


 Cite this: *RSC Adv.*, 2020, **10**, 12730

Received 27th February 2020

Accepted 19th March 2020

DOI: 10.1039/d0ra02503h

rsc.li/rsc-advances

Synthesis of 1,2,4-azadiphosphole derivatives based on vanadium-catalyzed [2+2+1] cycloaddition reactions of azobenzenes with phosphaalkynes†

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A new synthetic method is described to construct 1,2,4-azadiphosphole derivatives based on vanadium-catalyzed [2+2+1] cycloaddition reactions. Reactions of azobenzenes as nitrogen sources with phosphaalkynes as phosphorous counterparts in the presence of $\text{VCl}_2(\text{thf})_2$ as a catalyst afford the corresponding 1,2,4-azadiphospholes.

Phosphorus heterocycles have provided important structural motifs to explore materials science and coordination chemistry.¹ To access diverse skeletons, development of new and efficient synthetic methods is quite important. In addition to the conventional synthetic methods typically forming carbon-phosphorous single bonds, the use of phosphaalkynes as substrates is beneficial to construct phosphorous-containing π -systems.² Stoichiometric reactivity of phosphaalkynes with transition metal complexes has been studied extensively,³ but catalytic reactions of phosphaalkynes under transition metal catalysis have been limited to several sporadic examples.^{4,5} Recently, our group has reported catalytic [2+2+2] cycloaddition reactions to produce phosphabenzenes and [3+2] cycloaddition reactions to produce 1,3-azaphospholes based on the use of phosphaalkynes as substrates.⁵ To investigate further utility of phosphaalkynes to prepare aromatic compounds containing phosphorus atoms, we have focused on the synthesis of 1,2,4-azadiphospholes as next targets.

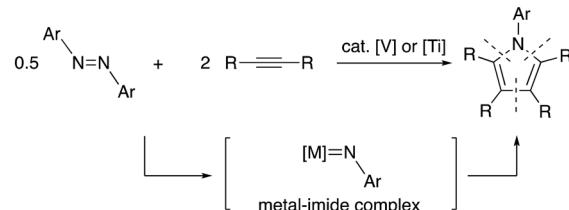
Synthetic examples of 1,2,4-azadiphospholes have been limited to only a few reports.^{6,7} To the best of our knowledge, the first synthesis of the 1,2,4-azadiphosphole skeleton was reported in 1991, where a 1,2,4-azadiphosphole derivative was prepared based on a thermal dimerization of an amino-substituted phosphaalkyne.^{6a} Later, other groups reported stoichiometric reactions of titanium- and vanadium-imide complexes as nitrogen sources with phosphaalkynes.^{6b-d} Although these stoichiometric reactions provided effective

synthetic methods of 1,2,4-azadiphospholes, transition metal-catalyzed synthesis of 1,2,4-azadiphospholes has never been achieved until now.

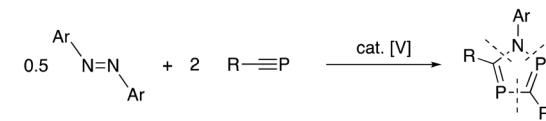
Recently, titanium-catalyzed [2+2+1] cycloaddition reactions have been reported by Tonks and co-workers to prepare pyrroles from reactions of azobenzenes with alkynes (Scheme 1a).⁸ In this reaction system, titanium-imide species generated from azobenzenes worked as a key intermediate. More recently, a similar pyrrole synthesis using vanadium-catalyzed reaction system has been reported by Tonks, Mashima, Tsurugi and co-workers.⁹

Based on the research background, we have envisaged metal-catalyzed [2+2+1] cycloaddition reactions of azobenzenes with phosphaalkynes to produce 1,2,4-azadiphospholes (Scheme 1b). As a result, we have found that some vanadium complexes worked as effective catalysts toward the formation of 1,2,4-azadiphospholes. Herein, we report experimental results in detail.

a) Previous Works: Synthesis of Pyrroles



b) This Work: Synthesis of 1,2,4-Azadiphospholes



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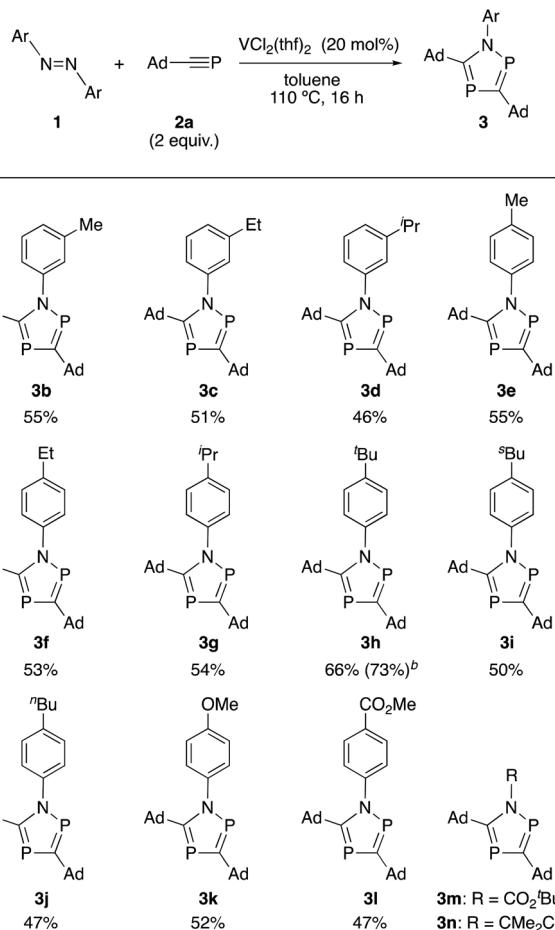
† Electronic supplementary information (ESI) available. CCDC 1974229. For ESI and crystallographic data in CIF or other electronic format see DOI: [10.1039/d0ra02503h](https://doi.org/10.1039/d0ra02503h)

Scheme 1 Catalytic [2+2+1] cycloaddition reactions with azobenzenes as nitrogen sources in heterocycle synthesis.



First, investigation of reaction conditions was carried out with the use of azobenzene (**1a**) and 1-adamantylphosphaethyne (**2a**) as typical substrates. When the reaction of **1a** (1 equiv.) with **2a** (2 equiv.) in the presence of 20 mol% of $\text{VCl}_3(\text{thf})_3$ was carried out in toluene at 110 °C for 16 hours, the desired 1,2,4-azadiphosphole (**3a**) was obtained in 48% yield (Table 1, entry 1). Replacing $\text{VCl}_3(\text{thf})_3$ with $\text{VBr}_3(\text{thf})_3$ and $\text{VCl}_3(\text{py})_3$ was not effective in the current reaction system (Table 1, entries 2 and 3). Then, we investigated the use of $\text{VCl}_2(\text{thf})_2$, $\text{VCl}_2(1,4\text{-dioxane})_2$ and $\text{VI}_2(\text{thf})_4$. Among these catalysts, $\text{VCl}_2(\text{thf})_2$ showed the highest reactivity to afford the desired product **3a** in 60% yield (Table 1, entries 4–6). Next, addition of ligands was examined. When bidentate phosphine ligands such as 1,1-bis(diphenylphosphino)methane (dpmm) or 1,2-bis(diphenylphosphino)ethane (dppe) was used, only lower yields of the product were obtained (Table 1, entries 7 and 8) while no formation of the desired product was observed when 2,2'-bipyridine was used as a ligand (Table 1, entry 9). Separately, we confirmed no formation of **3a** in the absence of vanadium complexes. Based on these results, we have chosen the use of $\text{VCl}_2(\text{thf})_2$ as the optimal catalyst.

With the optimized reaction conditions in hand, the use of other substrates was investigated. The use of various functionalized azobenzene derivatives was examined (Scheme 2). When 3-methyl-, 3-ethyl- and 3-isopropyl-substituted azobenzenes were used, the corresponding products (**3b**, **3c** and **3d**) were obtained in 55%, 51% and 46% yield, respectively. Effect of alkyl groups at the 4-position of the benzene rings in azobenzene was also examined. Introduction of methyl, ethyl, isopropyl, *tert*-butyl, *sec*-butyl and *n*-butyl groups afforded the corresponding products (**3e**–**3j**) in good yields. The reaction system was tolerant toward oxygen functional groups such as 4-methoxy and 4-methoxycarbonyl groups to give the desired products (**3k** and **3l**) in 52% and 47% yields, respectively. Unfortunately, an



Scheme 2 Reactions of azobenzene with 1-adamantylphosphaethyne **2a**. ^aReactions of azobenzenes **1** (0.1 mmol) with **2a** (0.2 mmol) in the presence of $\text{VCl}_2(\text{thf})_2$ (20 mol%) in toluene (2.0 mL) at 110 °C for 16 h. ^b¹H NMR yield with C_6Me_6 as an internal standard.

Table 1 Investigation of reaction conditions^a

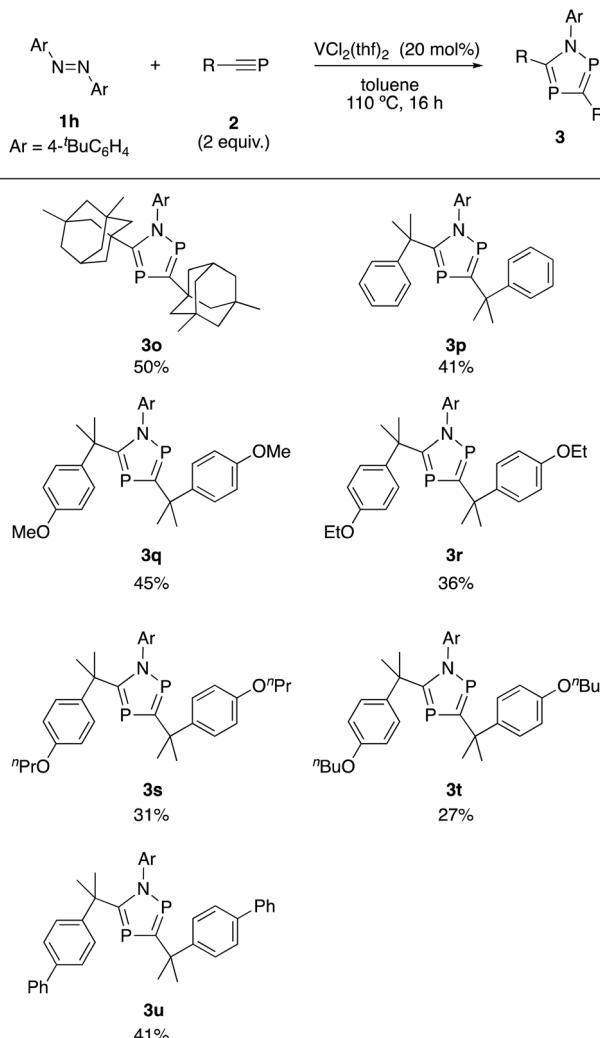
Entry	[V] catalyst	Ligand	Yield (%)	Reaction conditions		
				1a	2a (2 equiv.)	[V] (20 mol%)
1	$\text{VCl}_3(\text{thf})_3$	—	48			ligands (20 mol%)
2	$\text{VBr}_3(\text{thf})_3$	—	42			
3	$\text{VCl}_3(\text{py})_3$	—	0			
4	$\text{VCl}_2(\text{thf})_2$	—	60			
5	$\text{VCl}_2(1,4\text{-dioxane})_2$	—	47			
6	$\text{VI}_2(\text{thf})_4$	—	27			
7	$\text{VCl}_2(\text{thf})_2$	dpmm	27			
8	$\text{VCl}_2(\text{thf})_2$	dppe	20			
9	$\text{VCl}_2(\text{thf})_2$	2,2'-Bipyridine	0			

^a Reactions of **1a** (0.10 mmol) with **2a** (0.20 mmol) in the presence of a catalyst (20 mol%) and a ligand (20 mol%) in toluene (2.0 mL) at 110 °C for 16 h.

azodicarboxylate ester was not applicable in this reaction system resulting in no formation of the corresponding product (**3m**). We also examined 2,2'-azobis(isobutyronitrile) as an aliphatic azo compound, but the corresponding product (**3n**) was not obtained at all.

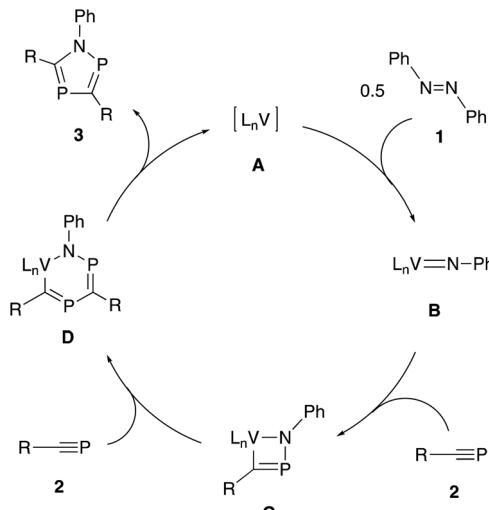
Next, the use of various phosphaalkynes was investigated (Scheme 3). A phosphaalkyne bearing 3,5-dimethyl-1-adamantyl moiety was successfully transformed into the corresponding product (**3o**) in 50% yield. The use of phosphaalkyne bearing a benzene ring was also successful to afford the corresponding product (**3p**) in 41% yield. Introduction of various alkoxyphenyl moieties into the phenyl ring was also investigated and the corresponding products were obtained in moderate yields (**3q**–**3t**). When the biphenyl substituent was introduced in phosphaalkyne, the corresponding product (**3u**) was obtained in 41% yield.

As mentioned above, recently vanadium-catalyzed [2+2+1] cycloaddition reactions of azobenzenes with alkynes to afford the pyrroles were reported.⁹ In this reaction system, bis(trimethylsilyl)aniline was used as an additive along with $\text{VCl}_3(\text{thf})_3$ catalyst, and a vanadium-bis(imide) complex was proposed to be a catalytically active species. Bis(trimethylsilyl)aniline



Scheme 3 Reactions of 1,2-di(4-*tert*-butyl)diazene **1h** with phosphaalkynes **2**. ^aReactions of **1h** (0.1 mmol) with phosphaalkynes **2** (0.2 mmol) in the presence of $\text{VCl}_2(\text{thf})_2$ (20 mol%) in toluene (2.0 mL) at 110 °C for 16 h.

supplies an imide moiety on the vanadium center through a redox neutral ligand exchange process and the second imide moiety comes from azobenzene substrates through an oxidative process, where the generated vanadium-bis(imide) complex is supposed to undergo further reactions to give the pyrroles.



Scheme 5 Plausible reaction pathway.

According to the experimental result, we investigated the effect of bis(trimethylsilyl)aniline as an additive in the current reaction system (Scheme 4). When bis(trimethylsilyl)aniline (20 mol%) was added along with $\text{VCl}_2(\text{thf})_2$ catalyst in the reaction of **1a** with **2a**, the yield of **3a** did not improve. This result suggests that the introduction of imide moiety from bis(trimethylsilyl)aniline was not effective in this reaction system. Previously, vanadium-mono(imide) complexes were reported to react stoichiometrically with phosphaalkynes to give the corresponding 1,2,4-azadiphospholes.^{6b,c} Based on the experimental result, we consider that a vanadium-mono(imide) species may work as a catalytically active species in the current reaction system.

Based on these observations, a plausible reaction pathway is shown in Scheme 5. First, vanadium complex **A** reacts with an azobenzene **1** to give vanadium-imide complex **B**. Then, [2+2] cycloaddition reaction occurs between **B** and a phosphaalkyne **2** to afford a four-membered ring intermediate **C**. Subsequent insertion of the second phosphaalkyne **2** forms a six-membered ring intermediate **D**. Finally, reductive elimination affords the desired 1,2,4-azadiphosphole **3** accompanied by the regeneration of the initial vanadium complex **A**.

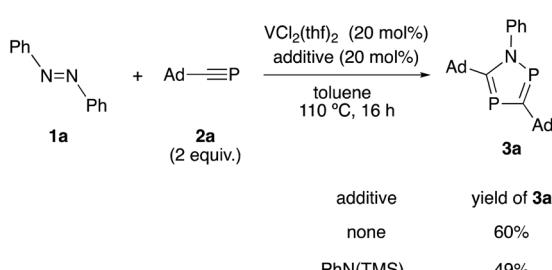
In summary, we have succeeded in the development of the first vanadium-catalyzed [2+2+1] cycloaddition reactions of azobenzenes with phosphaalkynes to synthesize a variety of 1,2,4-azadiphospholes. We believe the present study has opened a new aspect of synthetic application for the utilization of phosphaalkynes as building blocks in the construction of phosphorous-containing heterocyclic skeletons.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The present project was supported by CREST, JST (grant JPMJCR1541). We acknowledge Grants-in-Aid for Scientific



Scheme 4 Effect of bis(trimethylsilyl)aniline as additive.



Research (Grants JP17H01201, JP15H05798, JP18K19093, and JP19K15556) from JSPS and MEXT.

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