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Cobalt- or Rhodium-Catalyzed Synthesis of 1,2-Dihydrophosphete Oxides via C–H Activation and Formal Phosphoryl Migration

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A highly stereo- and chemoselective intermolecular coupling of diverse heterocycles with dialkynylphosphine oxides has been realized via cobalt/rhodium-catalyzed C–H bond activation. This protocol provides an efficient synthetic entry to functionalized 1,2-dihydrophosphete oxides in excellent yields via merger of C-H bond activation and formal 1,2-migration of the phosphoryl group. Compared with traditional methods of synthesis of 1,2-dihydrophosphetes that predominantly relied on stoichiometric metal reagents, this catalytic system features high efficiency, a relatively short reaction time, atom-economy, and operational simplicity. Photophysical properties of selected 1,2-dihydrophosphete oxides are also disclosed.

Introduction

Organophosphorus molecules are an important class of compounds which are not only widely utilized as ligands or organocatalysts for diverse transformations but also function as drugs and bioactive molecules.[1] The development of efficient methods for the synthesis of functionalized organophosphorus compounds has attracted continuous attention.[2] In particular, four-membered phosphrous compounds have found vast applications in the studies of catalysis, medicinal chemistry, and material sciences (Figure 1).[3] For instance, compound **I** is known as a new organic catalyst that enables the reductive C–N cross-coupling of functionalized nitroalkanes with arylboronic acids, and compound **II** exhibits unique photophysical properties, while compound **III** is employed as a useful chiral bidentate ligand. However, efficient methods to access four-membered phosphacycles, especially 1,2-dihydrophosphete (oxides), only remain sporadic. In 1985, Mathey and co-workers reported synthesis of metal complexes of 2-keto-1,2-dihydrophosphetes via CO insertion into a P–C bond of phosphirene-chromium, -molybdenum, and -tungsten pentacarbonyl complexes as a result of ring expansion.[4] After that, they further disclosed coupling of electron-poor phospha-alkene P-W(CO)$_5$ complexes with electron-rich alkynes via [2 + 2] cycloadditions (Scheme 1a1).[5] In 1989, Knobler reported the reaction of diphenyltitanacyclobutene with phenyldichlorophosphine, allowing the first isolation of free 1,2-dihydrophosphetes (Scheme 1a2).[6] In 2021, Pietschnig and co-workers established a transition-metal free annulation reaction between 1,3-diynes and phosphanides (Scheme 1a3).[7] Recently, Gates accomplished cyclization of 1-phosphabutadiene and isolated Au- and Pd-stablized 1,2-dihydrophosphete complexes (Scheme 1a4).[8]

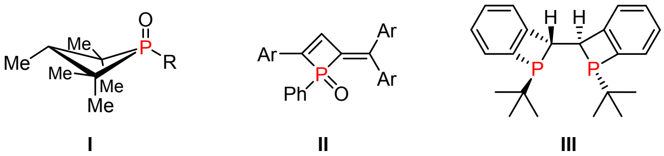

Figure 1. Selected examples of four-membered phosphacycles.

Rearrangement reactions provide straightforward and efficient accesses to complex organic frameworks via structural reorganizations.[9] In 1989, Lukehart developed stoiciometric reactions of trialkynylphosphine oxide and platinium hydride that involves Pt-H addition and rearrangement reactions (Scheme 1b1).[10] In 1997, Majoral reported synthesis of metalacycle-supported 1,2-dihydrophosphete via coupling of bis(alkynyl)phosphines with zirconocene-benzynes (Scheme 1b2).[11] Very recently, Cummins realized phosphinidene transfer to cyclopropenones for synthesis of phosphet-2-ones(Scheme 1b3).[12] Despite these strategies, the majority systems require the employment of stoichiometric amounts of metal reagents such as zirconium, platinum, titanium, and tungsten complexes. In addition, the reaction scope is also limited due to compatibility issues. Therefore, efficient synthesis of 1,2-dihydrophosphetes from readily available reagents still awaits further development.

We reasoned that 1,2-dihydrophosphetes can be accessed via catalytic manipulation of the triple bond in dialkynylphosphine (oxides). Indeed, metal-catalyzed coupling of dialkynylphosphine oxides/sulfides delivered various powerful strategies to create complex phosphacycles.[13] The

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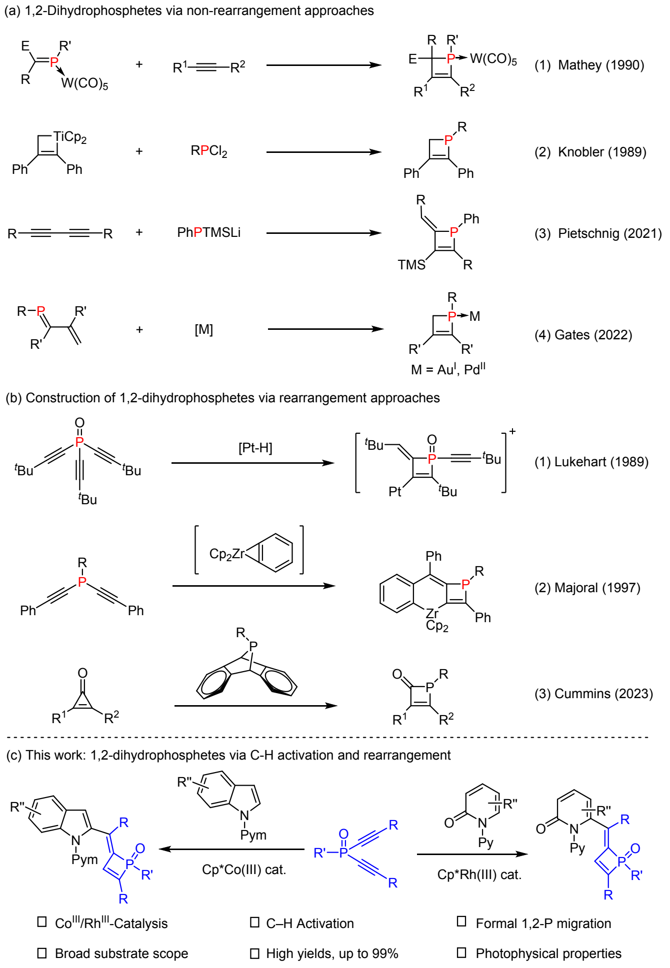
C≡C bond in the dialkynylphosphine is expected to readily participate as a special π-bond in C−H activation reactions, and the resulting alkenyl phosphine intermediate may also undergo rearrangement to give complex structures. While significant achievements have been made in C−H bond activation catalyzed by transition metals such as Pd, Rh, Ru, Ir, Mn, and Co,[14] P-containing substrates are generally less explored either as the arene or the coupling reagent.[15] Consequently, catalytic construction of four-membered phosphacycles remains a formidable challenge. By taking advantage of ready availability of arenes, our objective was to synthesize 1,2-dihydrophosphetes via integration of C−H bond activation and migration of the P atom in the reactive intermediate. Herein, we report the development of cobalt^{III} or rhodium^{III}-catalyzed C−H activation of diverse classes of heteroarenes and coupling with dialkynylphosphine oxides, which affords a series of rare 1,2-dihydrophosphete oxides in high yields (Scheme 1c). The mechanism of this reaction has also been briefly explored.

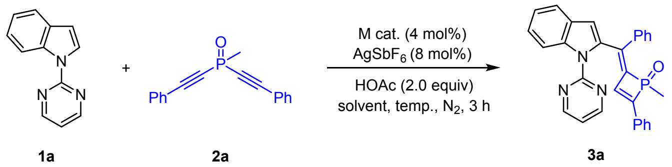


Scheme 1. Synthesis of 1,2-Dihydrophosphetes.

Results and Discussion

We commenced our studies with optimization of reaction parameters of the coupling of 1-(pyrimidin-2-yl)-1*H*-indole **1a** and methylbis(phenylethynyl)phosphine oxide **2a** (Table 1). The reaction occurred at 100 °C in the presence of a $Cp^*Co(CO)I_2/AgSbF_6$ catalyst in DCE for 3 h, and the desired four membered P^V=O product (**3a**) was isolated in 95% yield. It was found that $Cp^*Co(CO)I_2$ showed superiority to other catalysts such as $[Cp^*RhCl_2]_2$ and $[Cp^*Co(MeCN)_3](BF_4)_2$ (Table 1, entries 1−3). The screening of solvents showed that TFE was the best choice (Table 1, entries 4−8), and a nearly quantitative yield was realized when the reaction was performed at 100 °C (entry 8). In addition, the reaction efficiency was slightly effected when the reaction temperature was lowered from 100 °C to 60 °C (entries 8-12).

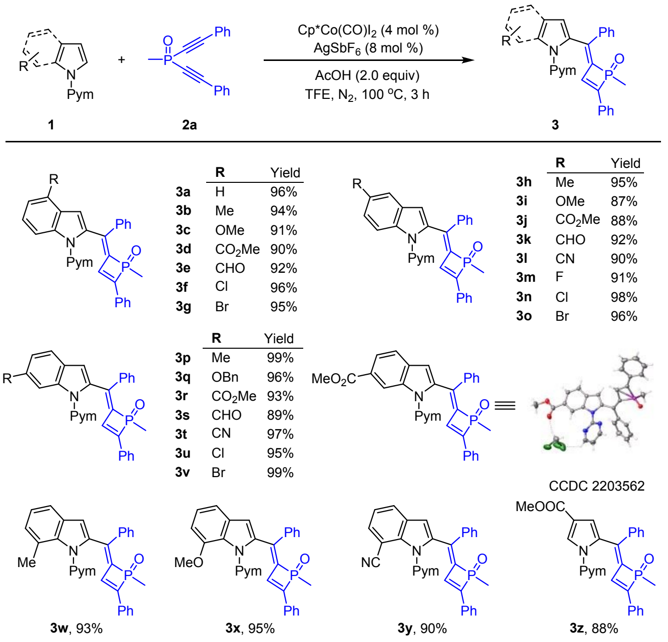
Table 1. Optimization Studies.[a]



entry	catalyst	solvent	temp. (°C)	yield (%)[b]
1	$[Cp^*RhCl_2]_2$[c]	DCE	100	78
2	$[Cp^*Co(MeCN)_3](BF_4)_2$	DCE	100	93[d]
3	$Cp^*Co(CO)I_2$	DCE	100	95
4	$Cp^*Co(CO)I_2$	MeCN	100	43
5	$Cp^*Co(CO)I_2$	THF	100	trace
6	$Cp^*Co(CO)I_2$	EA	100	35
7	$Cp^*Co(CO)I_2$	dioxane	100	40
8	$Cp^*Co(CO)I_2$	TFE	100	98
9	$Cp^*Co(CO)I_2$	TFE	90	96
10	$Cp^*Co(CO)I_2$	TFE	80	91
11	$Cp^*Co(CO)I_2$	TFE	70	90
12	$Cp^*Co(CO)I_2$	TFE	60	93

[a] The reactions were carried out with **1a** (0.13 mmol), **2a** (0.10 mmol), M cat. (4 mol %), $AgSbF_6$ (8 mol%) and HOAc (2.0 equiv) in a solvent (1.0 mL) under N_2 for 3 h. [b] Isolated yields. [c] $AgSbF_6$ (16 mol%) was used. [d] No $AgSbF_6$ was used.

With the optimized conditions established, we next evaluated the generality of this transformation (Scheme 2). Indoles with a variety of functionalities at the 4-position such as methyl, methoxy, halogens, ester group and formyl reacted smoothly to give the corresponding products **3a**−**3g** in excellent yields. Besides, other functional groups such as electron-donating (Me, OBn), -withdrawing (CO_2Me, CHO and CN), and halogen groups (F, Cl and Br) at the C-5 position of the indoles were all generally tolerated, and the corresponding products (**3h**−**3o**) were isolated in high yields. Indoles bearing a 6-substituent underwent rapid coupling with **2a** in good to excellent chemical yields (up to 99% yield, **3p**-**3v**). The structure of **3r** was confirmed by X-ray crystallographic analysis.[16] 7-Substituted indoles were also viable, affording the desired coupling products in good efficiency (**3w**–**3y**). Moreover, a pyrrole substrate was also amenable to this transformation, delivering the desired product **3z** in 88% yield.



	R	Yield
3a	H	96%
3b	Me	94%
3c	OMe	91%
3d	CO$_2$Me	90%
3e	CHO	92%
3f	Cl	96%
3g	Br	95%

	R	Yield
3h	Me	95%
3i	OMe	87%
3j	CO$_2$Me	88%
3k	CHO	92%
3l	CN	90%
3m	F	91%
3n	Cl	98%
3o	Br	96%

	R	Yield
3p	Me	99%
3q	OBn	96%
3r	CO$_2$Me	93%
3s	CHO	89%
3t	CN	97%
3u	Cl	95%
3v	Br	99%

Scheme 2. Substrate Scope of Indoles by Cobalt-Catalysis.[a,b] (a) Conditions: indoles **1** (0.26 mmol), dialkynylphosphine oxide **2a** (0.20 mmol, 1.0 equiv), Cp*Co(CO)I$_2$ (4.0 mol%), AgSbF$_6$ (8 mol%), HOAc (2.0 equiv) in 2.0 mL of TFE under N$_2$ at 100 °C for 3 h. (b) Isolated yields.

The scope of the dialkynylphosphine oxides was next investigated (Scheme 3). Examination of the *para*- and *meta*-substituents in the benzene ring of the diyne terminus revealed that both electron-withdrawing and -donating groups were tolerated, providing products **4a**–**4f** in 88–97% yields. The reaction worked well when a 1-naphthyl-substituted substrate was used, delivering the product **4g** in 80% yield. Besides, dialkynylphosphine oxides containing heteroaryl groups in the alkyne unit were also applicable, and 2- and 3-thienyl groups produced the desired products **4h** and **4i** in 94% and 85% yield, respectively. Gratifyingly, alkenyl-substituted substrates afforded satisfactory results as in the isolation of product **4j** in 88% yield. Cyclic and linear alkyl substituents were all tolerated under the reaction conditions with corresponding **4k**–**4m** being isolated in 72-81% yields. Of note, changing the P-methyl group diyne to a P-phenyl one led to the desired product **4n** in high isolated yield. To our disappointment, replacing the methyl group on the phosphorus center with a methoxyl or *tert*-butyl group failed to deliver any desired product.

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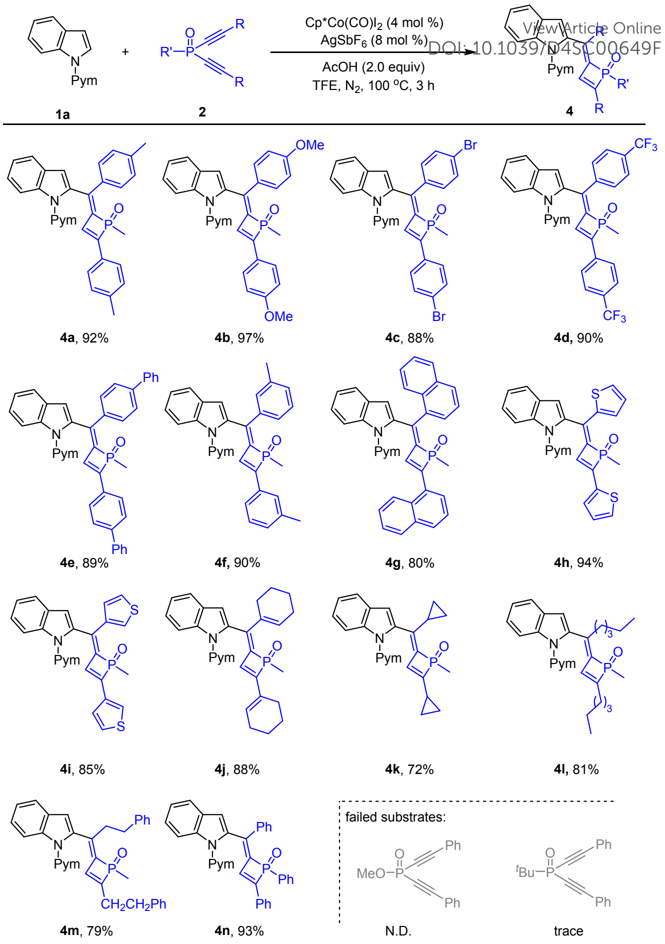

Scheme 3. Substrate Scope of Dialkynylphosphine Oxides by Cobalt Catalysis.[a,b] (a) Conditions: indoles **1a** (0.26 mmol), dialkynylphosphine oxides **2** (0.20 mmol, 1.0 equiv), Cp*Co(CO)I$_2$ (4.0 mol%), AgSbF$_6$ (8 mol%), and HOAc (2.0 equiv) in TFE (2 mL) under N$_2$ at 100 °C for 3 h. (b) Isolated yields.

To further expand the scope of arenes, 2-pyridones were then examined. The coupling 2-pyridone **5a** and dialkynylphosphine oxides **2a** only gave poor efficiency when using with the same Cp*Co(Co)I$_2$ catalyst. To our delight, when catalyzed by [Cp*RhCl$_2$]$_2$/AgSbF$_6$ in DCE, the desired product was isolated in 92% yield (see Supporting Information for details). The scope of the 2-pyridone substrate was then explored using the dialkynylphosphine oxides **2a** as a coupling partner (Scheme 4). Thus, 2-pyridones bearing a series of substituents such as methyl, methoxyl, benzyloxyl, halogen, cyano and trifluoromethyl at the C3- or C4-positions were all compatible in this reaction, delivering the corresponding products in consistently high yields (**6b**–**6l**, 78-93% yield). 6-Bromo-isoquinoinone was tolerated under the reaction conditions and the coupling afforded the corresponding products **6m** in 85% yield, which was confirmed by X-ray crystallographic studies.[17] 2-Pyridone bearing a 5-methyl-*N*-pyridinyl group reacted smoothly to give product **6n** in 90% yield. Regarding the dialkynylphosphine oxides, our results indicated that a series of phenyl, naphthyl, heteroaryl, and alkyl groups in the alkyne were all tolerated, furnishing the corresponding 1,2-dihydrophosphete oxides in good to high

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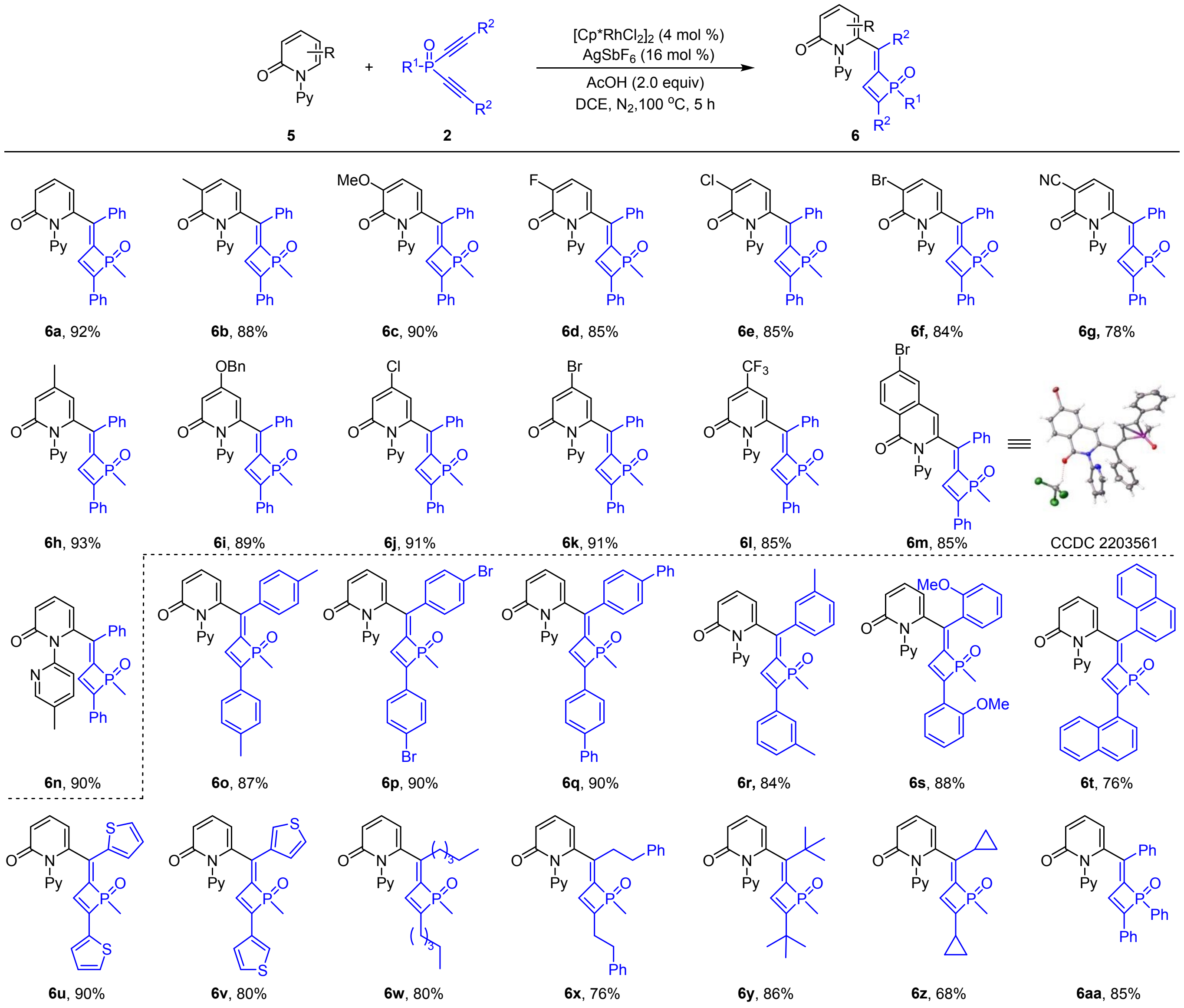
yields (**6o**–**6z**, 68-90%). The tolerance of bulky ^{t}Bu groups in **6y** may provide mechanistic insights (vide infra).



Scheme 4. Scope of 2-Pyridones and Dialkynylphosphine Oxides by Rhodium Catalysis.[a,b] (a) Conditions: 2-pyridones **5** (0.26 mmol), dialkynylphosphine oxides **2** (0.20 mmol, 1.0 equiv), [Cp*RhCl$_2$]$_2$ (4.0 mol%), AgSbF$_6$ (16 mol%), HOAc (2.0 equiv) in 2.0 mL of DCE under N$_2$ at 100 °C for 5 h. (b) Isolated yields.

The photophysical properties of six products were briefly investigated (Figure 2 and Table 2). Compounds **3a**–**4h** displayed an intense absorption band in the UV/Vis region centered at 370 nm, attributed to the π–π* transitions of the extended π-conjugated system. Besides, these derivatives exhibited blue emissions. The fluorescent emission maxima appeared in arrange of 470–504 nm (Table 2). These results may indicate their potential for applications in photoelectronics.

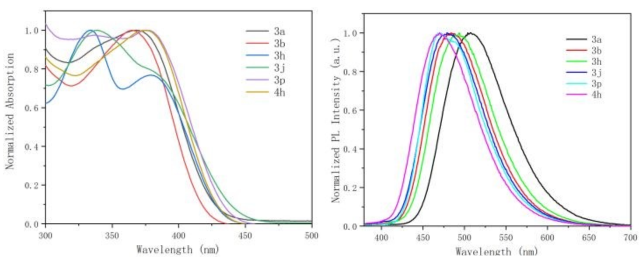


Figure 2. Normalized Absorption (left) and Emission (right) Spectra of **3a**, **3b**, **3h**, **3j**, **3p**, and **4h** in DCM (1×10-5 M).

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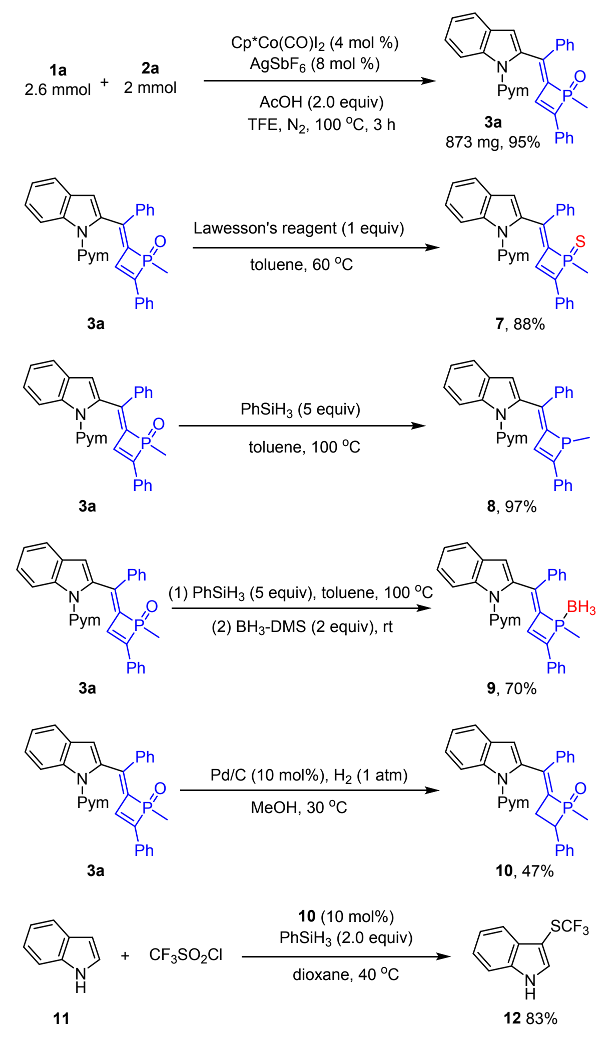
compound	$\lambda_{abs}{}^{a}$ (nm)	$\lambda_{em}{}^{b}$ (nm)	$\Phi_F{}^{c}$
3a	368	504	0.0383
3b	365	484	0.0478
3h	334, 379	494	0.0282
3j	339	479	0.0305
3p	346, 375	470	0.0430
4h	374	470	0.0288

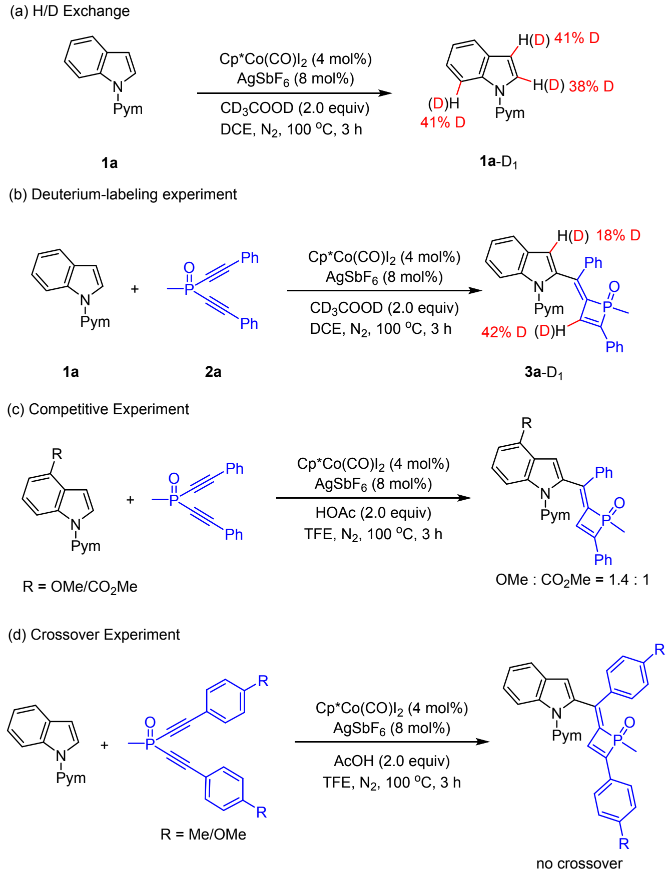
Table 2. Photophysical properties of selected products (1×10^{-5} M in DCM).

[a] Absorption maxima. [b] Fluorescent emission maxima. [c] Absolute quantum yields (determined with an integrating sphere system)



Scheme 5. Synthetic Applications of a Product.

Synthetic applications of a representative product have been demonstrated (Scheme 5). The reaction of **1a** and dialkynylphosphine oxide **2a** was scaled up to a mmol scale, from which product **3a** was isolated in 95% yield. Treatment of **3a** with Lawesson's reagent afforded the phosphine sulfide **7** in high yield. The phosphine oxide **3a** was reduced by $PhSiH_3$ to give phosphine **8** in excellent yield. Reduction of the phosphine oxide by $PhSiH_3$ followed by protection by borane gave the adduct **9** in 70% yield. Tetrahydrophosphete oxide **10** was formed in 47% yield under a palladium/H_2 reductive system. Meanwhile, the tetrahydrophosphete oxide **10** as an organic phosphine catalyst could catalytic deoxygenation of CF_3SO_2Cl and reaction with indole to afford C3-trifluoromethylsulfenylation indole **12** in 83% yield.[3j]



Scheme 6. Mechanistic Studies.

Preliminary mechanistic studies were conducted to gain insight into the reaction mechanism (Scheme 6 and 7). First, H/D exchange experiment was conducted using CD_3COOD as deuterium source, and H/D scrambling was observed at the C2, C3, and C7 of indole **1a** (Scheme 6a), supporting the reversibility of C–H activation at these positions under the reaction conditions. A deuterium labeling experiment was then performed using **1a** and **2a** in the presence of CD_3COOD (Scheme 6b), and analysis of the product by ^1H NMR spectroscopy revealed that the 3-position of the indole and olefinic C–H of dihydrophosphete ring was substantially deuterated. The significant deuteration at the olefinic C–H position likely suggests protonolysis of a Co–C bond in the catalytic cycle. Parallel competitive reactions of two electronically distinguishable indoles **1b** (R = OMe) and **1d** (R = CO_2Me) have been conducted, and the more electron-rich indole tends to react with slightly higher reactivity (Scheme 6c). Next, a crossover experiment using a mixture of **2a** (R = Me) and **2b** (R = OMe) was then performed, and HRMS analysis of the

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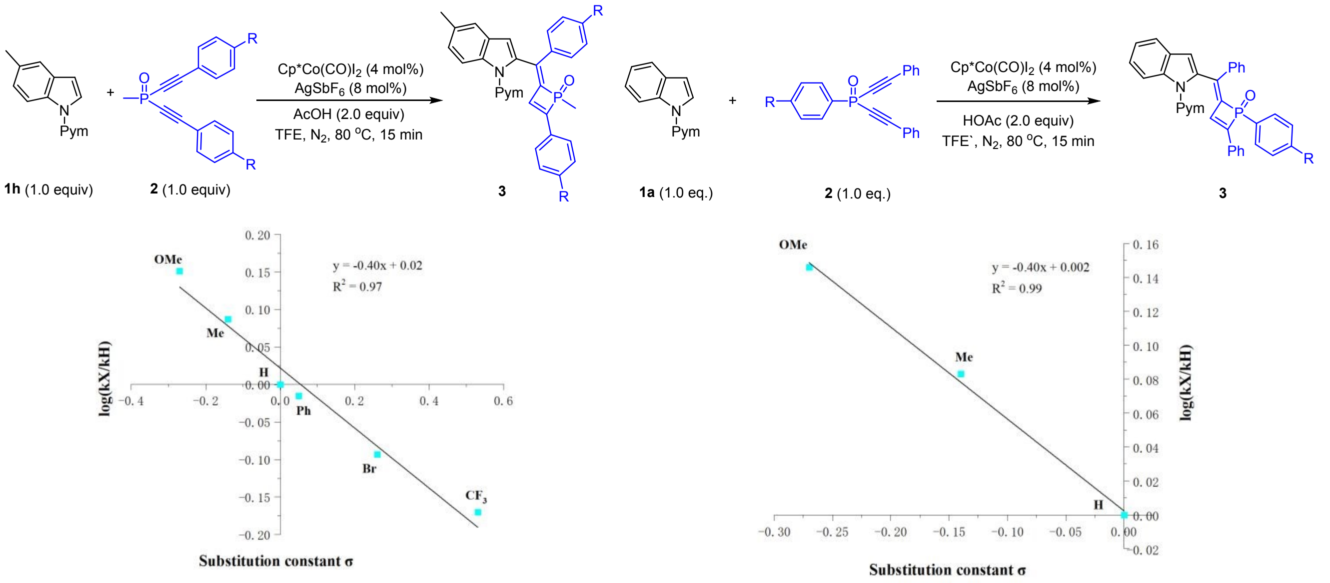
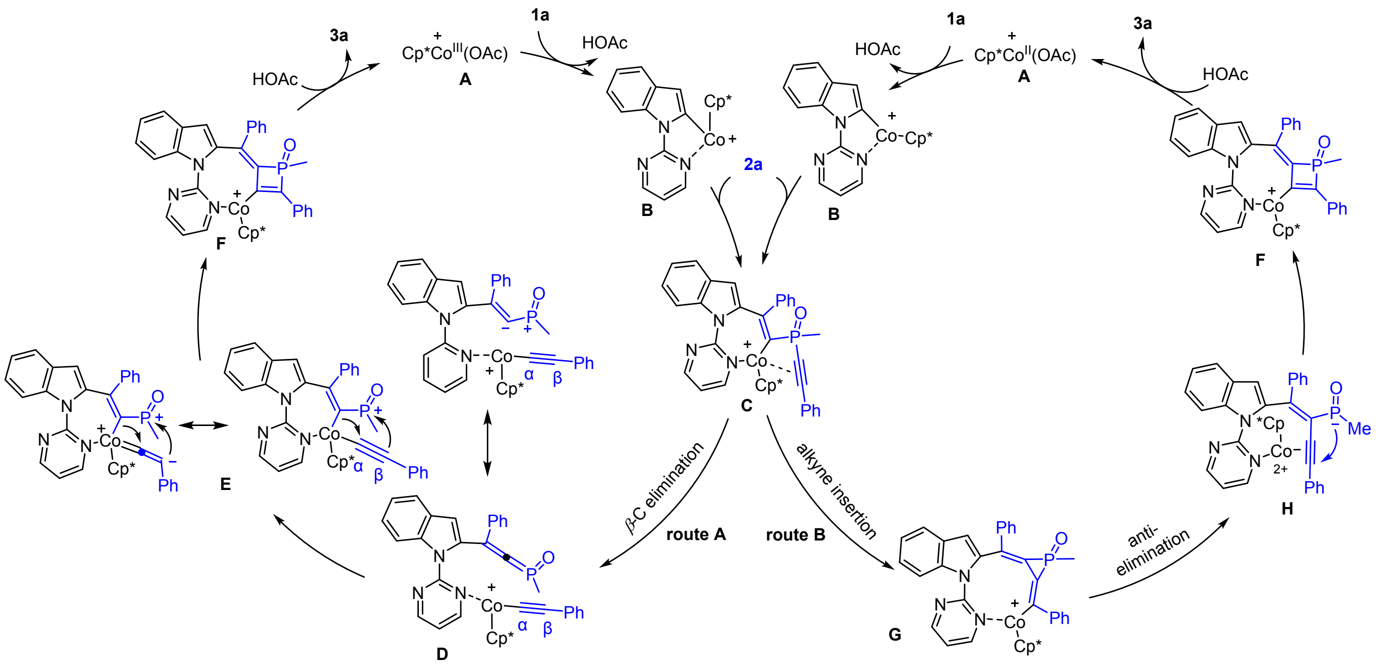
product mixture indicated that no crossover product was present, revealing an intramolecular P=O migration process (Scheme 6d). Moreover, Hammett studies were also performed for a series of indoles with various substituents at the C5-position (see Supporting Information for details) and for a series of dialkynylphosphine oxides bearing different para substituents (Scheme 7). A linear correlation was observed for each series through the Hammett plot. A negative *ρ* value (-0.40 for the dialkynylphosphine oxide series) and (-1.18 for the indole series (see Supporting Information for details)) was observed for each plot, and this outcome suggests positive charge accumulation in the transition state, which is stabilized by an electron-donating substituent.



Scheme 7. Hammett studies for the cobalt-catalyzed systems.



Scheme 8. Proposed Possible Reaction Pathways.

On the basis of these results and related literature reports of C–H activation-coupling with alkynes, a plausible mechanism for the Co(III)-catalyzed system is proposed in Scheme 8. Starting form a Co (III) caboxylate species, C–H activation occurs at the C(2) position to give the intermediate **B** via cyclometaltion. Subsequently, the resulting Co–C(2) bond undergoes migratory insertion into an alkyne unit of the incmoing diyne **2a**, forming an alkenylcobalt intermediate **C**. At this stage, two pathways are possible. In route A (Scheme 8 left), β-C(alkynyl) elimination is proposed to give a cobalt alkynyl intermediate with a pendant phosphonium ylide (**D**). Coordination of the carbanion leads to an alkenyl intermediate **E**, and the subsequent α insertion of the Co-alkenyl bond into the vinylidene-like C(α) triggers a nucleoplic addition of the C(β) to the phosphonium center. The resluting intermediate **F** undergoes protonolysis to release the final product and completes the catalytic cycle. Alternatively in route B (Scheme 8 right), the intermediate **C** is proposed to undergo the 2nd migratory insertion into the alkyne to generate a three-membered phosphacycle (**G**). Anti-elimination[18] of the phosphinate anion gives an enyne intermediate **H**, where the alkyne unit is activated toward 4-*endo*-dig cyclization to form the same intermediate **F**. While it is challenging to unequivocally distinguish between these two pathways by experimental methods, we tend to prefer the route A based on the kinetic studies. Hammett plots (Scheme 7) of both series of Co-catalyzed reactions supported the intermediacy of key cationic species that is stabilized by EDGs. Accordingly, the route A is more likely. On the other hand, the isolation of product **6y** in good yields under the Rh-catalyzed conditions starting from the diyne with *tert*-butyl termini also argues against the route B. This is because the formation of the corresponding rhodium congener of intermediate **G** will cause strong steric repulsions between the metal center and proximal ^{t}Bu group.

Conclusions

In summary, a series of 1,2-dihydrophosphete oxides were efficiently synthesized through a cobalt/rhodium-catalyzed C−H alkenylation/P=O migration sequence via the coupling of indoles/2-pyridone with dialkynylphosphine oxides. A large array of functional groups were tolerated in this catalytic system. The photophysical properties of selected products indicate the potentiallity of 1,2-dihydrophosphetes as electroluminescent materials. Mechanistic studies have been performed and Hammett studies suggest build-up of positive charges in the catalytic cycle, and the P-alkynyl group likely undergoes beta-elimination and migratory insertion. Asymmetric reactions of related chemistry of diynes are underway in our laboratory.

Data availability

Further details of the experimental procedure, ^{1}H and ^{13}C NMR, and X-ray crystallographic data for products **3r** and **6m** are available in the ESI.

Author Contributions

X.L. and G.Z. conceived the idea and directed the project. S.X. and R.M. performed the experiments. X.L. and S.X. wrote the manuscript.

Conflicts of interest

The authors declare no competing financial interests.

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