JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 30 Aug 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Phosphorus Radical-initiated Cascade Reaction to Access 2-Phosphoryl Substituted Quinoxalines

Yan Liu,[a,d] Xiao-Lan Chen,[a,b,*] Fan-Lin Zeng,[a] Kai Sun,[a] Chen Qu,[c] Lu-Lu Fan,[a] Zi-Long An,[a] Rui Li,[a] Chun-Feng Jing,[a] Sheng-Kai Wei,[a] Ling-Bo Qu,[a] Bing Yu,[a,*] Yuan-Qiang Sun,[a,*] and Yu-Fen Zhao[a,b]

[a] College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450001, China

[b] The Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen 361005, China

[c] Department of Chemical and Biomolecular Engineering, University of Notre Dame, Notre Dame 46556, Indiana, United States

[d] College of biological and pharmaceutical engineering, Xinyang Agriculture & Forestry University, Xinyang, 464000, China

ABSTRACT: An effective radical cascade cyclization strategy was developed, by which a wide range of 2-phosphoryl substituted quinoxalines were prepared in one-pot *via* reaction of *ortho*-diisocyanoarenes with diarylphosphine oxides in the presence of $AgNO_3$ under mild reaction conditions.

INTRODUCTION

Organophosphorus compounds occupy an important position in pharmaceutical chemistry, biochemistry, material chemistry and organic synthesis, where phosphorus substituents modify biological responses, medicinal properties, and material functions, or act as ligands of transition metals.[1] It is well known that heterocycles are basic structural skeletons existing in abundant pharmaceutical molecules.[2] Among them, heterocycle-containing organophosphorus compounds compose of an important part of biologically active molecules. In the past few decades, substantial efforts have been devoted to the development of synthetic methodologies for the diverse types of heteroarenes with phosphoryl substituents. Among them include direct autoxidative phosphorylation of heteroarenes and Ni-catalyzed inert C-O/P-H cross-coupling reaction.[3] Within the past twenty years, a great deal of growth in C-P bond formation based on the transition-metal-catalyzed C-H bond activation, towards a large variety of phosphoryl substituted heteroarenes, has been observed.[4] Even though the direct incorporation of phosphoryl moieties into heteroarenes *via* direct C-H bond activation and direct autoxidative phosphorylation mentioned above are atom economic synthetic strategies compared to traditional synthetic methods,[5] the heteroarenes must be available and used as the starting reactants. Recently, a number of achievements have been made regarding using phosphorus-centered radical-triggered cascade cyclization reactions to build up various phosphoryl substituted heteroarenes.[6] In comparison with the transition-metal-catalyzed C-H bond activation strategies, those cascade reactions can incorporate the phosphoryl substituted group simultaneously into cyclic ring construction in one step, showing much higher atom and step economy.

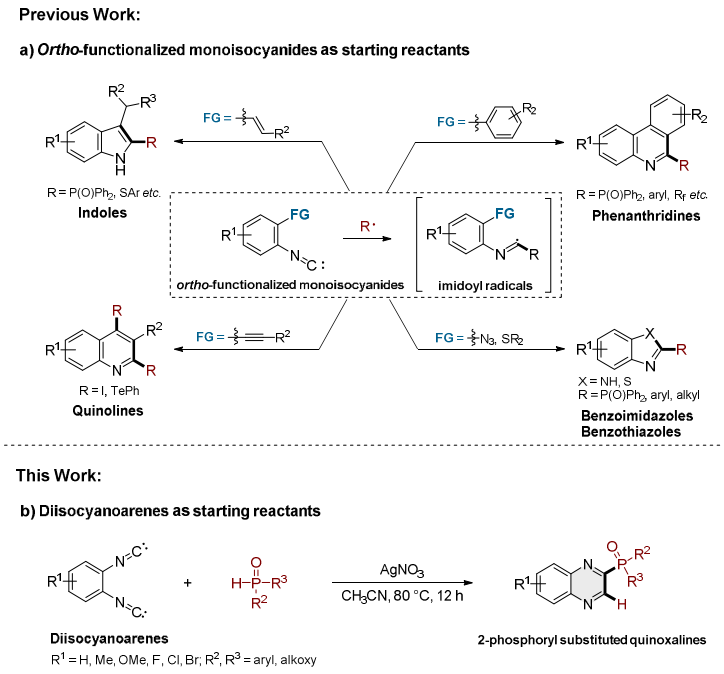
Isocyanides as versatile building blocks have been used for synthesis of broad variety of nitrogen-containing molecules that are key motifs in pharmaceutical and biological chemistry.[7] For

example, they have been extensively employed in acid-promoted multicomponent reactions,[8] such as Passerini[9] and Ugi reaction,[10] for the preparation of libraries of druglike moledules.[11] Additionally, isocyanides, in the past decades, have also found numerous applications in transition-metal catalyzed insertion chemistry.[12] It is worth mentioning that, in recent years, *ortho*-functionalized aromatic isocyanides have emerged as valuable building blocks in radical cascade chemistry for the synthesis of various *N*-heterocycle skeletons.[13] As depicted in Scheme 1a, a number of *ortho*-functionalized aromatic monoisocyanides have been used as radical acceptors to react with heteroatom (P, S or Si, etc.)- or carbon-centered radicals to generate various imidoyl radicals, and then after intramolecular addition of the imidoyl radicals to their *ortho*-functionalities to synthesize various *N*-heterocycles, including indoles,[14] quinolines,[15] phenanthridines,[16] benzoimidazoles[17] and benzothiazole.[18] It is worth emphasizing that, in spite of significant progresses achieved in the construction of different *N*-heterocycles using *ortho*-functionalized monoisocyanides as starting reactants, the practical and efficient strategy concerning the use of *ortho*-diisocyanobenzenes to build up substituted quinoxalines by a free radical-initiated cascade cyclization reaction has rarely been developed. Only methods for preparation of the iodinated (perfluoro)alkyl quinoxalines, have been reported by Studer and Yu *et al*.[19]

Over the past few years, phosphorus-centered radical-triggered cascade cyclization reactions have been widely explored aiming at accessing structurally diverse phosphorus-containing compounds with polycyclic frameworks, mainly including phosphoryl-substituted polycyclics,[20] *N*- or *O*-heteropolycyclics,[21] and spirocyclics,[22] as well as phosphorus-heteropolycyclics.[23] Despite significant progresses have been made in this area, the practical and efficient strategy by using phosphorus-centered radical-triggered cascade cyclization reaction to access phosphoryl substituted quinoxalines has not yet been established. As part of our continuing interest in the development of

novel phosphorus radical-involved reactions,[24] herein we report a novel and efficient phosphorus radical-involved cascade cyclization strategy, by which a wide range of 2-phosphoryl substituted quinoxalines were prepared in one-pot *via* reaction of *ortho*-diisocyanoarenes with diarylphosphine oxides in the presence of $AgNO_3$ under mild reaction conditions (Scheme 1b). To the best of our knowledge, this is the first example of constructing a series of 2-phosphoryl substituted quinoxalines *via* phosphorus radical-induced cascade cyclization reaction.

Scheme 1. Radical cyclization reactions of *ortho*-functionalized aromatic isocyanides.

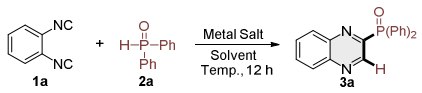


RESULTS AND DISCUSSION

We initiated this study by establishing optimal experimental conditions using the model reaction of *ortho*-diisocyanoarene **1a** with diphenylphosphine oxide **2a** in the presence of different sliver salts under open-air condition for 12 h, as summarized in Table 1. Initially, 2.0 equiv. of silver ions, from AgOAc, Ag_2CO_3, Ag_2O, $AgNO_3$ and $AgSbF_6$, respectively, were tested in CH_3CN at 80 °C for 12 h

(entries 1-5). The reaction time (12 h) was determined by TLC. It was pleased that AgOAc, Ag_2CO_3, Ag_2O and $AgNO_3$ did give good results, delivering the product **3a** in 57-74% yields, and among them, $AgNO_3$ gave the highest yield (74%) (entry 4). While in contrast, $AgSbF_6$ failed to yield the product (entry 5). The effects of solvents on the model reaction were also examined and compared (entries 4, 6-10). It was found that the reaction efficiencies were notably affected by the solvents employed. It can be seen that no or trace product was observed when DMF or THF was employed (entries 6, 8), while, in contrast, product **3a** was obtained in 13%, 45% and 61% yields when DMSO, 1,4-dioxane and toluene were employed, respectively (entries 7, 9-10). Thus, CH_3CN was still the best solvent among those tested. The effects of reaction temperatures on the model reaction were investigated as well (entries 4, 11-12). The results showed that the yield of **3a** was increased from 44% to 74% with the increase of the temperature from 60 to 80 °C and then decreased to 59% as the temperature was further increased to 100 °C. Afterwards, the amount of $AgNO_3$ was further examined (entries 4, 13-14). It was observed that the yield was dramatically increased from 38% to 74% as the amount of $AgNO_3$ was raised from 1.0 to 2.0 equiv. and the yield was almost kept unchanged as the amount of $AgNO_3$ was continuously increased up to 3.0 equiv. Several other initiation methods reported for generation of the phosphoryl radicals[25] were tested, as shown in Table 1 entry 15-19. In contrast, relatively low or trace yields of **3a** were obtained when manganese salts, $AgNO_3/K_2S_2O_8$, $AgNO_3/Mg(NO_3)_2{\cdot}6H_2O$ and $AgNO_3/Zn(NO_3)_2{\cdot}6H_2O$ were used as phosphorus radical initiators. Thus, after intensive experimentation, the optimized reaction conditions were established as follows: **1a** (0.5 mmol), **2a** (1.0 mmol), $AgNO_3$ (2.0 equiv.) were mixed in CH_3CN, at 80 °C for 12 h under open air condition.

Table 1. Optimization of reaction conditions.[a]



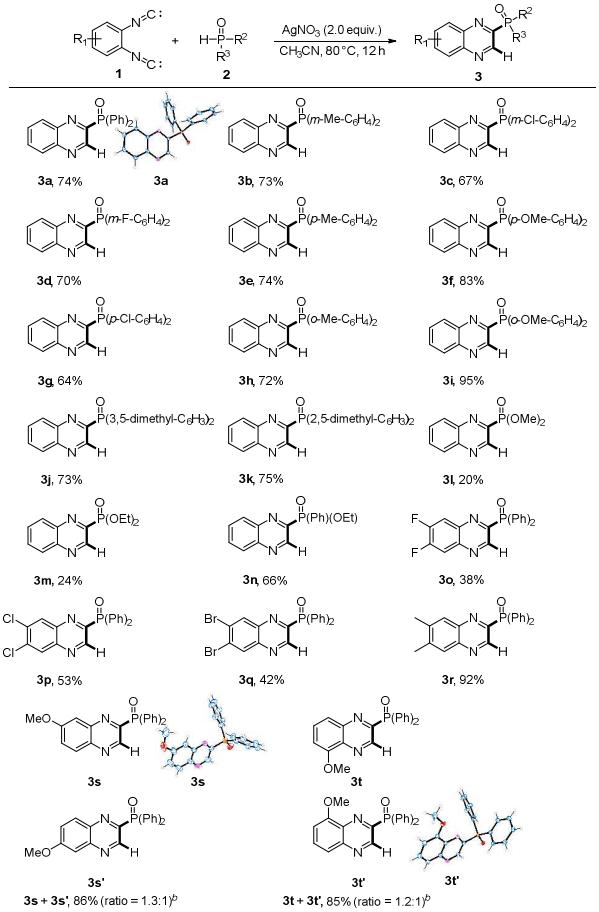
Entry	Metal Salt (equiv.)	Solvent	Yield[b] (%)
1	AgOAc (2.0)	CH_3CN	58
2	Ag_2CO_3 (1.0)	CH_3CN	59
3	Ag_2O (1.0)	CH_3CN	57
4	$AgNO_3$ (2.0)	CH_3CN	74
5	$AgSbF_6$ (2.0)	CH_3CN	N.D.
6	$AgNO_3$ (2.0)	DMF	N.D.
7	$AgNO_3$ (2.0)	DMSO	13
8	$AgNO_3$ (2.0)	THF	Trace
9	$AgNO_3$ (2.0)	1,4-dioxane	45
10	$AgNO_3$ (2.0)	toluene	61
11[c]	$AgNO_3$ (2.0)	CH_3CN	44
12[d]	$AgNO_3$ (2.0)	CH_3CN	59
13	$AgNO_3$ (1.0)	CH_3CN	38
14	$AgNO_3$ (3.0)	CH_3CN	73
15	$Mn(OAc)_2$ (2.0)	CH_3CN	54
16	$Mn(acac)_2$ (2.0)	CH_3CN	49
17[e]	$AgNO_3$ (0.2)	CH_3CN	52
18[f]	$AgNO_3$ (0.1)	CH_3CN	Trace
19[g]	$AgNO_3$ (0.1)	CH_3CN	Trace

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), metal salt, in solvent (5.0 mL) with stirring at 80 °C for 12 h. [b]Isolated yield of the product **3a**. [c]Reaction at 60 °C. [d]Reaction at 100 °C. [e]$K_2S_2O_8$ (2.0 equiv.) was added. [f]$Mg(NO_3)_2{\cdot}6H_2O$ (0.5 equiv.) was added. [g]$Zn(NO_3)_2$ (0.5 equiv.) was added.

With the optimized conditions established, we next explored the substrate scope by examining various *ortho*-diisocyanoarenes **1** and diarylphosphine oxides **2**, and the results were illustrated in Scheme 2. As it can be seen, various diphenylphosphine oxides, including those bearing electron-withdrawing groups (-F, -Cl) and electron-donating substituents (-Me, -OMe), reacted with *ortho*-diisocyanobenzene (**1a**) itself under the optimized conditions, giving the resulting diphenyl(quinoxalin-2-yl) phosphine oxides **3a-k** in good to excellent yields (64-95%). Their electronic effects were examined. It can be seen that no obvious electronic effect was observed when substituents (-Me, -F, -Cl) were present at *meta*-position of the phenyl rings in diphenylphosphine oxides (**3b-d**). Whereas, an obvious electronic effect was observed when the substituents (-Me, -OMe, -Cl) were present at *para*- position of the phenyl rings, showing relatively high yields with those bearing electron-donating substituents, compared to those bearing electron-withdrawing substituents (**3e-g**). In addition to various diarylphosphine oxides, more kinds of organophosphorus reagents were investigated (**3l-n**). The results showed that the reactions of two dialkyl *H*-phosphonates, both dimethyl *H*-phosphonate and diethyl *H*-phosphonate, with *ortho*-diisocyanobenzene afforded low yields (**3l-m**). The poor reactivities of dialkyl *H*-phosphonates might be due to their higher theoretical bond dissociation energies (BDE) of the P-H bonds.[26] In contrast, the reaction of ethyl phenylphosphinate with *ortho*-diisocyanobenzene gave a relatively good yield of product **3n**. Subsequently, various *ortho*-diisocyanobenzenes bearing different substituents were employed to react with diphenylphosphine oxide **2a**, producing the resulting diphenyl(quinoxalin-2-yl) phosphine oxides **3o-r** in moderate to excellent yields. The results from cases **3o-r** indicated that the *ortho*-diisocyanobenzene bearing electron-donating substituent (-Me) afforded an obviously high yield (**3r**) than those bearing electron-withdrawing substituents (-F, -Cl, -Br) (**3o-q**). Finally, the 4-MeO- and 3-MeO- substituted

1,2-diisocyanobezenes were applied as substrates to explore the regioselectivity of the reaction (**3s-t**). The results showed that low regioselectivities were observed, but excellent overall yields of **3s** + **3s'** and **3t** + **3t'** were achieved (86% and 85%), with two regioisomers in ratio of 1.3: 1 and 1.2: 1, respectively. Among the target products obtained, the structures of **3a**, **3s** and **3t'** were further confirmed by X-ray crystallography.[28]

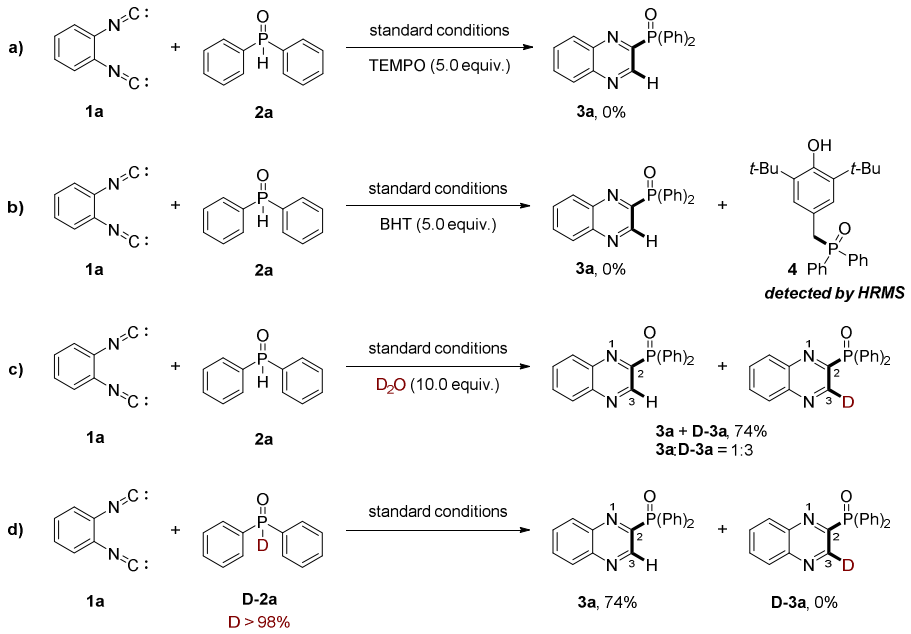
Scheme 2. Synthesis of 2-phosphoryl quinoxaline derivatives.[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol) and $AgNO_3$ (1.0 mmol) in CH_3CN (5.0 mL) at 80 °C for 12 h. Isolated yields were given. [b]Regioisomer ratio was determined by ^{31}P NMR.

We then carried out several control experiments and online mass spectrometry detection to gain mechanistic insight into the transformation. When (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), two commonly used radical scavengers, were added into the reaction, respectively. No desired product **3a** was obtained in either case, suggesting that this transformation might occur *via* a radical process (Scheme 3a-b). It is worth illustrating that when the control reaction was performed with BHT under standard reaction conditions (Scheme 3b), the product **4** was detected by high resolution mass spectrometry (HRMS) (Figure S1), reminding that diphenylphosphoryl radical ($\cdot P(O)Ph_2$) was produced and trapped by BHT.[20a, 21d] Additional control experiments were also performed to know where 3-H in product **3a** (Scheme 3c-d) came from. The result from ^1H NMR spectrum indicated that **1a** reacted with **2a** in the presence of 10.0 equiv. deuteroxide (D_2O) under standard conditions, resulting in the product **D-3a** with the deuterium atom at the 3-position of quinoxaline (Scheme 3c). And then, we used deuterium-labeled diphenylphosphine oxide to reaction with **1a** under standard conditions (Scheme 3d). The result from ^1H NMR spectrum showed that none of the deuterium-labeled product **D-3a** was obtained in this reaction. All those results indicated that the hydrogen atom in the 3-position of product **3a** might come from water in the surroundings instead of **2a** (for details, see Supporting Information). In addition, for knowing important intermediates formed during the reaction process, the model reaction solution was also analyzed by HRMS. A noticeable peak at *m/z* 436.9967, which should correspond to hydrogen molecular ion $[C_{20}H_{14}AgN_2OP+H]^+$ (Figure S5), was observed.

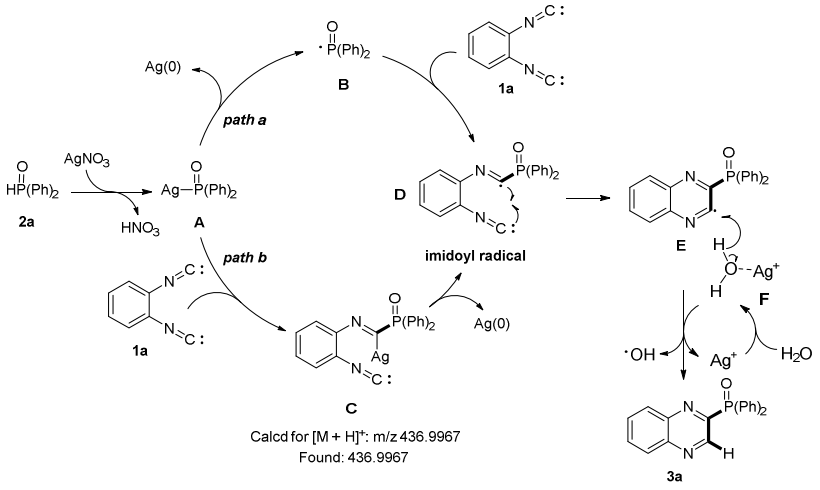
Scheme 3. Control experiments for mechanistic study.



The mechanism is proposed based the experimental outcomes and previous reports, as shown in Scheme 4. Initially, an exchange reaction of diphenyl phosphine oxide with $AgNO_3$ generates (diphenylphosphoryl)silver **A**,[20b, 21f] which then homolytically cleaves its Ag-P bond to form diphenylphosphoryl radical **B** and Ag(0) metal. Subsequently, a radical cascade cyclization is triggered by diphenylphosphoryl radical **B**. The addition of phosphoryl radical **B** to the terminal carbon of isocyano group of **1a** forms imidoyl radical intermediate **D** (path a), which subsequently undergoes an intramolecular cyclization, rendering the radical intermediate **E**. It has reported that Lewis acids can somehow activate water to make the O-H bonds in water more easily to be homolytically cleaved.[27] Here silver ion acts as a Lewis acid to combine with H_2O to form silver complex **F** in which O-H bond is more activated compared to that of a free water molecule. Then radical **E** abstracts a hydrogen atom from **F** to give final product **3a**. Alternatively, imidoyl radical intermediate **D** can also be formed by path b. (diphenylphosphoryl)silver **A** acts as a phosphoryl

radical-like species to add to the terminal carbon of isocyano group of **1a** directly, forming complex **C**, which then quickly delivers imidoyl radical intermediate **D** following with the loss of Ag(0). As mentioned above, the model reaction had been monitored by mass spectrometry experiment. The ion peak $[C_{20}H_{14}AgN_2OP+H]^+$ appearing at *m/z* 436.9967 reasonably corresponds to complex **C**.

Scheme 4. Proposed Mechanism.



CONCLUSION

In conclusion, we reported a novel and efficient radical cascade cyclization, by which a wide range of 2-phosphoryl substituted quinoxalines were prepared in one-pot *via* reaction of *ortho*-diisocyanoarenes with diarylphosphine oxides in the presence of $AgNO_3$ under mild reaction conditions (Scheme 1b). The cascade reaction is mainly constituted by the formation of imidoyl radicals followed by intramolecular cyclization. Importantly, the key intermediates for the radical cascade cyclization reaction were identified by HRMS. To the best of our knowledge, this is the first synthetic strategy for preparation of 2-phosphoryl substituted quinoxalines *via* phosphorus-radical-induced cascade cyclization reaction. Great advantages of the strategy include

experimental simplicity and efficiency, mild reaction conditions and easy work-up. Further applications of this strategy are underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. All reagents were used without further purification. TLC was performed on silica gel plates (F254, 200-300 mesh) using UV light (254/366 nm) for detection and column chromatography was performed on neutral alumina (200-300 mesh). ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{31}P NMR (162 MHz) and ^{19}F NMR (376 MHz) were measured on a Bruker Avance 400 MHz spectrometer. Proton chemical shifts δ were given in ppm using tetramethylsilane as internal standard. All NMR spectra were recorded in $CDCl_3$ at room temperature (20 ± 3 °C). To display multiplicities and signal forms correctly the following abbreviations were used: s = singlet, d = doublet, t = triplet, m = multiplet. ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. High resolution mass spectra (HRMS) were taken with a 3000-mass spectrometer, using Waters Q-Tof MS/MS system using the ESI technique. X-ray single-crystal diffraction data were collected on a Bruker SMART1000 CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å) at variable temperatures.

General procedure for the synthesis of quinoxalines 3. In a 25 mL flask, *ortho*-diisocyanobenzene **1a** (1.0 equiv., 0.5 mmol) was dissolved in CH_3CN (5 mL, 0.1 M), then $HP(O)Ph_2$ **2a** (2.0 equiv., 1.0 mmol) and $AgNO_3$ (2.0 equiv., 1.0 mmol) were added. The mixture was allowed to stir at 80 ^{o}C for 12 h and monitored by TLC. After substrate **1a** was completely consumed, the reaction was cooled to room temperature. Then, CH_2Cl_2 (10 mL) and H_2O (10 mL) was subsequently added to the resulting mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL ×

2). All combined organic solutions were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral alumina (petroleum ether/ethyl acetate = 2: 1 (V/V)) to afford the desired product **3a**.

Diphenyl(quinoxalin-2-yl)phosphine oxide (**3a**): Yellow solid (0.224 g, 74% yield), mp 171–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.19–8.12 (m, 2H), 8.02–7.93 (m, 4H), 7.87–7.77 (m, 2H), 7.58–7.45 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (s), 151.6 (s), 146.5 (s), 146.3 (s), 142.7 (d, *J* = 2.3 Hz), 142.2 (d, *J* = 17.1 Hz), 132.4–131.9 (m), 130.9 (s), 130.8 (s), 130.2 (d, *J* = 1.1 Hz), 129.6 (d, *J* = 1.9 Hz), 128.6 (d, *J* = 12.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.35 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{16}N_2OP$ 331.0995, found 331.0993.

Quinoxalin-2-yldi-m-tolylphosphine oxide (**3b**): Yellow solid (0.265 g, 74% yield), mp 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.16–8.06 (m, 2H), 7.82–7.68 (m, 6H), 7.36–7.29 (m, 4H), 2.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (s), 151.9 (s), 146.5 (s), 146.3 (s), 142.6–142.1 (m), 138.5 (d, *J* = 12.2 Hz), 133.1 (d, *J* = 2.8 Hz), 132.4 (d, *J* = 9.3 Hz), 131.8 (d, *J* = 6.5 Hz), 130.7 (d, *J* = 9.2 Hz), 130.2 (s), 129.6 (d, *J* = 1.7 Hz), 129.2 (d, *J* = 9.8 Hz), 128.4 (d, *J* = 13.0 Hz), 21.5 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.81 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_2OP$ 359.1308, found 359.1308.

Bis(3-chlorophenyl)(quinoxalin-2-yl)phosphine oxide (**3c**): Yellow solid (0.266 g, 67% yield), mp 157–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.21 (dd, *J* = 10.4, 1.9 Hz, 2H), 8.01–7.86 (m, 6H), 7.58–7.53 (m, 2H), 7.49–7.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (s), 150.2 (s), 146.4 (s), 146.2 (s), 142.9 (d, *J* = 2.4 Hz), 142.1 (d, *J* = 17.4 Hz), 135.2 (d, *J* = 16.3 Hz), 133.8 (s), 132.8 (d, *J* = 2.7 Hz), 132.4 (s), 131.8 (d, *J* = 10.4 Hz), 131.1 (s), 130.4–129.9 (m), 129.8 (d, *J* = 1.9 Hz). ^{31}P NMR

(162 MHz, $CDCl_3$) δ 17.20 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}Cl_2N_2OP$ 399.0215, found 399.0211.

Bis(3-fluorophenyl)(quinoxalin-2-yl)phosphine oxide (**3d**): Yellow solid (0.256 g, 70% yield), mp 143–145 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.18 (d, *J* = 9.0 Hz, 2H), 7.94–7.63 (m, 6H), 7.54–7.45 (m, 2H), 7.32–7.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (d, *J* = 17.5 Hz), 161.2 (d, *J* = 17.5 Hz), 151.5 (s), 150.2 (s), 146.2 (d, *J* = 22.4 Hz), 142.9 (d, *J* = 2.1 Hz), 142.1 (d, *J* = 17.4 Hz), 134.1 (d, *J* = 5.7 Hz), 133.0 (d, *J* = 5.4 Hz), 132.4 (s), 131.1 (s), 130.8 (dd, *J* = 14.4, 7.5 Hz), 130.2 (s), 129.7 (d, *J* = 1.3 Hz), 127.8 (dd, *J* = 8.8, 3.2 Hz), 119.8 (dd, *J* = 21.2, 2.3 Hz), 118.9 (dd, *J* = 22.8, 10.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.39 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.35 (d, *J* = 6.0 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}F_2N_2OP$ 367.0806, found 367.0797.

Quinoxalin-2-yldi-p-tolylphosphine oxide (**3e**): Yellow solid (0.261 g, 73% yield), mp 178–180 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.19–8.09 (m, 2H), 7.88–7.76 (m, 6H), 7.28 (d, *J* = 5.7 Hz, 4H), 2.38 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (s), 152.1 (s), 146.4 (d, *J* = 22.0 Hz), 142.7 (dd, *J* = 22.2, 2.5 Hz), 142.2 (d, *J* = 17.0 Hz), 132.2 (d, *J* = 10.0 Hz), 131.8 (s), 130.4 (d, *J* = 42.3 Hz), 129.6 (d, *J* = 1.7 Hz), 129.30 (d, *J* = 12.7 Hz), 128.9 (s), 127.8 (s), 21.7 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.13 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_2OP$ 359.1308, found 359.1308.

Bis(4-methoxyphenyl)(quinoxalin-2-yl)phosphine oxide (**3f**): White solid (0.324 g, 83% yield), mp 182–184 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.18–8.11 (m, 2H), 7.89–7.78 (m, 6H), 6.98 (dd, *J* = 8.8, 2.3 Hz, 4H), 3.83 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 2.9 Hz), 153.6 (s), 152.4 (s), 146.4 (d, *J* = 22.1 Hz), 142.6 (d, *J* = 2.3 Hz), 142.2 (d, *J* = 17.0 Hz), 134.0 (d, *J* = 11.0 Hz), 131.2 (d, *J* = 116.5 Hz), 130.2 (d, *J* = 0.9 Hz), 129.6 (d, *J* = 1.8 Hz), 122.8 (d, *J* = 111.9 Hz), 114.2 (d,

J = 13.4 Hz), 55.4 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.23 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_2O_3P$ 391.1206, found 391.1197.

bis(4-chlorophenyl)(quinoxalin-2-yl)phosphine oxide (**3g**): Yellow solid (0.255 g, 64% yield), mp 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.18 (dd, *J* = 15.3, 7.9 Hz, 2H), 8.01–7.73 (m, 6H), 7.48 (dd, *J* = 8.4, 2.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (s), 150.7 (s), 146.4 (s), 146.2 (s), 142.9 (d, *J* = 2.3 Hz), 142.1 (d, *J* = 17.4 Hz), 139.3 (d, *J* = 3.5 Hz), 133.4 (d, *J* = 10.4 Hz), 132.3 (s), 131.1 (s), 130.2 (s), 130.1 (d, *J* = 0.9 Hz), 129.8 (d, *J* = 1.9 Hz), 129.1 (d, *J* = 13.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.77 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}Cl_2N_2OP$ 399.0215, found 399.0205.

quinoxalin-2-yldi-o-tolylphosphine oxide (**3h**): Yellow solid (0.258 g, 72% yield), mp 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.19–8.06 (m, 2H), 7.87–7.78 (m, 2H), 7.49–7.38 (m, 4H), 7.29 (dd, *J* = 7.4, 4.7 Hz, 2H), 7.23–7.16 (m, 2H), 2.48 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (s), 152.1 (s), 147.2 (d, *J* = 22.6 Hz), 143.1 (d, *J* = 8.5 Hz), 142.5 (d, *J* = 2.2 Hz), 142.0 (d, *J* = 17.1 Hz), 133.1 (d, *J* = 12.0 Hz), 132.4 (d, *J* = 2.7 Hz), 132.2–131.8 (m), 130.7 (s), 130.5–130.0 (m), 129.6 (d, *J* = 1.8 Hz), 129.2 (s), 125.6 (d, *J* = 12.8 Hz), 21.9 (d, *J* = 4.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.76 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_2OP$ 359.1308, found 359.1309.

Bis(2-methoxyphenyl)(quinoxalin-2-yl)phosphine oxide (**3i**): White solid (0.370 g, 95% yield), mp 183–185 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.85–7.72 (m, 4H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.14–7.10 (m, 2H), 6.94 (dd, *J* = 8.2, 5.5 Hz, 2H), 3.56 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (d, *J* = 2.9 Hz), 155.1 (s), 153.8 (s), 147.0 (d, *J* = 27.9 Hz), 142.6–141.7 (m), 134.9–134.6 (m), 131.1 (s), 130.4 (d, *J* = 1.3 Hz), 129.9 (s), 129.1 (d, *J* = 2.2 Hz),

121.2 (d, *J* = 12.3 Hz), 119.1 (s), 118.0 (s), 111.1 (d, *J* = 6.6 Hz), 55.4 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.97 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_2O_3P$ 391.1206, found 391.1204.

Bis(3,5-dimethylphenyl)(quinoxalin-2-yl)phosphine oxide (**3j**): Yellow solid (0.282 g, 73% yield), mp 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.92–7.78 (m, 2H), 7.30 (dd, *J* = 19.0, 11.7 Hz, 4H), 7.19 (dd, *J* = 7.6, 4.8 Hz, 2H), 2.39 (s, 6H), 2.26 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (s), 152.4 (s), 147.2 (d, *J* = 22.6 Hz), 142.4 (d, *J* = 2.2 Hz), 142.0 (d, *J* = 17.1 Hz), 139.7 (d, *J* = 8.6 Hz), 135.2 (d, *J* = 12.7 Hz), 133.5 – 133.2 (m), 131.9 (t, *J* = 6.1 Hz), 130.6 (s), 130.3 (d, *J* = 0.9 Hz), 129.9 (s), 129.6 (d, *J* = 1.8 Hz), 128.9 (s), 21.5 (d, *J* = 4.1 Hz), 21.0 (s).^{31}P NMR (162 MHz, $CDCl_3$) δ 29.47 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{24}N_2OP$ 387.1621, found 387.1616.

Bis(2,5-dimethylphenyl)(quinoxalin-2-yl)phosphine oxide (**3k**): Yellow solid (0.290 g, 75% yield), mp 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.89–7.77 (m, 2H), 7.31 (dd, *J* = 13.9, 7.8 Hz, 2H), 7.12 (d, *J* = 3.8 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 2.44 (s, 6H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (s), 152.5 (s), 147.2 (d, *J* = 22.7 Hz), 143.0–142.8 (m), 142.4 (d, *J* = 2.2 Hz), 142.0 (d, *J* = 16.9 Hz), 133.0 (dd, *J* = 46.0, 11.9 Hz), 131.8 (s), 130.6 (s), 130.3 (d, *J* = 0.8 Hz), 129.5 (d, *J* = 1.9 Hz), 127.0 (s), 126.3 (d, *J* = 13.2 Hz), 126.0 (s), 21.8 (d, *J* = 4.1 Hz), 21.4 (d, *J* = 1.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.87 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{24}N_2OP$ 387.1621, found 387.1612.

Dimethyl quinoxalin-2-ylphosphonate (**3l**): Yellow oil (0.048 g, 20% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.29–8.18 (m, 2H), 7.95–7.86 (m, 2H), 4.00 (d, *J* = 11.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (s), 146.2 (d, *J* = 27.9 Hz), 146.0 (s), 143.2 (d, *J* = 2.6 Hz), 142.3 (d, *J* =

21.5 Hz), 132.5–129.4 (m), 54.0 (d, J = 6.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 10.77 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{12}N_2O_3P$ 239.0580, found 239.0578.

Diethyl quinoxalin-2-ylphosphonate (**3m**): Yellow oil (0.064 g, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.28 (dd, J = 8.1, 1.7 Hz, 1H), 8.19 (dd, J = 8.3, 1.5 Hz, 1H), 7.94–7.86 (m, 2H), 4.44–4.31 (m, 4H), 1.43 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2 (s), 147.0 (s), 146.2 (d, J = 27.6 Hz), 143.1–142.2 (m), 132.1 (s), 130.9(s), 130.3 (s), 129.5 (d, J = 2.3 Hz), 63.6 (d, J = 6.1 Hz), 16.4 (d, J = 6.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.39 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{16}N_2O_3P$ 267.0893, found 267.0896.

Ethyl phenyl(quinoxalin-2-yl)phosphinate (**3n**): Yellow oil (0.197 g, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.23–7.99 (m, 4H), 7.88–7.77 (m, 2H), 7.60–7.45 (m, 3H), 4.30–4.23 (m, 2H), 1.43 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (s), 149.9 (s), 146.4 (s), 146.2 (s), 142.8–142.4 (m), 132.9 (d, J = 2.8 Hz), 132.4 (d, J = 10.0 Hz), 132.0 (s), 130.7 (s), 130.3 (d, J = 1.2 Hz), 129.5 (d, J = 1.9 Hz), 128.6 (d, J = 13.4 Hz), 62.3 (d, J = 6.3 Hz), 16.6 (d, J = 6.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.24 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}N_2O_2P$ 299.0944, found 299.0944.

(6,7-difluoroquinoxalin-2-yl)diphenylphosphine oxide (**3o**): White solid (0.139 g, 38% yield), mp 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.01–7.86 (m, 6H), 7.63–7.47 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (dd, J = 74.8, 16.4 Hz), 153.4 (s), 152.1 (s), 152.1 (dd, J = 73.2, 16.2 Hz). 146.7 (dd, J = 21.6, 2.4 Hz), 140.8–139.1 (m), 132.5 (d, J = 2.7 Hz), 132.1 (d, J = 9.7 Hz), 131.0 (dd, J = 105.3, 6.4 Hz), 128.6 (d, J = 12.4 Hz), 115.5 (dd, J = 39.2, 17.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.53 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.44 (d, J = 20.6 Hz), -127.36 (d, J = 20.6 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}F_2N_2OP$ 367.0806, found 367.0794.

(6,7-dichloroquinoxalin-2-yl)diphenylphosphine oxide (**3p**): Yellow solid (0.211 g, 53% yield), mp 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.31 (d, *J* = 2.5 Hz, 2H), 8.00–7.89 (m, 4H), 7.62–7.48 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4 (s), 153.2 (s), 147.4 (d, *J* = 21.6 Hz), 141.4 (d, *J* = 2.3 Hz), 140.7 (d, *J* = 17.3 Hz), 136.9 (s), 135.8 (s), 132.5 (d, *J* = 2.8 Hz), 132.1 (d, *J* = 9.7 Hz), 131.5 (s), 130.7–130.1 (m), 128.7 (d, *J* = 12.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.50 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}Cl_2N_2OP$ 399.0215, found 399.0218.

(6,7-dibromoquinoxalin-2-yl)diphenylphosphine oxide (**3q**): Yellow solid (0.204 g, 42% yield), mp 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.50 (d, *J* = 5.4 Hz, 2H), 8.01–7.89 (m, 4H), 7.66–7.46 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (s), 153.3 (s), 147.5 (d, *J* = 21.6 Hz), 141.7 (d, *J* = 2.2 Hz), 141.2 (d, *J* = 17.3 Hz), 133.8 (dd, *J* = 29.9, 1.5 Hz), 132.3 (dd, *J* = 45.4, 6.2 Hz), 131.4 (s), 130.4 (s), 129.2 (s), 128.7 (d, *J* = 12.4 Hz), 127.9 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.57 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}Br_2N_2OP$ 486.9205, found 486.9207.

(6,7-dimethylquinoxalin-2-yl)diphenylphosphine oxide (**3r**): Yellow solid (0.329 g, 92% yield), mp 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.00–7.90 (m, 4H), 7.88 (s, 2H), 7.55–7.43 (m, 6H), 2.48 (d, *J* = 9.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (s), 150.1 (s), 145.8 (s), 145.6 (s), 143.2 (s), 141.9–141.5 (m), 141.3 (d, *J* = 17.3 Hz), 132.3–132.1 (m), 131.3 (s), 129.0 (d, *J* = 0.9 Hz), 128.6–128.3 (m), 20.6 (s), 20.3 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.49 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_2OP$ 359.1308, found 359.1297.

(7-methoxyquinoxalin-2-yl)diphenylphosphine oxide (**3s**)*:* Yellow solid (0.175 g, 48% yield), mp 155–157 °C. Yellow solid (0.175 g, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.04–7.93 (m, 5H), 7.58–7.46 (m, 7H), 7.38 (d, *J* = 2.7 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (s), 149.3 (s), 148.0 (s), 146.8 (s), 146.6 (s), 144.7 (d, *J* = 2.3 Hz), 138.8 (d, *J* = 17.2 Hz), 132.1–132.3

(m), 131.3 (d, J = 5.6 Hz), 128.5 (d, J = 12.3 Hz), 124.6 (s), 106.4 (s), 56.0 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.75 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{18}N_2O_2P$ 361.1100, found 361.1095.

(6-methoxyquinoxalin-2-yl)diphenylphosphine oxide (**3s'**): Yellow solid (0.135 g, 38% yield), mp 126–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.04–7.93 (m, 5H), 7.58–7.46 (m, 7H), 7.38 (d, J = 2.7 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (s), 149.3 (s), 148.0 (s), 146.8 (s), 146.6 (s), 144.7 (d, J = 2.3 Hz), 138.8 (d, J = 17.3 Hz), 132.8–132.0 (m), 131.2 (s), 128.5 (d, J = 12.3 Hz), 124.6 (s), 106.4 (d, J = 1.7 Hz), 56.0 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.53 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{18}N_2O_2P$ 361.1100, found 361.1095.

(5-methoxyquinoxalin-2-yl)diphenylphosphine oxide (**3t**): Yellow solid (0.167 g, 46% yield), mp 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.00–7.92 (m, 4H), 7.78–7.72 (m, 2H), 7.58–7.47 (m, 6H), 7.18 (dd, J = 5.7, 3.2 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (d, J = 1.9 Hz), 153.3 (s), 152.0 (s), 145.2 (s), 145.0 (s), 143.1 (d, J = 17.0 Hz), 135.0 (d, J = 2.5 Hz), 132.5–131.8 (m), 130.9 (d, J = 4.6 Hz), 128.5 (d, J = 12.3 Hz), 121.7 (s), 109.6 (s), 56.5 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.29 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{18}N_2O_2P$ 361.1100, found 361.1097.

(8-methoxyquinoxalin-2-yl)diphenylphosphine oxide (**3t'**)*:* Yellow solid (0.139 g, 39% yield), mp 173–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.00–7.92 (m, 4H), 7.78–7.72 (m, 2H), 7.57–7.47 (m, 6H), 7.18 (dd, J = 5.7, 3.2 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (s), 150.9 (s), 149.6 (s), 146.7 (s), 146.5 (s), 143.5 (d, J = 2.3 Hz), 134.9 (d, J = 16.6 Hz), 132.5–132.0 (m), 131.2 (s), 128.5 (d, J = 12.3 Hz), 121.1 (d, J = 1.8 Hz),109.1 (s), 56.6 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.70 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{18}N_2O_2P$ 361.1100, found 361.1097.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

The spectra for all compounds and single-crystal X-ray data; the primary mechanistic studies of the reactions (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: chenxl@zzu.edu.cn.

* E-mail: bingyu@zzu.edu.cn.

* E-mail: sunyq@zzu.edu.cn.

ORCID

Xiaolan Chen: 0000-0002-3061-8456

Bing Yu: 0000-0002-2423-1212

Yufen Zhao: 0000-0002-8513-1354

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We acknowledge financial support from National Natural Science Foundation of China (Nos. 21501010, 21708035), the 2017 Science and Technology Innovation Team in Henan Province (No. 22120001), Major scientific and technological projects in Henan Province (No. 181100310500), China

Postdoctoral Science Foundation (No. 2017M620302), the Henan Postdoctoral Foundation, and the Key Laboratory for Chemical Biology of Fujian Province (Xiamen University) (No. 2017002)

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