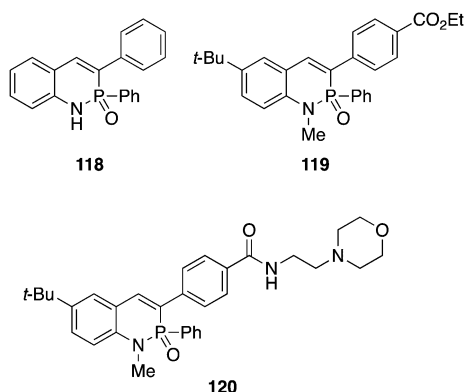
Cmpd	High-energy λ _{abs} (nm), ε (M ^{−1} cm ^{−1})	Low-energy λ _{abs} (nm), ε (M ^{−1} cm ^{−1})	λ _{em} (nm), ϕ ^b (%)	Stokes, shift ^c (nm, cm ^{−1})
114a	295, 15 800	390, 7200	475, 22	85, 4590
114b	310, 14 000	385, 7700	459, 9	74, 4190
115c	331, 14 000	351, 13 400	415, 45	64, 4390
115d	330, 4500	405, 21 000	489, 90	84, 4240

^a Values collected in CHCl₃ at room temperature. ^b Excited at 365 nm and collected using standards of quinine sulfate (in 0.1 M H₂SO₄) and anthracene in EtOH. ^c Calculated from low-energy ICT band.

Table 12 Association constants (K_a , M^{-1}) of receptors **117** with various anions in 10 vol% DMSO- d_6 /CDCl₃ at room temperature

Anion	117a	Relative affinity ^b	117b	Relative affinity ^c
HSO ₄ [−]	1420 (1480)	1	9600 (10 500)	1
NO ₃ [−]	40 (30)	0.028	105 (100)	0.011
Cl [−]	200	0.14	260	0.027
Br [−]	30	0.021	75	0.008
I [−]	— ^d	0	20	0.002
ClO ₄ [−]	— ^d	0	— ^d	0

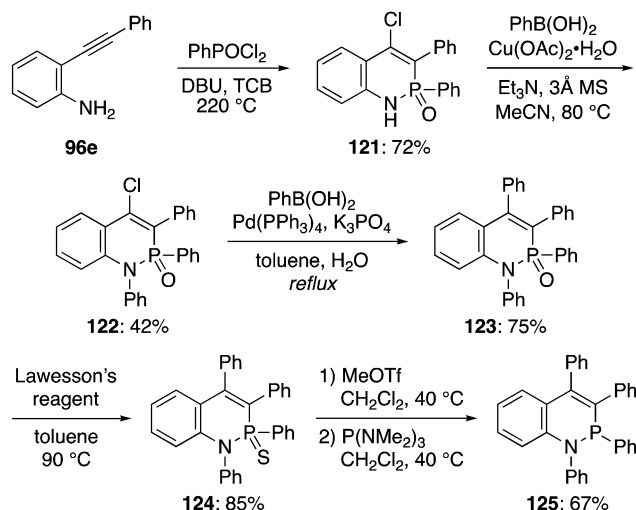
^a 1:1 binding fit. All reported association constants represent the average value from triplicate titrations. The values derived from ³¹P NMR titrations are given in parentheses. Uncertainties less than 15%. All anions used as TBA salts. ^b Relative to the ¹H NMR titration derived K_a of **117a**-HSO₄[−]. ^c Relative to the ¹H NMR titration derived K_a of **117b**-HSO₄[−]. ^d No binding or too weak to be quantified.

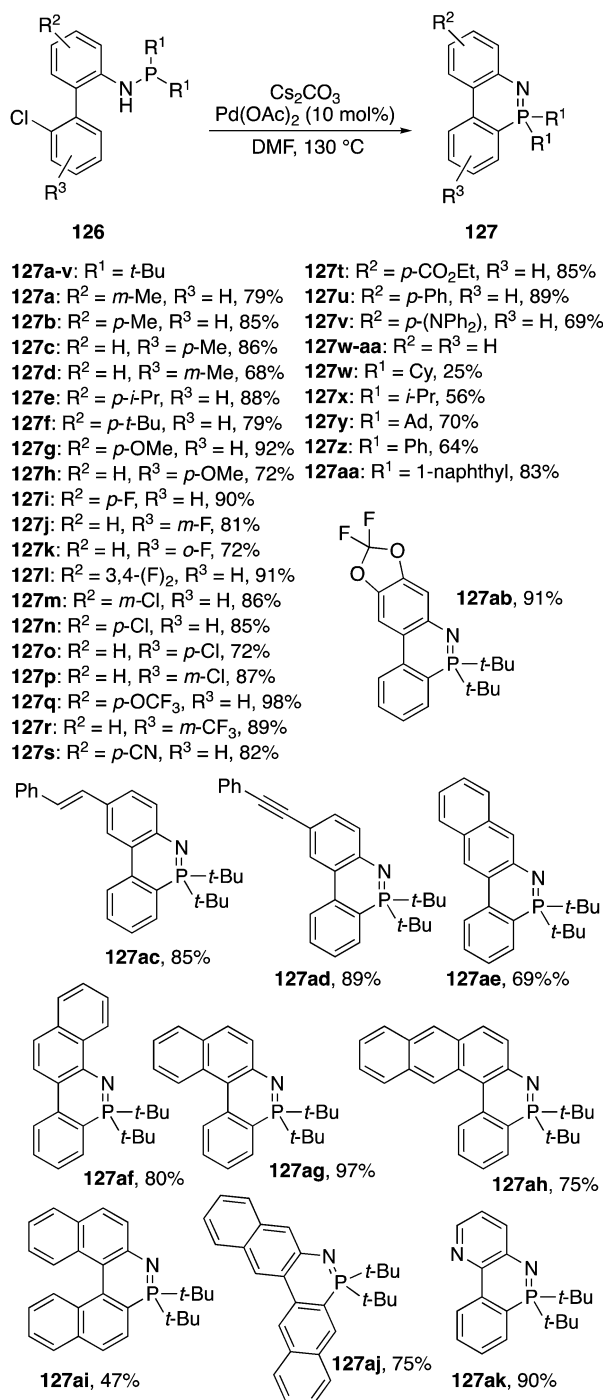
**Fig. 6** Benzo[e]-1,2-dihydro-1,2λ⁵-azaphosphinine 2-oxide cellular imaging dyes.

also maintained its weak emission ($\lambda_{em} = 452$ nm, $\phi = 23\%$) inside HeLa cells. Encouraged by this initial result, we developed successive generations **119** and **120**. Molecule **119** introduced both *N*-methyl substitution, which decreased pH sensitivity, and an aryl ester functional handle, which red-shifted the emission ($\lambda_{em} = 499$ nm, $\phi = 23\%$). Cytotoxicity measurements taken of **119** in HeLa cells suggested negligible cytotoxicity after 30 min in concentrations up to 150 μ M. The next iteration of the initial cell dyes, **120**, was designed with the addition of a morpholine appendage for sub-cellular targeting, as the morpholine group is commonly used for lysosome targeting due to its basic nature.⁹⁶ While **120** had almost the exact same emission as **119**, the quantum yield was significantly higher ($\lambda_{em} = 500$ nm, $\phi = 50\%$). To test specific subcellular localization of **120**, three different concentrations (1, 3, and 5 μ M) were co-incubated with 50 nM LysoTracker Deep Red in HeLa cells. The colocalization fidelity was measured using the Pearson correlation coefficient, revealing moderate colocalization for the three concentrations with Pearson coefficients of 0.49, 0.61, and 0.65 respectively. The success of this experiment was showing the cell permeability, lack of cytotoxicity, and broad pH stability range in the azaphosphinine core, suggesting future work could be done to further optimize successive generations of azaphosphinine dyes with subcellular targeting capabilities.

In 2021 Park and coworkers disclosed the preparation of a highly substituted benzo[e]-1,2λ³-azaphosphinine following a similar synthetic thread to previous publications, cyclizing *o*-(phenylethynyl)aniline **96e** with phenylphosphonyl dichloride (PhPOCl₂) under basic conditions at extremely high temperature (Scheme 47).⁹⁷ After screening a variety of bases, using 0.5 equivalents of DBU in 1,2,4-trichlorobenzene (TCB) furnished the desired product **121** good yield. Installation of two more phenyl substituents *via* Chan-Lam and Suzuki cross-coupling reactions gave **122** and **123**, respectively. Finally, to reduce the system from P^V to P^{III}, **123** was first thionated with Lawesson's reagent leading to **124** and then lastly methylated with MeOTf followed by P(NMe₂)₃ yielding **125**. Unlike its carbocyclic analogue tetraphenylnaphthalene (TPN), X-ray crystallographic analysis of **125** showed all four phenyl substituents were perpendicular to the core, indicating poor conjugation through the whole system; nonetheless, cyclic voltammetry of **125** revealed a diminished HOMO–LUMO energy gap compared to TPN (2.75 vs. 3.83 eV).

A recent addition to this field comes from Deng *et al.* in 2022, which took a new approach to the Pd-catalyzed route to dibenzo[*c,e*]-1,2λ⁵-azaphosphinines.⁹⁸ Instead of the typical approach, which until this point has involved P^V starting materials that are then incorporated into the final azaphosphinine, this publication used P^{III} phosphanamines **126**. Much like the similar work from Shi and coworkers⁶² published in 2023, the trivalent phosphorus starting materials are oxidized to the pentavalent state during the heteroannulation. However, unlike Shi and coworkers the reaction explored in this work did not involve any intermolecular condensations or additions to furnish the final azaphosphinines. Instead, halide functional handles on the biphenyl substituent of the phosphanamines were used to close the azaphosphinine ring and generate a series of dibenzo[*c,e*]-1,2λ⁵-azaphosphinines **127** (Scheme 48). In terms of substrate scope, Deng *et al.* first explored achiral phosphanamines with identical *P*-substituents. They synthesized a wide library of **127** containing functional

**Scheme 47** Synthesis of azaphosphinine **125**.

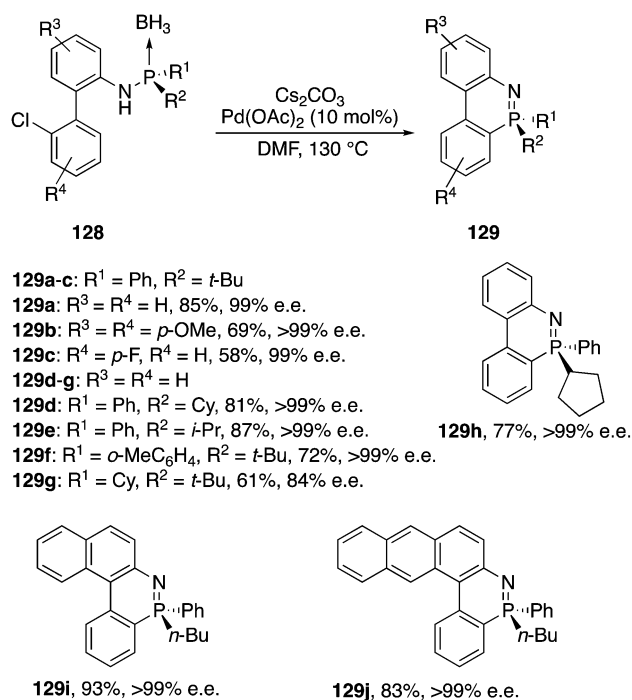


Scheme 48 Pd-catalyzed heteroannulation of achiral phosphanamines **126** to furnish dibenzo[*c,e*]-1,2λ⁵-azaphosphinines **127**.

groups of varying electronic character in the biphenyl backbone (**127a-w**) including alkenyl, alkynyl, heteroaromatic, and acene usions. Despite the wide variety of biphenyl substituents, the only derivative that saw a drop in yield from the usual 68–92% range was the binaphthyl derivative **127ai**. Next, several *P*-substituents were tried (**127w-aa**). It was noted that less sterically hindered groups such as cyclohexyl or *i*-Pr resulted in diminished yields.

Next, Deng *et al.* decided to investigate the stereospecificity in their heteroannulation. First a library of chiral phosphanamines were isolated *via* HPLC, then these enantioenriched starting materials were protected by complexing with borane to furnish **128**. These chiral complexes were then subjected to the same heteroannulation conditions developed previously to ultimately yield **129** (Scheme 49). In almost every substrate used, the chiral heteroannulation resulted in an excellent e.e. of > 99%. The extremely high and consistent stereoretention in such a comparatively simple system is very promising for future directions. Retention of stereocenters when converting directly from an acyclic to cyclic phosphorus species is a useful tool in the development of targeted phosphorus heterocycles, azaphosphinine or otherwise.

Deng *et al.* continue to note that **127** are quite emissive and display both solution and solid-state fluorescence with high quantum yields, with **127s** especially exhibiting 77% in CH₂Cl₂. Due to the range of λ_{em} in **127**, the authors calculated the frontier molecular orbitals of their dibenzo[*c,e*]-1,2λ⁵-azaphosphinines scaffold to determine what regions made the highest contributions to the HOMO and LUMO. Interestingly, it was found that C(2), located *para* to the nitrogen atom made the highest contribution to the HOMO and none to the LUMO. Conversely, C(9) located *para* to the phosphorus provided the opposite effect. The consequence of these contributions is represented in the photophysical properties of **127s** vs. **127r**. In the former, the electron-withdrawing nitrile lowers the energy of the HOMO, blueshifting the emission (450 nm), while the energy of the LUMO is lowered in the latter due to



Scheme 49 Retention of stereogenic *P*-center in heteroannulation of phosphanamine **128**.

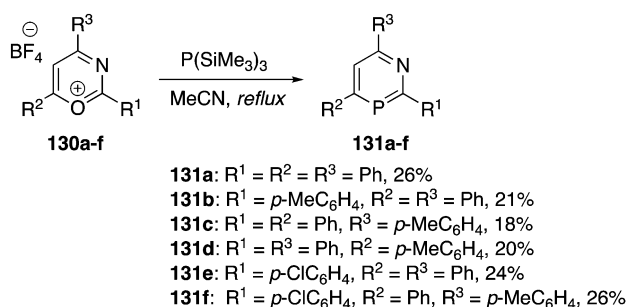
the trifluoromethyl substituent, leading to a redder emission (505 nm).

1,3-Azaphosphinines

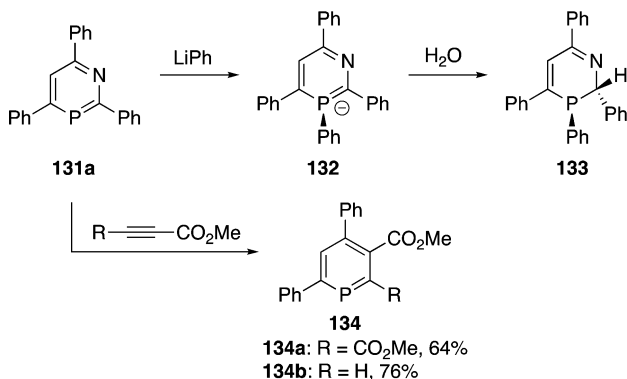
Heteroatom exchange

1,3-Azaphosphinines are significantly less studied than their 1,2-azaphosphinine counterparts, yet there are still several papers exploring their preparation and post-synthetic modification.⁹⁹ A vast majority of the methods used to prepare the 1,3λ³-azaphosphinine motif begin with a nitrogen-containing heterocycle to which a phosphorus atom is then added. One of the most direct and earliest examples of this was shown by Märkl and Dorfmeister in 1987.¹⁰⁰ Building off work forming 1,3-azaphospholes, they converted a series of triaryl-1,3-azapyrilium tetrafluoroborate salts **130** into the respective 1,3λ³-azaphosphinine products **131** in the presence of tris(trimethylsilyl)phosphane in modest yields (Scheme 50).^{101,102}

Treating the 2,4,6-triphenyl derivative **131a** with phenyl lithium added a phenyl group to the phosphorus center to afford phosphinyl anion **132**, and subsequent protonation by water gave non-aromatic 2,3-dihydro-1,3λ³-azaphosphinine **133** (Scheme 51). Alternatively, **131a** could react as a diene in a [4+2] cycloaddition with either DMAD or methyl propiolate followed by cycloreversion to extrude benzonitrile, forming phosphinines **134a** or **134b**, respectively, in good yields.



Scheme 50 Conversion of azapyrilium tetrafluoroborate salts to 1,3λ³-azaphosphinines **131**.



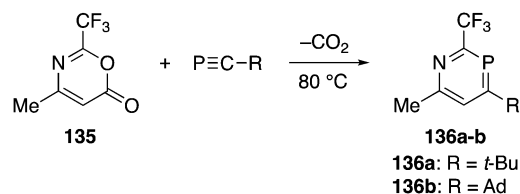
Scheme 51 Probing the reactivity of azaphosphinine **131a**.

Pericyclic/cycloadditions

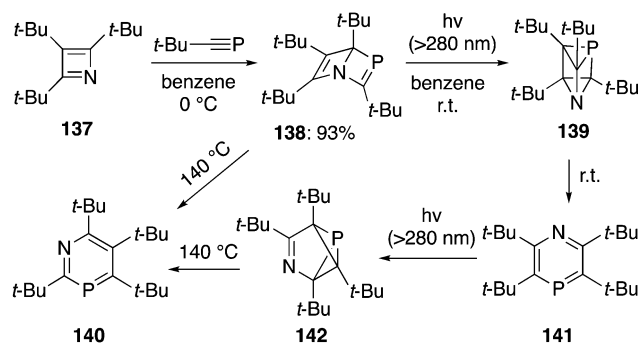
About the same time as Märkl's study, Appel *et al.* showed, also in 1987, that reaction of α-pyrone analogue **135** with two different phosphalkynes resulted in formation of 1,3λ³-azaphosphinines **136** (Scheme 52)¹⁰³ via Diels–Alder reaction and subsequent evolution of CO₂ gas. Yields were not reported for this reaction. While a brief study, it laid the groundwork for many future works by proving that the 1,3λ³-azaphosphinine moiety can be synthesized, isolated, and spectroscopically characterized. Specifically, several examples follow the cycloaddition/cycloreversion method instead of the above-mentioned heteroatom exchange, likely owing to synthetic flexibility.

In 1988, Regitz and coworkers explored the reactivity of tri-*t*-butylazete **137** and showed the molecule could undergo [4+2] cyclization with (2,2-dimethylpropylidene)phosphane to generate Dewar benzene-like **138** in very good yield (Scheme 53).¹⁰⁴ The authors then explored the reactivity of **138** upon exposure to heat and light, which isomerized to form prismane **139** and 1,3λ³-azaphosphinine **140**, respectively. Interestingly, prismane **139** slowly rearranged to 1,4λ³-azaphosphinine **141** at room temperature, which could then be irradiated to form azaphosphabenzvalene **142** that also aromatizes to **140** upon heating.¹⁰⁵ These unusual transformations all resemble those observed for the purely hydrocarbon benzene valence isomers (CH)₆.¹⁰⁶

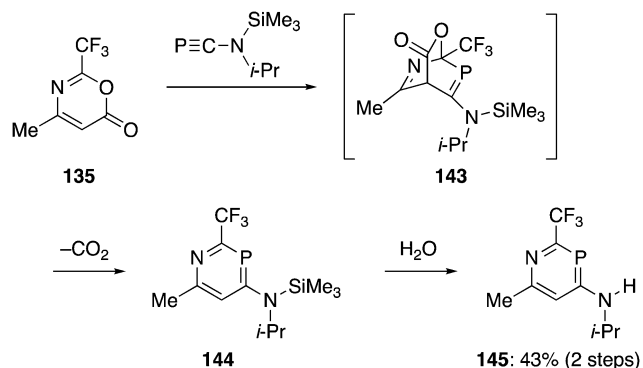
The next entry into the family of 1,3-azaphosphinines came in 1989, where Appel and Poppe expanded upon their initial work with oxazinone **135** by performing a cycloaddition with an *N*-silyl-phosphalkyne to produce intermediate **143**, which then extruded CO₂ gas to afford 4-silylamino-1,3λ³-azaphosphinine **144** (Scheme 54).¹⁰⁷ Subsequent hydrolysis afforded the final heterocycle **145** in moderate yield.



Scheme 52 Diels–Alder route to 1,3λ³-azaphosphinines **136**.



Scheme 53 Complex synthetic pathway leading to either 1,3λ³- or 1,4λ³-azaphosphinines.

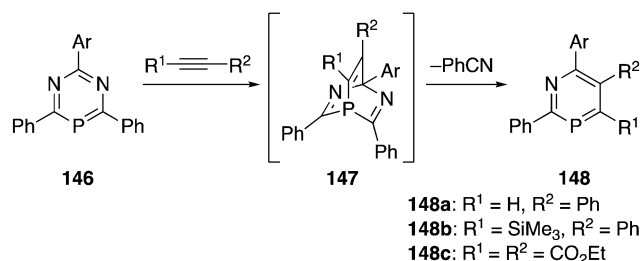


Scheme 54 Diels-Alder mediated synthesis of amine-bearing 1,3λ³-azaphosphinine **145**.

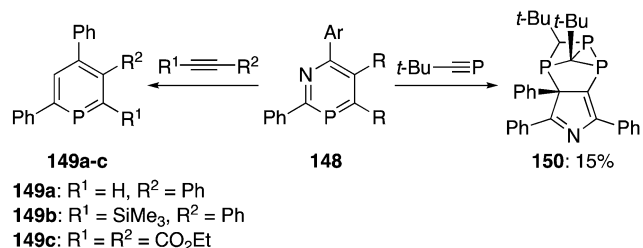
Next, in 1991, Märkl and Dörger showed that 1,5,3-diazaphosphinines **146** undergo [4+2] cycloaddition with internal alkynes to first form bicyclic structures **147** before undergoing cycloreversion to extrude benzonitrile and form 1,3λ³-azaphosphinines **148** (Scheme 55).¹⁰⁸

This reaction can be repeated with another equivalent of internal alkyne to extrude another equivalent of benzonitrile to afford phosphinine **149** (Scheme 56), for which no yields were reported.^{53,109,110} Interestingly, when treated instead with a phosphalkyne, 1,3λ³-azaphosphinines instead form an azaphosphabarrelene **150**.

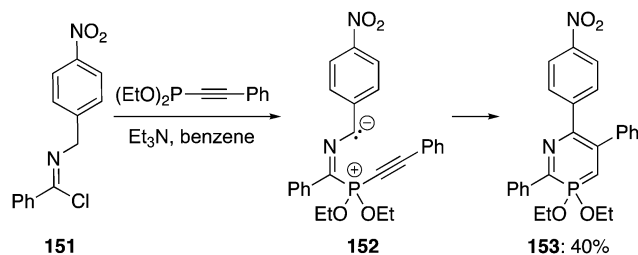
In 1986, the first example of a 1,3λ⁵-azaphosphinine was prepared by Galishev *et al.*¹¹¹ They first reacted imidoyl chloride **151** with diethyl(phenylethynyl)phosphonite to give zwitterion **152**, which then intramolecularly cyclized to form **153** (Scheme 57).



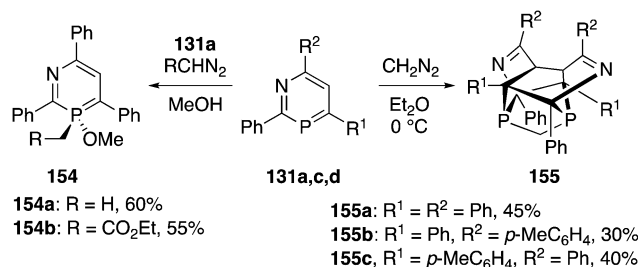
Scheme 55 Consecutive cycloaddition/cycloreversion pathway to furnish heavily substituted 1,3λ³-azaphosphinines **148**. No yields reported for **148**.



Scheme 56 Post-synthetic modification of **148** to either phosphinine **149** (left) or azaphosphabarrelene **150** (right).



Scheme 57 Generation of heavily substituted **153** via zwitterionic intermediate.

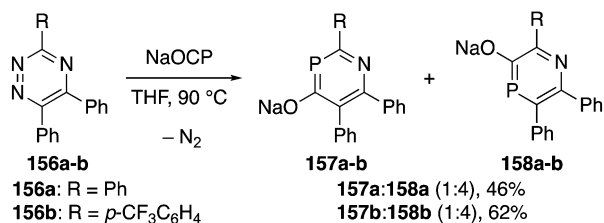


Scheme 58 Oxidation of **131** to P^V heterocycle **154** (left) or conversion to polycyclic **155** (right).

While studying the synthesis of similar 1,3λ⁵-azaphosphinines, the Märkl team reported that 1,3λ³-azaphosphinine **131a** can be oxidized to the corresponding 1,3λ⁵-azaphosphinine **154** upon treatment with diazoalkanes in alcohol solutions, adding both an alkyl group and a methoxy group in the process (Scheme 58). When run in ether rather than alcohol, however, the “dimeric” polycycle **155** was formed.¹¹²

In 1999, Le Floch and co-workers performed a computational study exploring a series of nitrogen and phosphorus heterocycles to better understand their structure and reactivity.¹¹³ This paper was a follow-up to previously published results that showed the 1,3,2-diazaphosphinine and 1,2-azaphosphinines reacted much more quickly with alkynes than their 1,3,5-diazaphosphinine and 1,3-azaphosphinine counterparts, respectively, due to increased dipolar characteristics.^{53,114} In this computational study, they concluded that the 1,3λ³-azaphosphinine scaffold was both planar and weakly aromatic, showing decreased shortening of the P–N double bond on average compared to the double bonds in pyridine or the double bond in phosphinine. They also determined the internal bond angles for the C–P–C, P–C–N, and C–N–C bond angles were 98.0°, 129.3°, and 120.1°, respectively. This C–P–C angle is significantly smaller than the C–N–C bond angle in pyridine (117.1°), which is likely the result of the longer P–C bonds. Also, increased s-character in the P lone pair that leads to more p-character in the P–C bonds since P is a higher Z (and more electropositive) element than N.

In 2018, Hansmann developed a novel inverse electron demand hetero-Diels-Alder reaction to form 1,3λ³- and 1,4λ³-azaphosphinines from several 1,2,4-triazine starting materials **156** (Scheme 59).¹¹⁵ This was achieved at 90 °C through the use

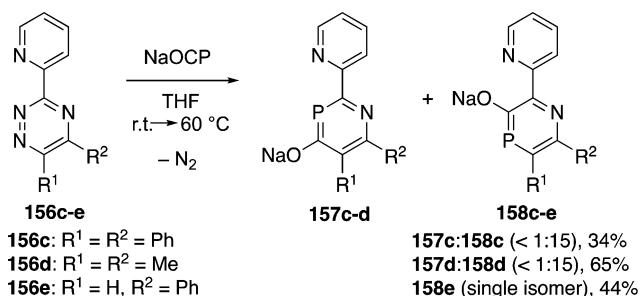


Scheme 59 Conversion of triazine **149** to mixture of corresponding 1,3λ³- and 1,4λ³-azaphosphinines.

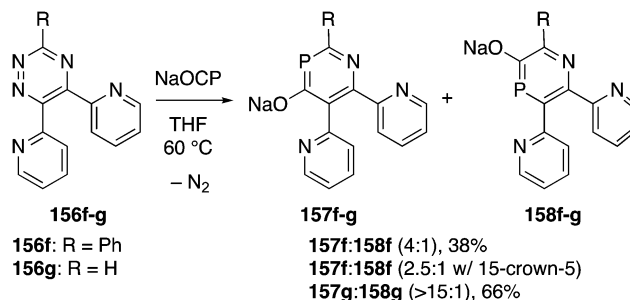
of sodium phosphoethynolate (NaOCP) and subsequent loss of N₂ gas to drive the reaction. The substituent groups on the starting triazine led to a dramatic difference in the ratio of formation of the 1,3λ³-azaphosphinine **157** compared to the competing 1,4λ³-derivative **158**. For instance, placement of phenyl rings in the 5- and 6-positions as well as either a phenyl or *p*-trifluoromethylphenyl group in the 3-position leads to formation of the 1,3λ³-azaphosphinine derivative **157** in a 1:4 ratio to the 1,4λ³-azaphosphinine **158** (Scheme 59). This ratio was determined through examination of the ³¹P NMR spectrum and comparison to predicted values determined through DFT; however, the computed thermodynamic stabilities of the two scaffolds were very close, with the 1,3λ³-derivative favored by 1.7 kcal mol⁻¹, suggesting that the mechanism of formation likely leads to this discrepancy.

To further examine the directing effects of the substituent groups, 2-pyridyl groups were introduced as ion tethers in multiple positions on triazine **156c-e**, resulting in dramatic shifts in the ratios of **157c-e** to **158c-e** (Scheme 60). In the 3-position, the 2-pyridyl on triazine **156** leads to a 1:15 ratio of 1,3λ³-azaphosphinine **157c-d** to 1,4-azaphosphinine **158c-d** upon treatment with NaOCP at 60 °C. This was true when starting with either diphenyltriazine **156c** or with dimethyltriazine **156d**. When starting with triazine **156e** at room temperature, however, only 1,4λ³-azaphosphinine **158e** was formed.

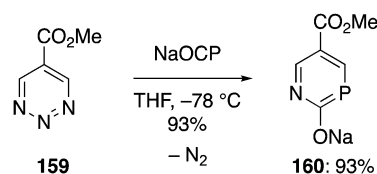
With the 2-pyridyl group on both the 5- and 6-positions and a phenyl group in the 2-position on triazine **156f**, treatment with NaOCP at 60 °C gave a 4:1 ratio of 1,3λ³-azaphosphinine **157f** to 1,4λ³-azaphosphinine **158f** (Scheme 61), likely due to the directing nature of the pyridyl groups. Interestingly, when running the same reaction in the presence of 15-crown-5, a reversed trend of 1:2.5 **157f:158f** was observed, supporting the idea that the Na⁺ ion plays a large directing role in the



Scheme 60 Use of 2-pyridyl directing group to dramatically favor 1,4λ³ product **158**.



Scheme 61 Reversed trend in selectivity for azaphosphinine isomer based on substitution pattern of starting triazine **156**.



Scheme 62 Use of 1,2,3-triazine **159** to give exclusively 1,3λ³ product **160**.

product ratio. To further favor the 1,3λ³-azaphosphinine product **157g**, the reaction was run with a hydrogen in place of the phenyl group, which led to a 15:1 **157g:158g** ratio in good yields.

Lastly, when starting from 1,2,3-triazene **159** and treating it with NaOCP at -78 °C in THF, the sodium salt of 1,3λ³-azaphosphinine 2-oxide **160** was solely formed (Scheme 62), confirming the versatility of this synthetic route.

Intramolecular cyclization reactions

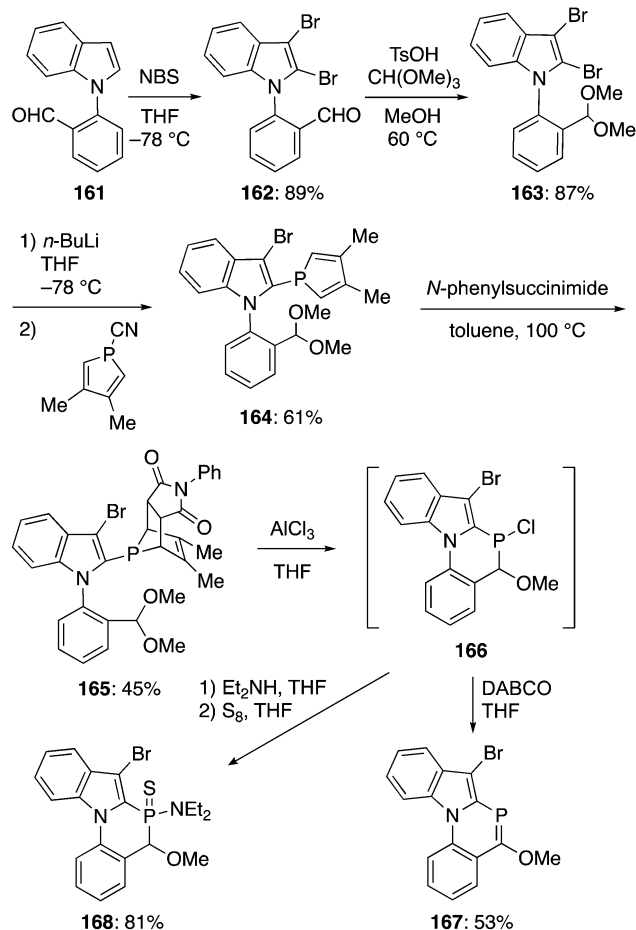
In 2018, Mathey and coworkers explored a more conjugated system containing the 1,3-azaphosphinine moiety.¹¹⁶ Bromination of **161** with *N*-bromosuccinimide (NBS) afforded indole **162**, which was then protected as the dimethoxy acetal **163** (Scheme 63). Lithiation and subsequent addition to *P*-cyano-3,4-dimethylphosphole gave phosphorus- and nitrogen-containing structure **164**. The phosphole ring then underwent a [4+2] cycloaddition with *N*-phenylsuccinimide to first furnish **165**, which upon treatment with AlCl₃ gave *P*-chloro intermediate **166**. Elimination of HCl with 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded 1,3λ³-azaphosphinine **167** in a good yield. Alternatively, reaction of **166** with Et₂NH and then S₈ gave thionated 1,3λ³-azaphosphinine 3-sulfide **168** in excellent yield.

To explore the reactivity of π-extended **167**, heating in MeOH at 60 °C gave dimethoxy product **169** in very good yield (Scheme 64). Additionally, the phosphorus-containing double bond could undergo a Diels-Alder reaction with 2,3-dimethyl-1,3-butadiene in toluene at 100 °C to furnish heterocycle **170**, which could be oxidized with H₂O₂ to afford the respective 1,3λ⁵-heterocycle **171** in excellent yield.

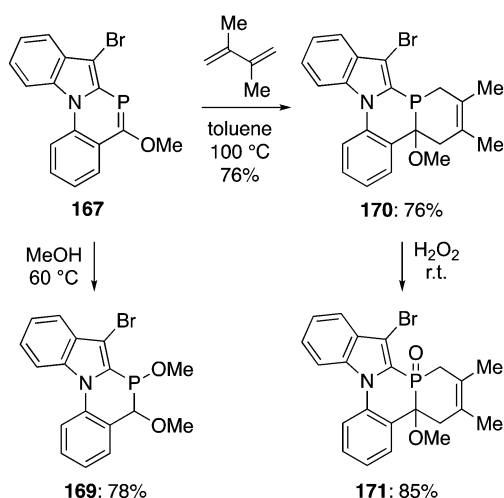
1,4-Azaphosphinines

Bis-β-ketophosphane oxide cyclization

One of the earliest examples of a 1,4-dihydro-1,4λ⁵-azaphosphinine 4-oxide comes from Aguiar and coworkers in

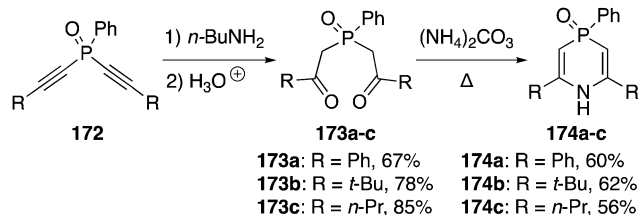


Scheme 63 Synthetic pathway to π -extended $1,3,\lambda^3$ -azaphosphinine **167** and corresponding $1,3,\lambda^5$ -azaphosphinine sulfide **168**.



Scheme 64 Synthesis of dimethoxy **169** (left) and consecutive Diels-Alder/oxidation to give product **171** (right).

1971.³⁶ Unlike most early publications in this review, their synthesis was not primarily concerned with just pushing the bounds of novel heteroaromatics, but rather, designing new



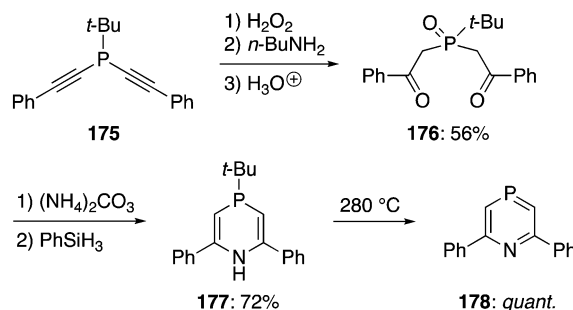
Scheme 65 Synthesis of 1,4-dihydro-1,4 λ^5 -azaphosphinine 4-oxide **174**.

bioactive species. Starting from (diethynyl)phenylphosphane oxides **172**, conjugate addition of butylamine followed by hydrolysis afforded the corresponding bis- β -keto-phosphane oxides **173** (Scheme 65). Lastly, **173** were cyclized with ammonium carbonate to furnish the desired dihydro product **174**. As apparent from the next few entries in this review, this particular technique of synthesizing an azaphosphinine scaffold was extremely influential and facilitates much of the early work performed on the 1,4-isomer.

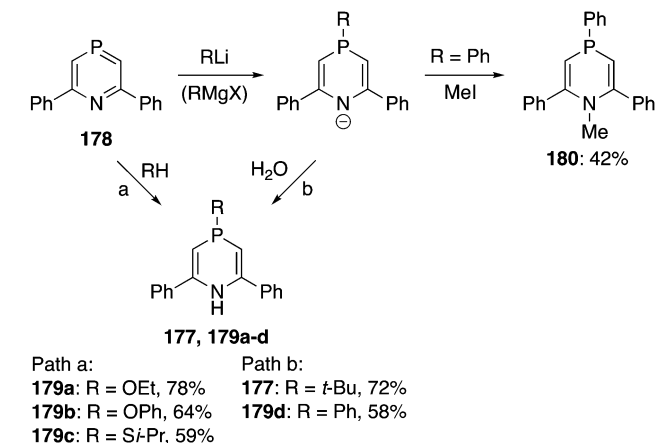
The earliest published example of any non-fused, aromatic λ^3 -azaphosphinine came from Märkl and Matthes in 1972.³² The initial interest for this system arose from curiosity surrounding previously synthesized azaarsine heterocycles. Their synthetic approach involved thermolyzing a dihydro precursor to the fully aromatized system (Scheme 66). The success of this technique led to it being used later in some of the other early syntheses of $1,4\lambda^3$ -azaphosphinines.^{66,68} The first four steps of their syntheses are directly analogous to that of Aguiar *et al.* but use a suitable 'leaving group' (*t*-Bu) instead of a Ph ring. Bis(phenylethynyl)-*t*-butylphosphane **175** was oxidized and the water formally added to the alkynes to give bis- β -keto-phosphane oxide **176**. This was cyclized with ammonium carbonate and reduced to P^{III} with phenylsilane to afford **177**, which lastly was thermolyzed to furnish the desired 2,6-diphenyl-1,4 λ^3 -azaphosphinine **178**.

Like prior azaphosphinine examples, the differences in the heteroatom electronegativity meant that **178** was quite electrophilic (Scheme 67). Several dihydro products (**177**, **179**, **180**) could be synthesized through the attack of various nucleophiles at the phosphorus center, followed by either protonation or methylation to afford the secondary or tertiary amino species, respectively.

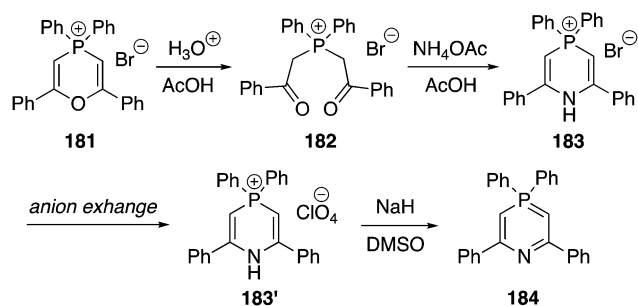
Also in 1972, Mebazaa and Simalty were developing their synthesis of the first non-fused $1,4\lambda^5$ -azaphosphinine, a pathway



Scheme 66 Synthesis of 2,6-diphenyl-1,4 λ^3 -azaphosphinine **178**.

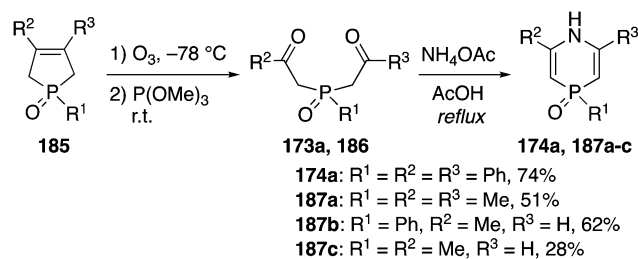
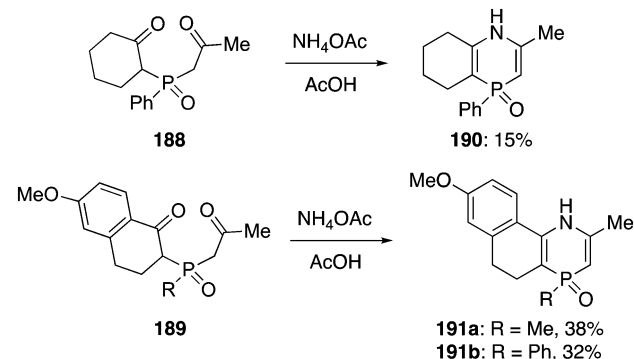


Scheme 67 Dihydro-products resulting from attack of various nucleophiles.

Scheme 68 Synthesis of 2,4,4,6-tetraphenyl-1,4λ⁵-azaphosphinine **184**.

that would become standard for nearly a decade in the development of such species (Scheme 68).¹¹⁷ Starting from phosphonium pyran salt **181**, hydrolysis furnished bis-β-keto-phosphane oxide **182**. Analogous to the previous two 1,4-azaphosphinine syntheses, **182** was cyclized with ammonium acetate to yield **183**.^{32,36} Anion exchange gave the perchlorate salt **183'**, which was subsequently deprotonated with NaH to furnish 2,4,4,6-tetraphenyl-1,4λ⁵-azaphosphinine **184**. While the exact method of anion exchange was not reported in the paper, a similar publication from the same authors used sodium perchlorate;¹¹⁸ no product yields were reported for either. The authors make the case for the aromaticity of their target **184** through the UV-Vis spectra and its dramatic change upon protonation. However, through the modern perspective noted at the beginning of this review, while there may be a degree of delocalization *via* the ylidic nature of **184**, there is no “aromaticity” as one would typically define it.

In 1984, Quin *et al.* expanded upon the synthetic pathway initially developed by Aguiar.^{36,119} They had been examining methods of converting phospholene oxides **185** into bis-β-keto-phosphane oxides **173a** and **186** *via* ozonolysis (Scheme 69).¹²⁰ Their alternative approach to generating the acyclic starting material of the 1,4-dihydro-1,4λ⁵-azaphosphinine 4-oxide scaffold **174a** and **187** facilitated novel functional groups and substitution patterns. While their substrate scope was primarily limited to phenyl and methyl groups, they were able to furnish heterocycles with only one substituent α to the nitrogen atom,

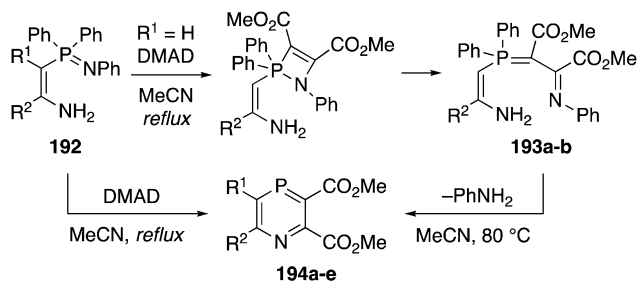
Scheme 69 Ozonolysis-based approach to 1,4-dihydro-1,4λ⁵-azaphosphinine 4-oxides **174a** and **187**.Scheme 70 Additional examples of ring-fused 1,4-dihydro-1,4λ⁵-azaphosphinine 4-oxides.

which was not achievable with previous symmetric bis-β-keto-phosphane oxides. While there was limited analytical data provided for the compounds, the ¹³C NMR spectra showed a strong upfield shift (91–93 ppm) of the olefinic carbon β to the nitrogen atom, suggesting a transfer of electron density from the nitrogen atom to this carbon similar to enamines.

By 1990, Quin and Marsi published a more comprehensive work on phosphorus heterocycles derived from more exotic bis-β-keto-phosphane oxides **188** and **189** (Scheme 70).¹²¹ While many of these species do not fit the scope of this review, there were a few interesting examples that explore the possibilities of extension *via* saturated ring fusion such as **190** and **191**.

Pericyclic/cycloaddition reactions

Work from Barluenga *et al.* began to emerge around this time that was focused on developing alternative pathways to 1,4-azaphosphinines. Some of the limitations of the aforementioned bis-β-keto-phosphane oxides were (i) a lack of functionalization at the 3- and 5-positions and (ii) the harsh conditions required to reduce the phosphorus atom from P^V to P^{III}.¹²² A popular technique in the early days of 1,2-azaphosphinine chemistry, Barluenga used cycloaddition/electrocyclization reactions to his advantage. Starting from previously described phosphazene **192** (Scheme 71),³⁵ reaction with DMAD proceeded through a [2+2] cycloaddition/4 π -electron ring-opening to furnish acyclic intermediate **193** (where R¹ = H), which upon further heating yielded azaphosphinine **194** after loss of an equivalent of aniline. If R¹ was an alkyl substituent, the reaction furnished **194** directly, likely proceeding *via* the same



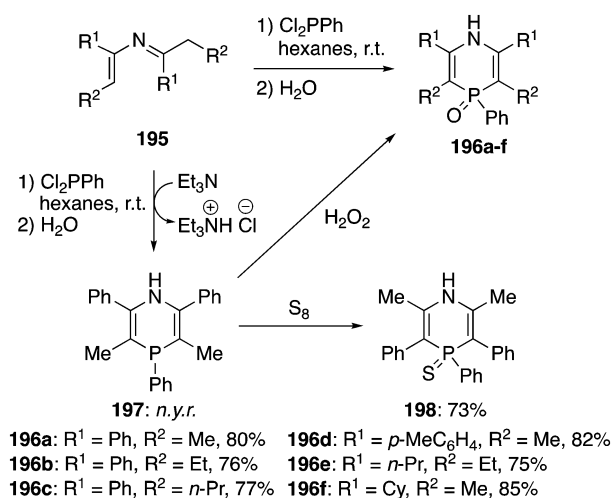
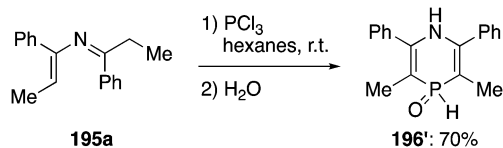
- 193a-b, 194a-b:** $R^1 = H$
193a: $R^2 = p\text{-MeC}_6\text{H}_4$, 86%
193b: $R^2 = \text{Cy}$, 82%
194a: $R^2 = p\text{-MeC}_6\text{H}_4$, 80%
194b: $R^2 = \text{Cy}$, 77%
194c: $R^1 = \text{Me}$, $R^2 = p\text{-MeC}_6\text{H}_4$, 76%
194d: $R^1 = \text{CH}_2\text{CH}=\text{CH}_2$, $R^2 = p\text{-MeC}_6\text{H}_4$, 79%
194e: $R^1 = \text{Bn}$, $R^2 = \text{Cy}$, 78%

Scheme 71 Synthesis of azaphosphinines **194**.

mechanism with the corresponding derivatives of **193** being too reactive to isolate.

Barluenga *et al.* soon departed from the cycloadditions route and instead examined the reactivity of 2-aza-1,3-dienes, which were gaining popularity in Diels–Alder type reactions.¹²³ The authors hypothesized that these 2-aza-1,3-dienes could also be employed as nucleophiles in cyclization reactions using suitable electrophiles. Reacting several 2-aza-1,3-dienes **195** with dichlorophenylphosphane led to a mild, one-pot synthesis of the corresponding tetrasubstituted 1,4λ⁵-azaphosphinin-2-ones **196** (Scheme 72). The authors could trap trivalent **197** by removing *in situ*-generated HCl with Et₃N, and subsequently showed that **197** could be oxidized to either oxide **196** or sulfide **198** with H₂O₂ or S₈, respectively.

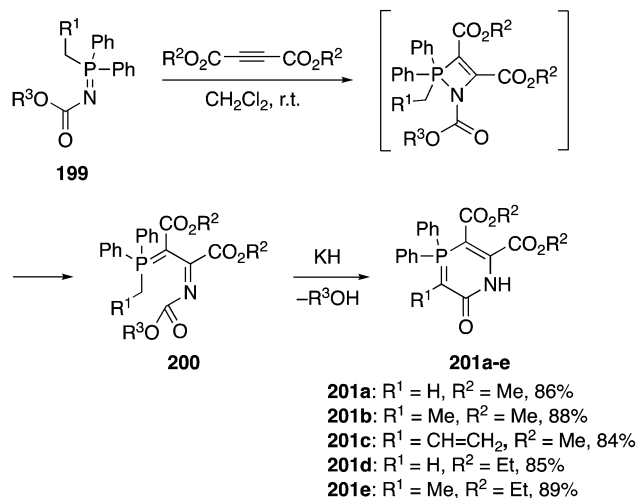
Barluenga *et al.* also showed that substituting phosphorus trichloride for dichlorophenylphosphane in the cyclization could furnish **196'** (Scheme 73).

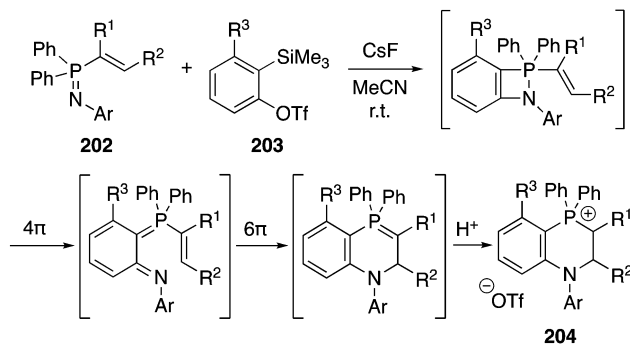
Scheme 72 One-pot cyclization to form 1,4-dihydro-1,4λ⁵-azaphosphinines **196**.Scheme 73 Synthesis of secondary 1,4λ⁵-azaphosphinine 4-oxide **196'**.

Barluenga *et al.* returned to the cycloaddition route in a 1990 publication concerning the synthesis of 2-oxo-1,4λ⁵-azaphosphinines.¹²⁴ Just prior to this report, the same authors had described a method for formation of conjugated phosphonium ylides using phosphazenes and DMAD, then subsequently converting them to phosphole derivatives.¹²⁵ The reaction between one of the two alkyne diesters, DMAD or diethyl acetylenedicarboxylate (DEAD), and the *N*-alkoxycarbonylphosphazene **199** is proposed to proceed *via* [2+2] cycloaddition and subsequent electrocyclic ring opening to yield the conjugated phosphonium ylides **200** (Scheme 74). This is a similar process to the group's earlier work on formally conjugated 1,4λ³-azaphosphinines.¹²² However, for these derivatives the *N*-alkoxycarbonyl functionality served as an electrophile, in which deprotonation of the CH₂ unit next to P and cyclocondensation ultimately furnished azaphosphinines **201** in excellent yields.

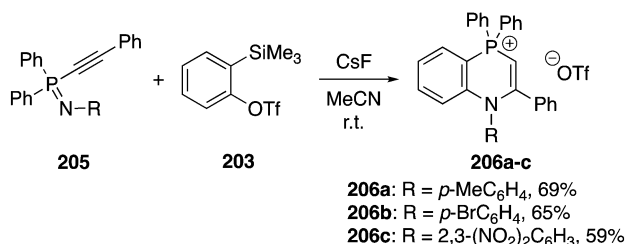
In 2011, Alajarin *et al.* reinvestigated generating azaphosphinine scaffolds from phosphazene-alkyne cycloaddition.¹²⁶ Unlike previous works that used diester-functionalized alkynes, this study involved *in situ*-generated benzyne derivatives. The reaction of phosphazenes **202** with various *o*-trimethylsilylphenyl triflates **203** furnished the saturated benzo[*b*]-tetrahydro-1,4-azaphosphonium triflate **204** *via* the cycloaddition/electrocyclization mechanism proposed in Scheme 75. While the authors do generate several derivatives of this species, the saturated nature of the azaphosphinine ring puts it beyond the scope of this review aside from this single mention.

Importantly, Alajarin *et al.* applied the reaction strategy outlined in Scheme 75 to several *P*-alkynyl-λ⁵-phosphazenes

Scheme 74 Cycloaddition/intramolecular cyclization route to 1,4λ⁵-azaphosphinin-2-ones **201**. R^3 is either Me or Et.



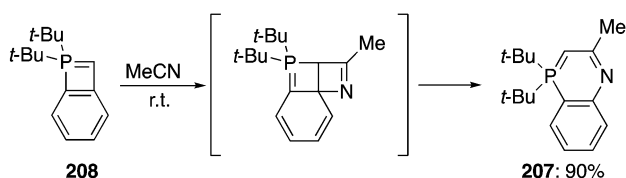
Scheme 75 Proposed general mechanism to generate tetrahydro species **204**.



Scheme 76 Phosphazene **205** heteroannulation with benzyne to give azaphosphinines **206**.

205 and produced the corresponding benzo[*b*]-1,4-dihydro-1,4-azaphosphininium triflates **206** (Scheme 76). The proposed mechanism is believed to be the same for both **204** and **206**. One could imagine if an unprotected nitrogen atom could survive this synthesis, the whole ring system could be deprotonated with strong base like the synthesis by Mebazaa and Simalty.¹¹⁷

A very unusual contribution came from Bertrand and coworkers describing the use of a benzo-λ⁵-phosphete for the synthesis of a benzo[*b*]-1,4λ⁵-azaphosphinine **207** (Scheme 77).¹²⁷ Fused 1,4-azaphosphinines of any valence are extremely rare in the literature, and this novel approach took advantage of an even less-common substrate. This work hinges on the unusual stability of phosphetes. When fused to a benzene ring, phosphete ring **208** becomes highly reactive and sensitive to oxygen and moisture, likely due to the lengthened P–C bonds. This high reactivity gave rise to the unexpected formation of the benzo[*b*]-1,4λ⁵-azaphosphinine **207** in excellent yield when reacted with acetonitrile, the structure of which was supported by spectroscopic analysis. This

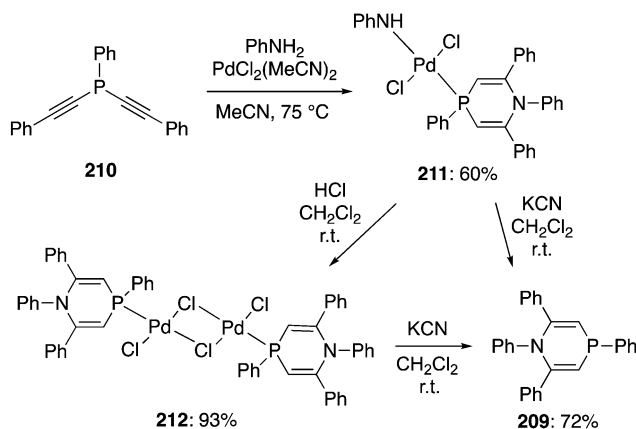


Scheme 77 Phosphete route to benzo[*b*]-1,4λ⁵-azaphosphinine **207**.

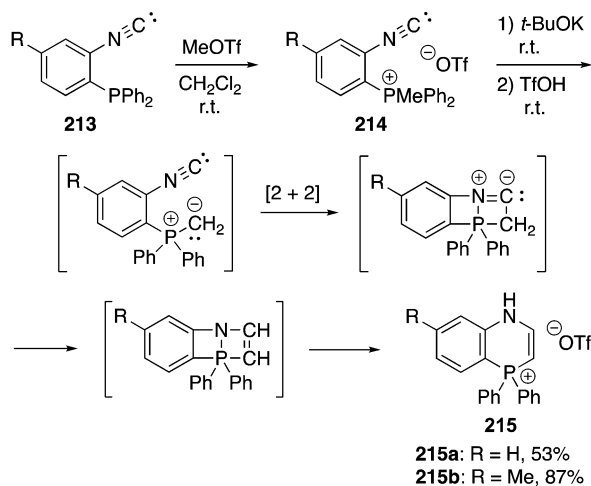
substitution pattern is unexpected because it must arise from cycloaddition of the C–C bond of the 4-membered ring in **208** with acetonitrile, rather than the expected cycloaddition with the P–C bond.

As is the case with the other azaphosphinine isomers, more modern research gravitates toward transition-metal catalyzed reactions. Accordingly, in 2002 Leung and coworkers published their work on the Pd-catalyzed synthesis of 1,2,4,6-tetraphenyl-1,4-dihydro-1,4λ³-azaphosphinine **209** (Scheme 78).¹²⁸ The primary benefit of this approach is the simplicity and one-pot nature of the reaction. Whereas no reactivity occurred between bis(phenylethynyl)phenyl phosphane **210** and aniline alone, addition of PdCl₂(MeCN)₂ allowed the reaction to proceed forming stable monomeric **211** and dimeric **212** azaphosphinine complexes with Pd that were confirmed *via* X-ray crystallography. This is an interesting and more modern take on the 1,4-dihydro-1,4λ³-azaphosphinines synthesized by Märkl and Matthes where the multistep oxidation and heteroannulation is replaced by a single catalytic step.³² The azaphosphinine ring could subsequently be liberated with the addition of KCN, affording **209**. The authors note that the geometry and bond lengths of the nitrogen atom in both cases are that of sp² hybridization, indicating delocalization around the azaphosphinine ring. The low-field NMR shift of the azaphosphinine proton signal (δ 7.73) suggests the presence of aromaticity within the λ³-azaphosphinine ring.

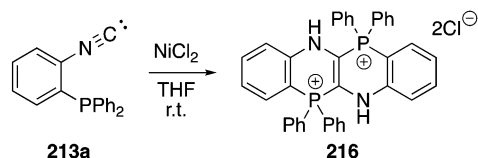
In 2015, Duan, Mathey and coworkers followed up on the efforts of both Alajarin and Leung to develop new routes to both benzo[*b*]-1,4-dihydro-1,4-azaphosphonium triflates and a transition metal catalyzed dimeric azaphosphonium species.^{126,128,129} *o*-Diarylphosphinoaryl isocyanides **213** are first methylated with MeOTf to give **214**, which are then treated with *t*-BuOK base and then triflic acid to yield azaphosphonium triflates **215** (Scheme 79). The proposed mechanism of this latter transformation involves deprotonation to form an ylidic species that undergoes [2+2] cycloaddition with the *o*-isocyanide moiety; a hydrogen shift, cycloreversion, and protonation complete the transformation. These salts are directly analogous to those prepared by Leung and



Scheme 78 Pd-catalyzed heteroannulation to give 1,2,4,6-tetraphenyl-1,4-dihydro-1,4λ³-azaphosphinine **209**.



Scheme 79 Intramolecular cyclization of *o*-diarylphosphinoaryl isocyanide ylides.



Scheme 80 Cyclization of isocyanide **213a** into dicationic **216**.

coworkers but without a *N*-atom substituent, as well as less substitution on the azaphosphininium ring itself.

Conversely, when **213a** is subjected to room temperature conditions in the presence of NiCl_2 an entirely different process occurs. Stable dicationic species **216** is the only isolable product of the reaction (Scheme 80). The authors note the mechanism of formation is not clear, and only provide NMR and X-ray crystallographic data in terms of analysis. Although the yield is omitted, this fused azaphosphininium species is quite novel in its chemistry and again begs the question if a strong base is used, would the heterocycle convert to the neutral $1,4\lambda^3$ -azaphosphinine like those of Mebazaa and Simalty?¹¹⁷

Comparing electronic properties of the azaphosphinine isomers

With such varied examples of azaphosphinines across several isomers and valences, it becomes easy to lose track of the exhibited properties, namely aromaticity, of each heterocycle. Only azaphosphinine compounds with an endocyclic $\text{P}^{\text{III}}=\text{X}$ double bond are formally aromatic. In this state the rings are analogous to both pyridine and phosphinine, the single heteroatom-containing nitrogen and phosphorus analogues. As noted earlier, the computational work from Le Floch and co-workers in 1999 sought to compare the aromaticities of $1,2\lambda^3$ - and $1,3\lambda^3$ -azaphosphinines not only to each other but also to pyridine and phosphinine.¹¹³ This work compared Nucleus Independent Chemical Shift (NICS) values¹³⁰

Table 13 Computed NICS values of relevant heterocycles computed by Le Floch (left) and Elguero (right)

Compound	NICS(0.5) ^a (ppm)	NICS(1) ^b (ppm)
Benzene	−11.5	−10.2
Pyridine	−10.6	−10.2
Phosphinine	−10.2	−9.7
$1,2\lambda^3$ -Azaphosphinine	−8.9	−9.2
$1,3\lambda^3$ -Azaphosphinine	−9.3	−9.6
$1,4\lambda^3$ -Azaphosphinine	—	−9.7
$1,3,2\lambda^3$ -Diazaphosphinine	−7.5	−8.5

^a Computed 0.5 Å above ring centers at GIAO-SCF/6-31+G*/B3LYP/6-31G* level. ^b Computed 1 Å above ring center at B3LYP 6-311++G/d,p level.

(Table 13, left), computed bond lengths, and computed bond angles. In the NICS calculations, negative values denote aromaticity. From these data there is a clear distinction between the aromaticities of the $1,2\lambda^3$ - and $1,3\lambda^3$ - isomers, with both being less aromatic than the single heteroatom species. The authors ascribe this difference to the dramatically different electronegativities of the nitrogen and phosphorus atoms, which cause more π -electron localization when the two are directly bonded. Interestingly, it is also noted that even though the $1,3\lambda^3$ -isomer is more aromatic, it is also less stable. While it is typically thought that increased aromaticity should lead to higher stabilities, this suggests that the opposite is true for these molecules. Upon further study of the molecular orbitals through NBO analysis, it was found that the placement of heteroatoms within the $1,3$ -azaphosphinine and $1,3,2$ -diazaphosphinine leads to electron distribution which limits electronic delocalization within the ring. This is rationalized computationally by calculating the [1,4] P–C₄ dipole in the $1,2\lambda^3$ -isomer as well as qualified by experimental observations made in a previous publication from this group.⁵³

In 2018, Elguero *et al.* published a computational study that calculated the NICS values for a large number of P–N heterocycles including several theoretical species such as the parent $1,2\lambda^3$, $1,3\lambda^3$, and $1,4\lambda^3$ -azaphosphinines (Table 13, right).¹³¹ The small differences in NICS values between the two studies are likely due to different levels of theory and different scanning distances used above the theoretical ring (0.5 vs. 1.0 Å). Regardless, both data sets follow the same basic trend of aromaticity in the azaphosphinine derivatives, with the later work by Elguero *et al.* suggesting that $1,4\lambda^3$ -azaphosphinine would be the most aromatic, rivaling that of phosphinine. Both studies include the benzene, pyridine, and phosphinine as reference values to their computations.

By comparison, pentavalent azaphosphinine rings cannot be described as aromatic. Modern computational and experimental work into the nature of pentavalent phosphorus indicate that the bonds are almost entirely ionic in nature. Due to the readily available electron density that is transferred to electronegative substituents (*e.g.*, N, O), a considerable amount of donation then occurs in the form of negative hyperconjugation. While this effect is in essence the distribution of electron density to adjacent bonds, it does not constitute aromaticity as

Pd ₂ dba ₃	Tris(dibenzylideneacetone)dipalladium(0)
Salox	Salicyloxazoline
SHP-1	Src homology 2-containing phosphatase-1
SRB	Sulforhodamine B
TCB	1,2,4-Trichlorobenzene
TPN	Tetraphenylnaphthalene
VC	Variable concentration

Conflicts of interest

There are no conflicts to declare.

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