



OPEN ACCESS

EDITED BY

Tieqiao Chen,
Hainan University, China

REVIEWED BY

Huafang Fan,
Northwest A&F University, China
Norio Nakata,
Saitama University, Japan

*CORRESPONDENCE

Akiya Ogawa,
✉ ogawa@omu.ac.jp

RECEIVED 27 February 2023

ACCEPTED 03 April 2023

PUBLISHED 25 May 2023

CITATION

Yamamoto Y, Mita S, Sato Y, Yano K and
Ogawa A (2023), Practical synthesis of
1,3-benzoazaphosphole analogues.
Front. Chem. 11:1174895.
doi: 10.3389/fchem.2023.1174895

COPYRIGHT

© 2023 Yamamoto, Mita, Sato, Yano and
Ogawa. This is an open-access article
distributed under the terms of the
[Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or
reproduction in other forums is
permitted, provided the original author(s)
and the copyright owner(s) are credited
and that the original publication in this
journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Practical synthesis of 1,3-benzoazaphosphole analogues

Yuki Yamamoto¹, Soichiro Mita¹, Yuki Sato¹, Kentaro Yano² and
Akiya Ogawa^{1*}

¹Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Sakai, Osaka, Japan, ²Functional Dye Division, Hayashibara Co., Ltd., Minami-ku, Okayama, Japan

Despite the promising pharmacological activity and material properties of five-membered heterocyclic compounds containing phosphorus and nitrogen, synthetic examples of them have been rather limited due to the instability of phosphorus toward air and water. In this study, 1,3-benzoazaphosphole analogues were selected as target molecules, and various synthetic routes were examined to establish a fundamental technology for the introduction of phosphorus groups into aromatic rings and formation of five-membered rings containing phosphorus and nitrogen by cyclization. As a result, we found that 2-aminophenyl(phenyl)phosphine is an extremely promising synthetic intermediate with high stability and easy handling. Furthermore, 2-methyl-3-phenyl-2,3-dihydro-1*H*-benzo[d][1,3]azaphosphole and 3-phenyl-2,3-dihydro-1*H*-benzo[d][1,3]azaphosphole-2-thione as synthetically useful 1,3-benzoazaphosphole analogues were successfully synthesized by using 2-aminophenyl(phenyl)phosphine as a key intermediate.

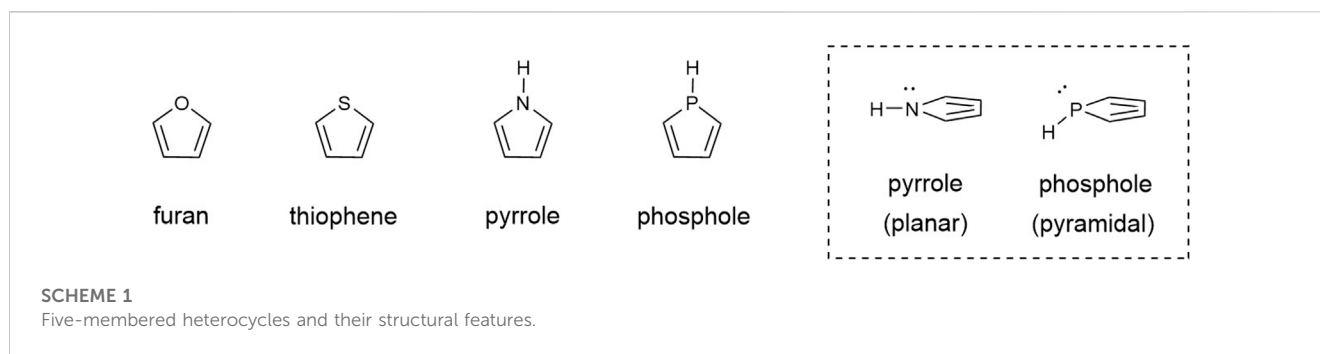
KEYWORDS

1,3-benzoazaphosphole analogues, 2-aminophenyl(phenyl)phosphine, practical synthesis route, stable phosphorus key intermediate, heterocycles

1 Introduction

Furan, pyrrole, thiophene, and their saturated compounds are representative five-membered heterocyclic compounds with good stability, and numerous derivatives have been synthesized. These heterocyclic compounds are indispensable in medical and agrochemical as well as materials chemistry (Baumann, et al., 2011; Jangir, et al., 2022). In sharp contrast, five-membered ring heterocyclic compounds containing phosphorus are more unstable than *O*-, *N*-, and *S*-heterocycles. For example, the three bonds around the nitrogen atom of pyrrole are planar, whereas the bonds around the phosphorus atom of phosphole, in which the nitrogen atom of pyrrole is replaced by a phosphorus atom, are pyramidal (Scheme 1). As a result, phosphole exhibits very low aromaticity (Egan, et al., 1971; Epitotis, et al., 1976; Mathey, et al., 1988; Cyrański, et al., 2002; Chesnut, et al., 2007). Because of such a structural feature, conjugated molecules involving phosphole and its analogs have recently attracted attention in the field of organic semiconductor development, including light-emitting and electronic materials (Hay, et al., 2001; Hissler, et al., 2003; Baumgartner, et al., 2004; Su, et al., 2006; Hobbs, et al., 2007; Crassous, et al., 2008; Matano, et al., 2009; Ren, et al., 2012). Despite their promising material properties, synthetic examples of five-membered ring heterocyclic compounds containing phosphorus are rather limited.

In order to take advantage of the properties of phosphorus and to realize diversity in combination with other heteroatoms, it is extremely desired to establish a fundamental



technology for the formation of five-membered rings containing phosphorus. From this viewpoint, in this study, we have studied the development of synthetic methods for the formation of five-membered heterocyclic rings containing phosphorus and nitrogen. In particular, we selected 3-phenyl-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole **1** as a target structure and specifically investigated the synthesis of 2-methyl-3-phenyl-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole **2** and 3-phenyl-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole-2-thione **3** in detail, that have never been synthesized before. Since 2-methylbenzothiazole, in which the PhP group of **2** is replaced with S, can be derived into a cyanine-type fluorescent dye using the methyl group at the 2-position as a clue, **2** might be a key intermediate for cyanine-type luminescent dyes bearing a 1,3-azaphosphole unit. In addition, **3** is expected to lead to an azaphosphole having a thiol group at the 2-position by iminothiolation and might cause bond-connection through sulfur (Scheme 2).

2 Materials and methods

2.1 Synthesis of ethyl (2-aminophenyl)(phenyl)phosphinate via Pd-catalyzed cross-coupling reaction

2-Bromoaniline **6a** (18 mmol, 3096.5 mg), ethyl phenylphosphinate **23** (17 mmol, 2892.6 mg), Pd(OAc)₂ (2 mol%, 76.3 mg), dppf (2.2 mol%, 207.3 mg), ⁱPr₂NEt (22.4 mmol, 3.8 mL), degassed DMF (72 mL), and dehydrated ethylene glycol dimethyl ether (8 mL) were added to a 300-mL three-neck round-bottom flask under an argon atmosphere, and the solution was heated at 115°C for 24 h. After the reaction, the solvents were removed under reduced pressure. AcOMe (50 mL) was added to the residue, and the organic layer was washed with saturated NaHCO₃ aq. (30 mL×2). The water layer was extracted with AcOMe (40 mL×3), and the combined organic layer was washed with brine (30 mL), dried with anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica-gel column chromatography (eluent: *iso*-hexane/AcOMe = 7 : 3 with 5% Et₃N) to obtain pure ethyl (2-aminophenyl)(phenyl)phosphinate **24** as brown oil in 62% isolated yield (Eq. 11).

Ethyl (2-aminophenyl)(phenyl)phosphinate (**24**) [CAS no. 93383-23-4] (Kyba, et al., 1984). Brown oil, 2741.9 mg, 62%; ¹H NMR (400 MHz, CDCl₃): δ 7.85–7.75 (m, 2H), 7.43–7.29 (m, 4H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.55–6.64 (m, 2H), 5.57 (bs, 2H), 4.18–4.00 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 161.9, 151.5 (d, *J*_{C-P} = 7.0 Hz), 133.0, 132.2 (d, *J*_{C-P} = 9.0 Hz), 131.9

(d, *J*_{C-P} = 139.0 Hz), 131.4, 130.5 (d, *J*_{C-P} = 10 Hz), 127.8 (d, *J*_{C-P} = 13.0 Hz), 116.0 (d, *J*_{C-P} = 10 Hz), 110.0 (d, *J*_{C-P} = 138.0 Hz), 60.5 (d, *J*_{C-P} = 6 Hz), 15.9 (d, *J*_{C-P} = 7 Hz); ³¹P NMR (162 MHz, CDCl₃): δ 36.1.

2.2 Reduction of ethyl (2-aminophenyl)(phenyl)phosphinate with DIBAL-H

Ethyl (2-aminophenyl)(phenyl)phosphinate **24** (14 mmol) dissolved in dehydrated Et₂O (15 mL) was transferred to a 500-mL three-neck flask, and DIBAL-H (1.0 M in hexane, 7.0 equiv.) was slowly added to the reaction mixture at 0°C for 2 h, and the reaction mixture was stirred at 25°C for 70 h. After the reaction, K₂HPO₄ aq. (0.5 M, 140 mL) was slowly added to the reaction vessel at 0°C for 1 h. The mixture was extracted with Et₂O (50 mL×5), and the combined organic layer was washed with brine (40 mL), dried with anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica-gel column chromatography (eluent: *iso*-hexane/AcOMe = 9 : 1 with 5% Et₃N) to obtain 2-(phenylphosphanyl)aniline (**25**) in 91% ³¹P NMR yield. Since the highly concentrated **25** could be potentially oxidized with air, the obtained **25** was stored under an argon atmosphere and directly used for the following reactions without any further purification (Table 2).

2-(Phenylphosphanyl)aniline (**25**) [CAS no. 67405-21-4] (Bennett et al., 2006). Pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.45–7.36 (m, 3H), 7.30–7.22 (m, 3H), 7.21–7.16 (m, 1H), 6.77–6.70 (m, 1H), 6.68–6.61 (m, 1H), 5.11 (d, *J*_{P-H} = 222 Hz, 1H), 3.89 (bs, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 149.5 (d, *J*_{C-P} = 8 Hz), 137.6 (d, *J*_{C-P} = 22 Hz), 133.5 (d, *J*_{C-P} = 10 Hz), 132.4 (d, *J*_{C-P} = 15 Hz), 131.2, 118.5 (d, *J*_{C-P} = 8 Hz), 115.9 (d, *J*_{C-P} = 10 Hz), 115.4; ³¹P NMR (162 MHz, CDCl₃): δ -59.4.

2.3 Synthesis of 2-methyl-3-phenyl-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole

2-(Phenylphosphanyl)aniline **25** (1.0 mmol), acetaldehyde (1.5 mmol, 90 wt% aq.), 4A MS (100 mg), and degassed toluene (1 mL) were placed in a 10-mL Schlenk tube, and the mixture was refluxed at 120°C for 48 h. After the reaction, the resulting solution was filtered, and the filtrate was concentrated under reduced pressure. Finally, the residue was purified by gel permeation chromatography (eluent: CH₂Cl₂) to obtain 2-methyl-3-phenyl-

2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole (**2**) in 82% ³¹P NMR yield (*anti/syn* = 49/51) (Eq. 14).

2-Methyl-3-phenyl-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole (**2**).

(*Anti*-isomer) Light yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.46–7.42 (m, 1H), 7.34–7.20 (m, 4H), 7.16–7.10 (m, 2H), 6.83–6.75 (m, 2H), 4.40–3.90 (m, 2H), 1.14–1.07 (m, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 155.7, 133.7 (d, *J*_{C-P} = 19 Hz), 133.6 (d, *J*_{C-P} = 27 Hz), 132.3 (d, *J*_{C-P} = 22 Hz), 130.8, 129.2, 128.1 (d, *J*_{C-P} = 6.7 Hz), 123.6 (d, *J*_{C-P} = 5.8 Hz), 119.0 (d, *J*_{C-P} = 7.7 Hz), 110.0, 54.7 (d, *J*_{C-P} = 12 Hz), 15.7; ³¹P NMR (162 MHz, CDCl₃): δ -18.2; HRMS (EI) *m/z* calcd for C₁₄H₁₄NP [M]⁺:227.0864, found: 227.0870.

(*Syn*-isomer) Pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.52–7.46 (m, 1H), 7.30–7.20 (m, 6H), 6.83–6.74 (m, 2H), 4.07 (bs, 1H), 3.90–3.83 (m, 1H), 1.42–1.34 (m, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 153.9, 139.0 (d, *J*_{C-P} = 22 Hz), 132.6 (d, *J*_{C-P} = 22 Hz), 131.5 (d, *J*_{C-P} = 22 Hz), 130.9, 128.4 (d, *J*_{C-P} = 6.7 Hz), 120.7 (d, *J*_{C-P} = 8.7 Hz), 118.6 (d, *J*_{C-P} = 7.7 Hz), 110.1, 57.5 (d, *J*_{C-P} = 12 Hz), 22.2 (d, *J*_{C-P} = 31 Hz); ³¹P NMR (162 MHz, CDCl₃): δ -6.9; HRMS (EI) *m/z* calcd for C₁₄H₁₄NP [M]⁺:227.0864, found: 227.0870.

2.4 Synthesis of 3-phenyl-1,3-dihydro-2*H*-benzo[*d*][1,3]azaphosphole-2-thione

2-(Phenylphosphanyl)aniline **25** (1.5 mmol), 1,1'-thiocarbonyldiimidazole (1.5 mmol), and degassed THF (5 mL) were placed in a 10-mL Schlenk tube, and the mixture was heated at 80°C for 48 h. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was purified by gel permeation chromatography (eluent: CH₂Cl₂) to obtain 3-phenyl-1,3-dihydro-2*H*-benzo[*d*][1,3]azaphosphole-2-thione (**3**) in 97% ³¹P NMR yield (Eq. 18).

3-Phenyl-1,3-dihydro-2*H*-benzo[*d*][1,3]azaphosphole-2-thione (**3**). Yellow solid; ¹H NMR (400 MHz, CDCl₃): δ 11.2 (bs, 1H), 7.50–7.44 (m, 3H), 7.40–7.30 (m, 4H), 7.24–7.18 (m, 1H), 7.13 (d, *J* = 8 Hz, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 213.7 (d, *J*_{C-P} = 31 Hz), 146.4 (d, *J*_{C-P} = 3 Hz), 132.7 (d, *J*_{C-P} = 19 Hz), 130.6 (d, *J*_{C-P} = 17 Hz), 130.3, 129.1 (d, *J*_{C-P} = 7 Hz), 127.9 (d, *J*_{C-P} = 11 Hz), 124.8 (d, *J*_{C-P} = 6 Hz), 112.4; ³¹P NMR (162 MHz, CDCl₃): δ 15.8; HRMS (EI) *m/z* calcd for C₁₃H₁₀NPS [M]⁺:243.0272, found: 243.0276.

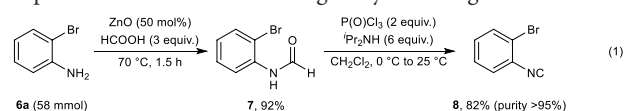
3 Results and discussion

Five-membered ring heterocyclic compounds with phosphorus and nitrogen have been largely limited in their synthetic routes compared to other five-membered ring heterocyclic compounds incorporating nitrogen, oxygen, or sulfur due to the instability of the trivalent phosphorus functional groups with air and water, the toxicity of the phosphorus-hydrogen compounds as synthetic intermediates, and the difficulty in handling the key intermediates for such phosphorus-nitrogen heterocycles. Therefore, the use of five-membered ring heterocyclic compounds with phosphorus and nitrogen in materials chemistry has been significantly restricted.

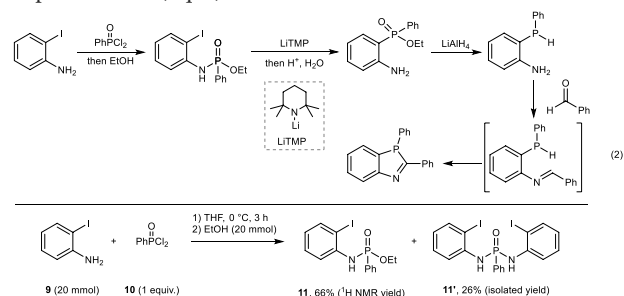
Thus, the development of versatile synthetic methods is strongly desired. As to 1,3-benzophospholes, for example, only two methods have mainly been used for their synthesis (Scheme 3).

Method 1 mainly uses a route with the key intermediate 2-aminophenylphosphine, which is highly oxidizable and highly toxic. Although this route gives high yields for each step, except the final alkylation (~60%), it requires hazardous purification of 2-aminophenylphosphine by distillation and use of a pyrophoric base (^tBuLi). Unfortunately, the substituent on the phosphorus atom is limited to an alkyl group (Issleib, et al., 1978; Walborsky, et al., 1978; Issleib, et al., 1981; Heinicke, et al., 1982; Heinicke, 1986; Rösch, et al., 1987; Heinicke, 1989; Bansal, et al., 1999; Niaz, et al., 2013; Niaz, et al., 2013). Method 2 involves the synthesis of *P*-substituted 2-aryl-1,3-benzazaphospholes using 2-(diarylphosphino)phenyl isocyanide as a key intermediate. In this route, the key intermediate isocyanide is air-stable, but suffers from low yields of phosphorus functionalization and cyclization (both 60%) and restriction of the 2-position of the 1,3-azaphosphole ring to an aryl group (Zhang, et al., 2015).

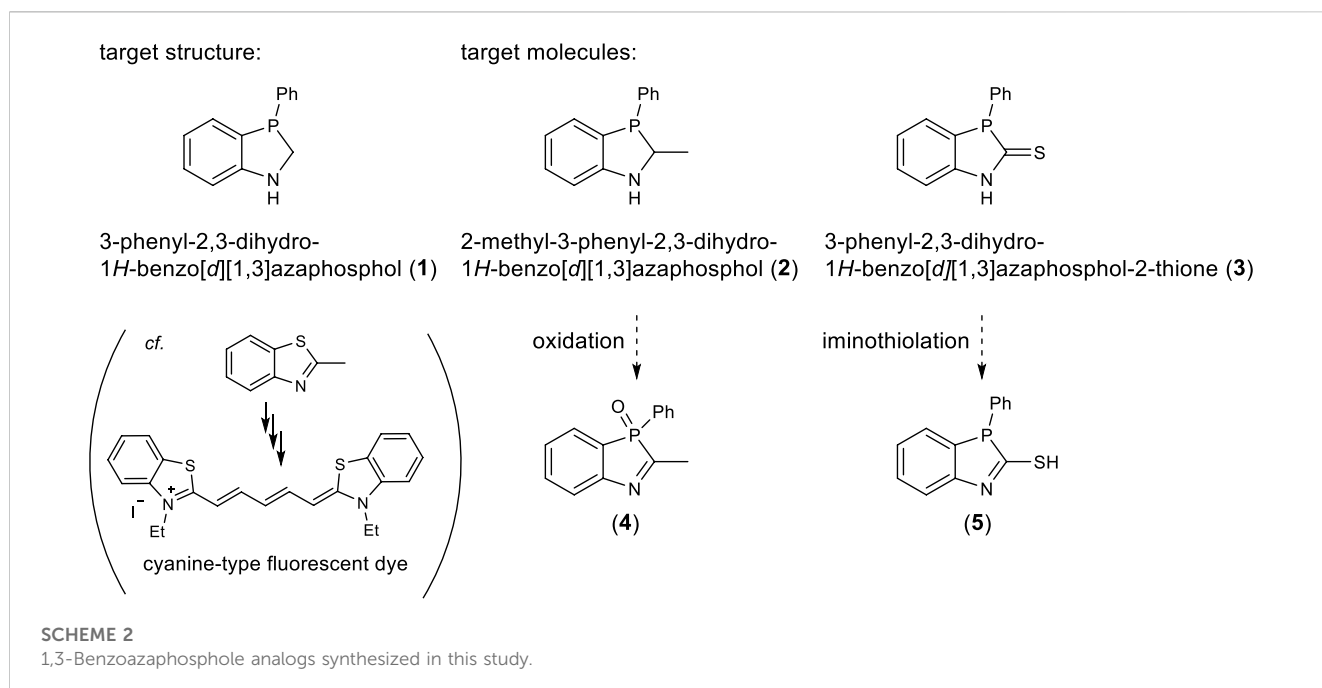
Since Method 1 requires toxic and air-sensitive 2-aminophenylphosphine as a key intermediate, we synthesized 1,3-azaphosphole derivatives by modifying Method 2. Treatment of 2-bromoaniline **6a** with ZnO/HCOOH afforded the formation of the corresponding formamide **7** in 92% yield, which led to formation of 2-bromophenyl isocyanide **8** in 82% yield by following dehydration (Eq. 1). However, the Br-Li exchange reaction of **8** and the following phosphination with Ph₂PCl required strict temperature control for inhibiting isocyanide oligomerization.



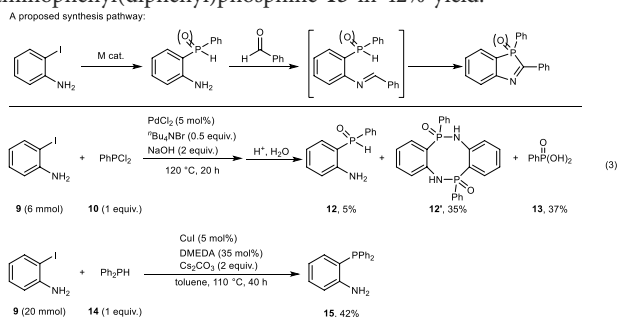
Thus, we next selected the imino group instead of the isocyanide group because the imino group is not susceptible to oligomerization. Before the imination reaction, the synthesis of 2-aminophosphinic ester was examined by rearrangement of the phosphino group. Then, LiAlH₄ reduction followed by imination might lead to the formation of 1,3-azaphosphole. The reaction of 2-iodoaniline **9** with phenylphosphonic dichloride **10** successfully afforded 2-iodophenylaminophosphinic ester **11** as the major product. However, the following lithiation from **11** did not proceed well (Eq. 2).



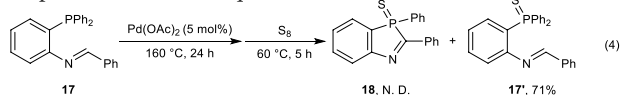
As described previously, the synthesis of arylphosphorus compounds via aryllithium intermediates requires a high level of synthesis techniques and is considered undesirable from the standpoint of versatility. Therefore, we next examined the synthesis of arylphosphorus compounds by transition-metal-catalyzed coupling reactions. A proposed synthesis pathway is



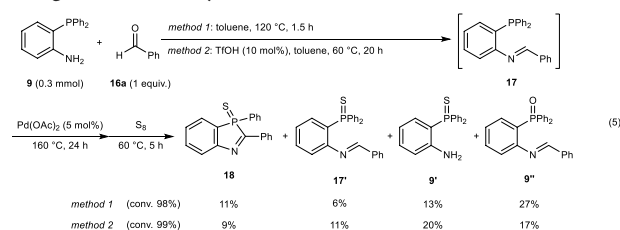
shown in Eq. 3. Although PdCl₂-catalyzed coupling of 2-iodoaniline **9** with phenylphosphonic dichloride **10** afforded 5% of the desired 2-aminophenyl(phenyl)phosphine oxide **12** along with its dimer **12'** (35%) due to the nucleophilic attack of the amino group at the phosphine, copper(I) iodide-catalyzed coupling reaction of 2-iodoaniline **9** with diphenylphosphine **14** successfully afforded 2-aminophenyl(diphenyl)phosphine **15** in 42% yield.



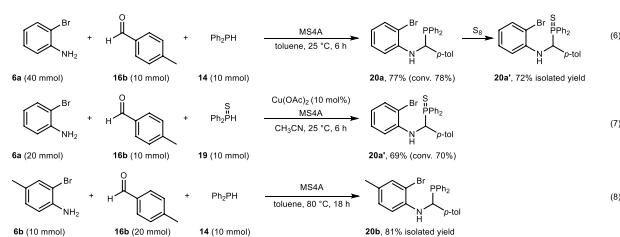
Then, we next examined the imine synthesis by dehydrative condensation from 2-aminophenyl-(diphenyl)phosphine **15** and benzaldehyde **16** (Table 1). When the condensation reaction of **15** and **16a** was conducted in the presence of molecular sieves at 25°C, the corresponding imine **17** was obtained in 12% yield (entry 1). Excess amounts of **16a** improved the yield of **17** (37%) (entry 3). Exchanging the solvent from toluene to methanol dramatically improved the yield (entry 5), and especially, 87% of the imine **17** was obtained when the reaction was conducted at 60°C (entry 6). However, attempted cyclization of the thus formed imine **17** using Pd(OAc)₂ as a catalyst failed, and **17** was recovered as a phosphine sulfide **17'** (Eq 4).



Thus, we attempted the Pd(OAc)₂-catalyzed cyclization using *in situ*-generated imine intermediate **17** (Eq 5). The imine generation was performed using two methods. After treatment with sulfur, the corresponding 1,3-benzophosphole sulfide **18** was obtained in ca. 10% yields. However, most of the imine intermediate did not undergo the desired cyclization.



To promote cyclization by bringing palladium closer to the reaction site, we attempted to synthesize (2-bromophenylamino) methylphosphine intermediate using the three methods, as shown in Eqs. 6–8. The three methods involve *in situ* formation of imine intermediate, followed by the addition of P–H species to the formed N=C bond, and the desired (2-bromophenylamino) methylphosphine intermediates were obtained in good yields. After the –P(S)Ph₂ group was reduced to the –PPh₂ group, the cyclization was examined under the conditions of Pd(OAc)₂ (10 mol %), DMF, 130°C, 12 h. Unfortunately, the desired cyclization did not occur.



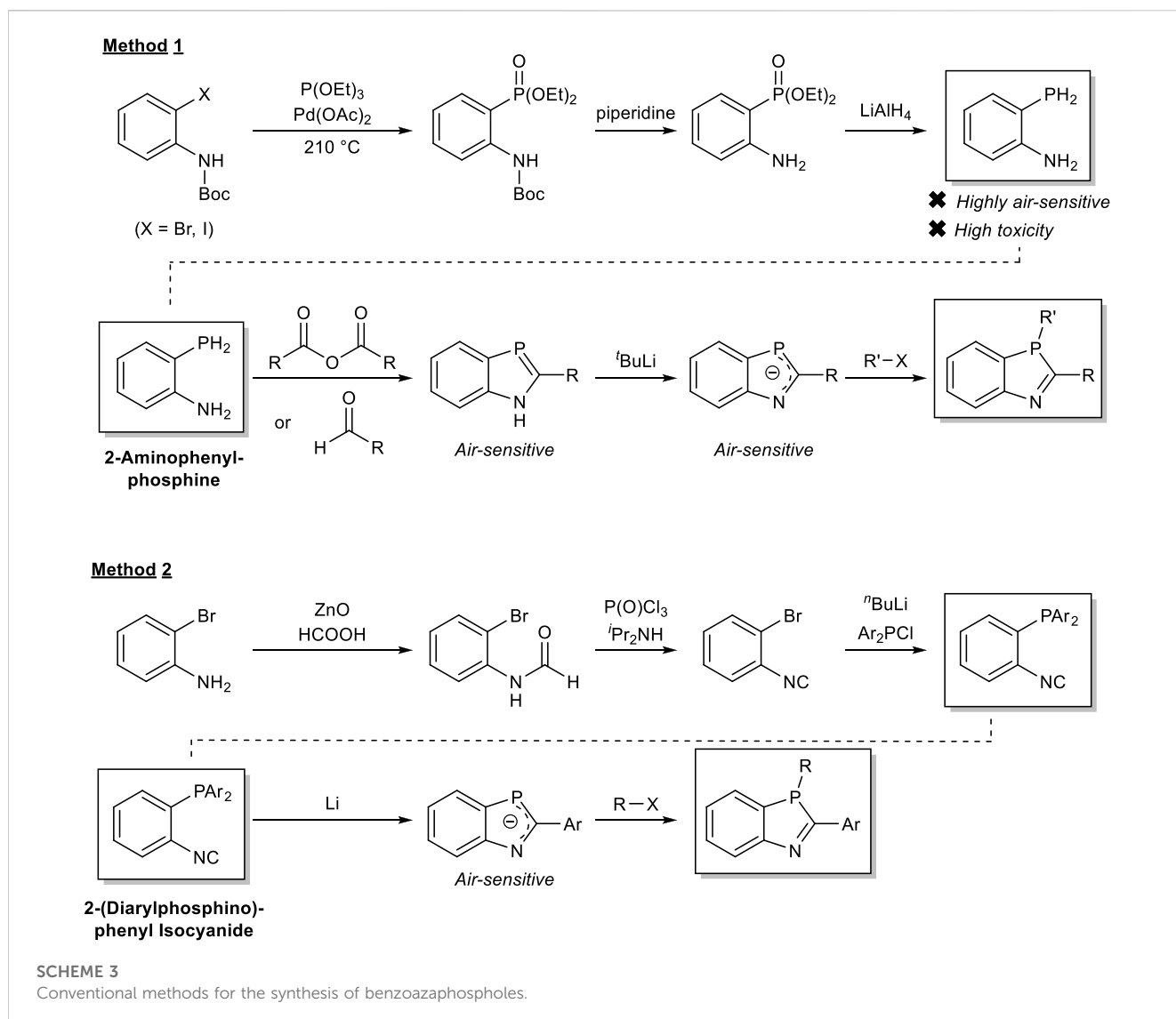
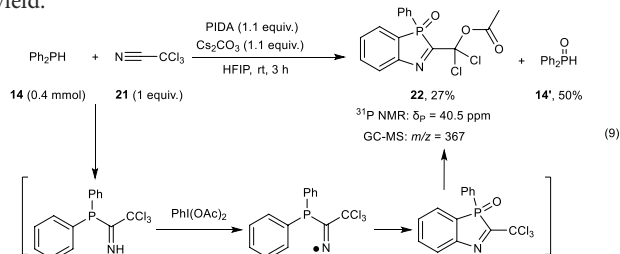


TABLE 1 Dehydrative condensation of 2-aminophenyl(diphenyl)phosphine **15** and benzaldehyde **16a**.

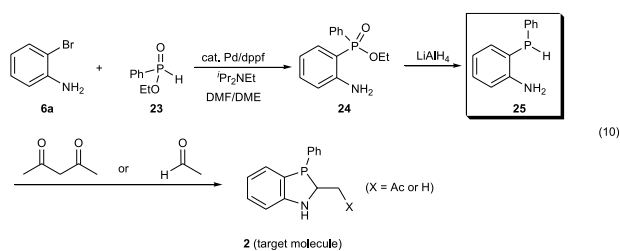
Entry	Temp. (°C)	16a (equiv.)	Solvent	Yield 17 (%) ^a
1	25	1	Toluene	12
2	25	2	Toluene	15
3	25	4	Toluene	37
4	25	1	CH ₃ CN	37
5	25	1	MeOH	64
6	60	1	MeOH	87

^aThe yields were determined by ³¹P NMR spectroscopy.

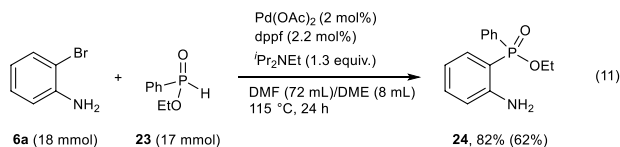
Since the Pd(OAc)₂-catalyzed dephenylative cyclization was difficult, we next examined the cyclization using a nitrogen radical as a key species (Eq. 9). Diphenylphosphine **14** was added to trichloroacetonitrile **21** to form an imine derivative, which was oxidized with PIDA (PhI(OAc)₂) to yield an imino radical. Radical cyclization and nucleophilic substitution of one chloro group by the acetoxy group afforded 1,3-azaphosphole derivative **22** in 27% yield.



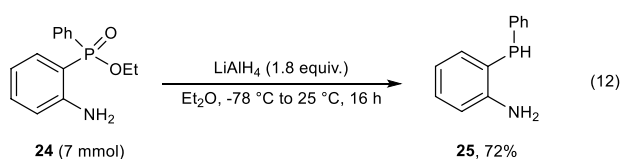
Since the aforementioned method did not achieve the construction of the 1,3-azaphosphole analogous skeleton, the known reaction was reviewed once, and the synthetic route was reconstructed (Berger et al., 2013). Phosphinic acid ester **24** is synthesized by C–P bond formation from 2-bromoaniline **6a** and PhP(O)(OEt)H **23** and then reduced with lithium aluminum hydride (LiAlH₄) to synthesize disubstituted phosphines **25**. The synthesized phosphine **25** undergoes cyclization with acetylacetone or acetaldehyde, constructing the 1,3-azaphosphole analogous skeleton (Eq. 10).



The palladium-catalyzed coupling reaction of 2-bromoaniline **6a** with PhP(O)(OEt)H **23** was examined. As shown in Eq. 11, the use of slightly excess amount of **6a** successfully resulted in good yield of the coupling product **24**.



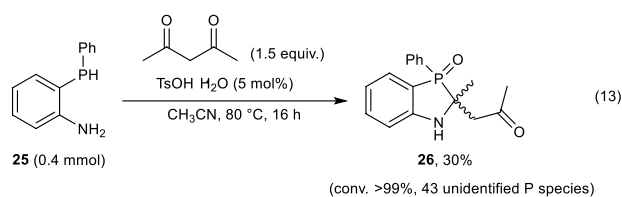
As we expected, the following reduction could be conducted using LiAlH₄, and 2-(phenylphosphanyl)aniline **25** was obtained in 72% yield (Eq. 12).



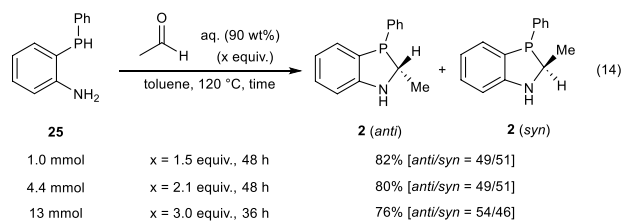
Surprisingly, 2-(phenylphosphanyl)aniline **25** is stable in air and can be purified by silica-gel column chromatography. Conventional synthetic methods of 1,3-benzoazaphosphole analogs require the use of reagents that are sensitive to air and moisture and highly toxic. In contrast, the use of air-stable **25** as a key synthetic intermediate provides a versatile and practical synthetic method for azaphospholes.

Phosphinic acid ester **24** could successfully be reduced using diisobutylaluminum hydride (DIBAL-H). As shown in Table 2, using excess DIBAL-H and prolonging the reaction time to 70 h dramatically improved the conversion of **24**, and **25** was obtained in up to 91% yield (entry 4).

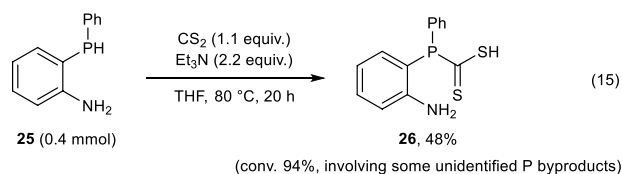
The synthesized phosphine **25** was then allowed to react with acetylacetone in the presence of a catalytic amount of TsOH to synthesize **2**; however, the desired reaction did not proceed efficiently, and compound **26** was obtained in 30% yields along with the generation of many unidentified phosphorus-containing species (Eq. 13).



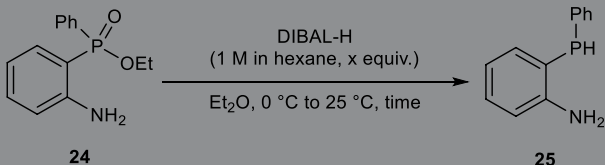
In contrast, when the solution of **25** (0.4 mmol) and acetaldehyde (1.2 equiv.) in toluene was heated at 120 °C for 20 h, the desired 2-methyl-3-phenyl-2,3-dihydro-1H-benzo[d][1,3]azaphosphole **2** was successfully obtained in 75% yield (*anti/syn* = 43/57). Prolonging the reaction time improved the yield of **2**. Furthermore, a gram-scale synthesis of **2** was successfully achieved (Eq. 14).



Moreover, we investigated the reactions of **25** with a variety of sulfurizing agents to synthesize 3-phenyl-2,3-dihydro-1H-benzo[d][1,3]azaphosphole-2-thione **3**, which is a synthetically interesting analogs of **2**. When carbon disulfide (CS₂) was used as the sulfurizing agent, (2-aminophenyl)(phenyl)phosphane-carbodithioic acid **26** was formed in 48% yield along with some unidentified phosphorus byproducts (Eq. 15).

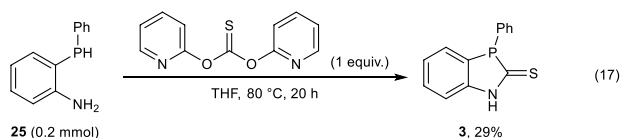
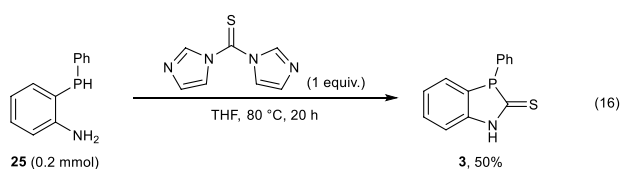


The reaction of **25** with 1,1'-thiocarbonyldiimidazole successfully afforded (**3**) in 50% yield, whereas the use of *O,O*-di-(pyridin-2-yl) carbonothioate resulted in the formation of (**3**) in 29% yield (Eqs. 16 and 17).

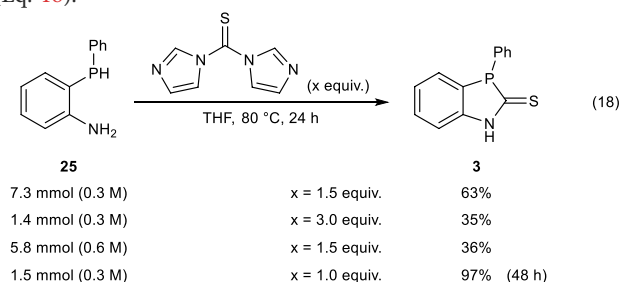
TABLE 2 Optimization of the reaction conditions for the reduction of **24** using DIBAL-H.


Entry	24 (mmol)	DIBAL-H (equiv.)	Time (h)	Yield of 25 (%) ^a
1	8	4.0	20	50
2	9	6.0	20	58
3	6	6.0	25	30
4	14	7.0	70	91
5	18	5.7	70	73

^aThe yields were determined by ³¹P NMR spectroscopy.



Encouraged by these results, we next investigated the scale-up synthesis of **3** using 1,1'-thiocarbonyldiimidazole. Although increasing the amount of 1,1'-thiocarbonyldiimidazole to 3 equiv. resulted in the formation of some unidentified compounds, using 1 equiv. of 1,1'-thiocarbonyldiimidazole and prolonging the reaction time to 48 h successfully afforded the desired **3** in up to 97% yield (Eq. 18).



4 Conclusion

In this study, 1,3-benzoazaphosphole was selected as a target molecule, and various synthetic routes were investigated to establish a fundamental technology for the formation of five-membered heterocycles containing phosphorus and nitrogen through the introduction of a phosphorus functional group into the aromatic

ring and the subsequent cyclization reaction. As a result, we found that 2-aminophenyl (phenyl)phosphine is an extremely promising synthetic intermediate with high stability and easy handling, and by using this air-stable phosphine as a key intermediate, we have succeeded in the practical synthesis of 3-benzoazaphosphole analogs, i.e., 2-methyl-3-phenyl-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole **2** and 3-phenyl-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole-2-thione **3**, for the first time.

We strongly hope that the synthetic strategy for azaphosphole derivatives presented in this study will be a new milestone in the construction of phosphorus-containing functional heterocycles and will significantly contribute to the further utilization of phosphorus-centered heterocyclic compounds in the field of organic synthesis and materials science.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Author contributions

Investigation: YY, SM, YS, KY, and AO; experiment: YY, SM, and YS; writing—original draft preparation: YY and AO; writing—review and editing: YY and AO; funding acquisition: YY and AO. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by JSPS KAKENHI Grant Numbers JP22H02124 and JP22J14638, the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Acknowledgments

This work was supported by the Nanotechnology Platform Program on Nara Institute of Science and Technology (NAIST). YY thanks the Japan Society for the Promotion of Science for the Research Fellowship for Young Scientists.

Conflict of interest

Author KY was employed by Functional Dye Division, Hayashibara Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Bansal, R. K., Gupta, N., Heinicke, J., Nikonov, G. N., Saguitova, F., and Sharma, D. C. (1999). 1*H*-1,3-Benzazaphospholes the organometallic route and a new three-step synthesis with reductive ring closure. *Synthesis* 1999, 264–269. doi:10.1055/s-1999-3394
- Baumann, M., Baxendale, I. R., Ley, S. V., and Nikbin, N. (2011). An overview of the key routes to the best selling 5-membered ring heterocyclic pharmaceuticals. *Beilstein J. Org. Chem.* 7, 442–495. doi:10.3762/bjoc.7.57
- Baumgartner, T., Neumann, T., and Wirges, B. (2004). The dithieno[3,2-*b*:2',3'-*d*] phosphole system: A novel building block for highly luminescent π -conjugated materials. *Angew. Chem. Int. Ed.* 43, 6197–6201. doi:10.1002/anie.200461301
- Bennett, J., Doyle, R. J., Salem, G., and Willis, A. C. (2006). Synthesis of a chelating hexadentate ligand with a P_3N_3 donor set. Crystal and molecular structure of $[OC-6-22]-[Co\{(R_p^*, R_p^* R_p^*)-CH_3C(CH_2)PPhC_6H_4NH_2-2\}_3](PF_6)_3$. *Dalton Trans.* 38, 4614–4622. doi:10.1039/b607847h
- Berger, O., Petit, C., Deal, E. L., and Montchamp, J. L. (2013). Phosphorus-carbon bond formation: Palladium-catalyzed cross-coupling of *H*-phosphinates and other P(O) *H*-containing compounds. *Adv. Synth. Catal.* 355, 1361–1373. doi:10.1002/adsc.201300069
- Chesnut, D. B., and Quin, L. D. (2007). The important role of the phosphorus lone pair in phosphole aromaticity. *Heteroat. Chem.* 18, 754–758. doi:10.1002/hc.20364
- Crassous, J., and Réau, R. (2008). π -Conjugated phosphole derivatives: synthesis, optoelectronic functions and coordination chemistry. *Dalton Trans.* 48, 6865–6876. doi:10.1039/b810976a
- Cyrański, M. C., Krygowski, T. M., Katritzky, A. R., and Schleyer, P. R. (2002). To what extent can aromaticity be defined uniquely? *J. Org. Chem.* 67, 1333–1338. doi:10.1021/jo016255s
- Egan, W., Tang, R., Zon, G., and Mislow, K. (1971). Barriers to pyramidal inversion at phosphorus in phospholes, phosphindoles, and dibenzophospholes. *J. Am. Chem. Soc.* 93, 6205–6216. doi:10.1021/ja00752a035
- Epitotis, N. D., and Cherry, W. (1976). On the aromaticity of phospholes and arsoles. *J. Am. Chem. Soc.* 98, 4365–4370. doi:10.1021/ja00431a003
- Hay, C., Hissler, M., Fischmeister, C., Rault-Berthelot, J., Toupet, L., Nyulászi, L., et al. (2001). Phosphole-containing π -conjugated systems: From model molecules to polymer films on electrodes. *Chem. Eur. J.* 7, 4222–4236. doi:10.1002/1521-3765(20011001)7:19<4222::aid-chem4222>3.0.co;2-3
- Heinicke, J. (1986). 1*H*-1,3-azaphosphole - neue phosphaaromaten. *Tetrahedron Lett.* 27, 5699–5702. doi:10.1016/s0040-4039(00)85304-6
- Heinicke, J., and Tzschach, A. (1982). C-metallierung an phosphaaromaten - 2-lithio-1-methyl-1,3-benzazaphosphol. *Tetrahedron Lett.* 23, 3643–3646. doi:10.1016/s0040-4039(00)88646-3
- Heinicke, J. (1989). Zur Synthese und Pyrolyse von Organoelementbenzasolderivaten des Phosphors, Arsens, Siliciums und Zinns. *J. Organomet. Chem.* 364, C17–C21. doi:10.1016/0022-328x(89)87152-9
- Hissler, M., Dyer, P. W., and Réau, R. (2003). Linear organic π -conjugated systems featuring the heavy Group 14 and 15 elements. *Coord. Chem. Rev.* 244, 1–44. doi:10.1016/s0010-8545(03)00098-5
- Hobbs, M. G., and Baumgartner, T. (2007). Recent developments in phosphole-containing oligo- and polythiophene materials. *Eur. J. Inorg. Chem.* 23, 3611–3628. doi:10.1002/chin.200744231
- Issleib, K., Vollmer, R., Oehme, H., and Meyer, H. (1978). 1,3-benzazaphosphole. *Tetrahedron Lett.* 19, 441–444. doi:10.1016/s0040-4039(01)91449-2
- Issleib, K., and Vollmer, R. (1981). Synthese und Eigenschaften Der 1,3-Benzazaphosphole. *Z. Anorg. Allg. Chem.* 481, 22–32. doi:10.1002/zaac.19814811004
- Jangir, N., PoonamDhadda, S., and Jangid, D. K. (2022). Recent advances in the synthesis of five- and six-membered heterocycles as bioactive skeleton: A concise overview. *ChemistrySelect* 7, e20210313. doi:10.1002/slct.202103139
- Kyba, E. P., and Clubb, C. N. (1984). Unsymmetrical chelating ligands. Synthesis of 1-mercapto-2-phosphinobenzenes with a variety of substituents on the ligating sites. *Inorg. Chem.* 23, 4766–4768. doi:10.1021/ic00194a069
- Matano, Y., and Imahori, H. (2009). Design and synthesis of phosphole-based π systems for novel organic materials. *Org. Biomol. Chem.* 7, 1258–1271. doi:10.1039/b819255n
- Mathey, F. (1988). The organic chemistry of phospholes. *Chem. Rev.* 88, 429–453. doi:10.1021/cr00084a005
- Niaz, B., Ghalib, M., Jones, P. G., and Heinicke, J. W. (2013a). π -Excess σ^2P ligands: Synthesis of biaryl-type 1,3-benzazaphosphole hybrid ligands and formation of $PP^--M(CO)_4$ chelate complexes. *Dalton Trans.* 42, 9523–9532. doi:10.1039/c3dt50981h
- Niaz, B., Iftikhar, F., Kindermann, M. K., Jones, P. G., and Heinicke, J. (2013b). Coplanar tetracyclic π -excess σ^2P ligands. *Eur. J. Inorg. Chem.* 2013, 4220–4227. doi:10.1002/ejic.201300342
- Ren, Y., and Baumgartner, T. (2012). Combining form with function – The dawn of phosphole-based functional materials. *Dalton Trans.* 41, 7792–7800. doi:10.1039/c2dt00024e
- Rösch, W., Faklam, T., and Regitz, M. (1987). Phosphorus compounds with unusual coordination - 201 1,2,3,4-triazaphospholes by [3+2]-cycloaddition of azides to a stable phosphalkyne. *Tetrahedron* 43, 3247–3256. doi:10.1016/S0040-4020(0190292-3)
- Su, H.-C., Fadhel, O., Yang, C.-J., Cho, T.-Y., Fave, C., Hissler, M., et al. (2006). Toward functional π -conjugated organophosphorus materials: Design of phosphole-based oligomers for electroluminescent devices. *J. Am. Chem. Soc.* 128, 983–995. doi:10.1021/ja0567182
- Walborsky, H. M., and Ronman, P. (1978). α . Addition and ortho metalation of phenyl isocyanide. *J. Org. Chem.* 43, 731–734. doi:10.1021/jo00398a046
- Zhang, L., Yu, W., Liu, C., Xu, Y., Duan, Z., and Mathey, F. (2015). The chemistry of ortho-(diarylphosphino)aryl isocyanides. *Organometallics* 34, 5697–5702. doi:10.1021/acs.organomet.5b00746

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2023.1174895/full#supplementary-material>