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Copper-Catalyzed [3+2] Cycloaddition Reactions of Isocyanoacetates with Phosphaalkynes to Prepare 1,3-Azaphospholes**

Wenbin Liang, Kazunari Nakajima,* Ken Sakata* and Yoshiaki Nishibayashi*

Abstract: A novel copper-catalyzed synthetic method is described for phosphorous- and nitrogen-containing heterocycles such as 1,3azaphospholes. Cycloaddition reactions of various isocyanoacetates with phosphaalkynes in the presence of copper bromide, dppm, and potassium carbonate afford the corresponding 1,3-azaphospholes in high yields with a complete selectivity. Some dppm-bridged dicopper complexes work as active species for the formation of 1,3azaphospholes.

 \boldsymbol{U} nsaturated heterocyclic compounds whose skeletons involve two distinct heteroatoms are important motifs in materials science and coordination chemistry due to unique electronic properties originated from the two heteroatoms.^[1] Five-membered ring skeletons containing nitrogen and phosphorous atoms i.e. 1,3azaphosphole and its derivatives have attracted particular interest, because 1,3-azaphospholes exhibit markedly different natures from the phosphorous-only five-membered cycles, phospholes. In general, phospholes are non-planar, non- (or less) aromatic, and unstable under aerobic conditions.^[1b,2] In sharp contrast, the phosphorous atom in 1,3-azaphospholes forms delocalized π -bonds. Hence, 1,3azaphospholes are planar, aromatic, and usually inert under air and moisture.^[1,3] Despite such attractive nature, synthetic methods for 1,3-azaphospholes have been limited. Actually, a number of arenefused 1,3-azphospholes have been prepared,^[3,4] but there have been a few examples for the synthesis of 1,3-azaphospholes with the

isolated ring system.^[5]

To develop a new method to construct such nitrogen- and phosphorous-containing heterocycles, we envisaged that [3+2] cycloaddition reactions between phosphaalkynes^[6,7] and nitrogenous counterparts under transition metal-catalysis might be an effective strategy. Previously, Regitz and co-workers reported Rh-catalyzed synthesis of 1,3-oxaphosphole derivatives via Rh-carbenoid intermediates.^[8] Recently, our group has succeeded in ironcatalyzed [2+2+2] cycloaddition reactions to afford phosphabenzene derivatives.^[9] However, the utilization of phosphaalkynes under a variety of transition metal catalysis has still been less explored.

As the nitrogenous counterparts, we have focused on alkyl isocyanides because alkyl isocyanides are broadly utilized as building blocks of various nitrogen-containing heterocycles.^[10] Actually, Yamamoto's and de Meijer's groups independently reported copper-catalyzed [3+2] cycloaddition reactions of isocyanoacetates with alkynes to give the corresponding pyrrole derivatives (Scheme 1a).^[11] This elegant construction of nitrogenous 5-membered rings such as pyrrole derivatives prompted us to investigate cycaloaddition reactions of phosphaalkynes with isocyanoacetates to afford the corresponding 1,3-azaphospholes. Herein, we report copper-catalyzed [3+2] cycloaddition reactions of phosphaalkynes with isocyanoacetates to afford the corresponding 1,3-azaphospholes (Scheme 1b).

cat. [Cu]

(a) Previous work: synthesis of pyrroles

B1------R² CN. CO2R

[*]	W. Liang, Prof. Dr. Y. Nishibayashi	alkyne	isocyanoacetate		
	Department of Systems Innovation, School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-8656 (Japan)			pyrrole	
	E-mail: ynishiba@sys.t.u-tokyo.ac.jp	(b) This work: s	ynthesis of 1,3-azapho	ospholes	
	Dr. K. Nakajima			ert ICul	
	Frontier Research Center for Energy and Resources, School of	P≡−R ¹	+ CN_CO ₂ R ²	$\xrightarrow{\text{cal. [Cu]}}$ N $CO_2 R^2$	
	zngineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-8656 (Japan)	phosphaalkyne	isocyanoacetate	R ¹	
	E-mail: nakajima@sys.t.u-tokyo.ac.jp			1,3-azaphosphole	
	Prof. K. Sakata	Scheme 1. Copper-catalyzed [3+2] cycloaddition reactions using isocyanides.			
	Faculty of Pharmaceutical Sciences, Toho University, Miyama,			
	Funabashi, Chiba 274-8510 (Japan)				
	E-mail: ken.sakata@phar.toho-u.ac.jp	At first, inve	stigation of react	ion conditions was carried out in	
		the cycloaddition	n reaction of 1-a	damantylposphaethyne (1a) with	
[**]	This work was supported by CREST, JST (JPMJCR1541). We thank	ethyl isocyanoace	etate (2a) as typi	cal substrates. Typical results are	
	JSPS KAKENHI Grant Numbers 26288044, 15H05798, 26870120,	shown in Table 1	. The reaction of	1 equiv of 1a with 2 equiv of 2a	
	16K05767, and 16K10160 from the Japan Society for the Promotion	in the presen	nce of CuI	(10 mol%), dppm (1,1-	
	of Science (JSPS) and the Ministry of Education, Culture, Sports,	bis(diphenylphos	phino)methane, 1	0 mol%), and K ₂ CO ₃ (60 mol%)	
	Science and Technology of Japan (MEXT).	was carried out in	n 1,4-dixoane at 1	00 °C for 18 h. After the reaction,	
۲	Supporting information for this article is available on the WWW	the correspond	ding 4-(1-adar	nantyl)-5-ethoxycarbonyl-1H-1,3-	
	under http://dx.doi.org/10.1002/anie.201xxxxxx.((Please delete if not	azaphosphole (3a	a) was obtained	in 62% yield (Table 1, entry 1).	
	appropriate))	Other copper salt	ts such as CuBr,	CuCl, and CuOTf 1/2C ₆ H ₆ were	

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also examined, and the highest yield of **3a** (92% yield) was obtained when CuBr was used as a catalyst (Table 1, entries 2-4). When amounts of CuBr and dppm were reduced to 5 mol%, the yield lowered, unfortunately (Table 1, entry 5). Then, effect of the ligand to CuBr was investigated. Dppe (1,2-bis(diphenylphosphino)ethane), dppp (1,3-bis(diphenylphosphino)propane), PPh₃ and dtbpy (4,4'-di*tert*-butyl-2,2'-bipyridyl) were less effective ligands than dppm (Table 1, entries 6-9). A small amount of isomeric product **3a'** was observed when dppe, PPh₃, and dtbpy were used as ligands (Table 1, entries 6, 8, and 9). Finally, we confirmed that the combination of CuBr, dppm, and K₂CO₃ is necessary to obtain **3a** in good yield (Table 1, entries 10-12).

Table 1. Reactions of ethyl 1-adamantlyphosphaethyne (1a) with isocyanoaceate (2a) under various conditions.^[a]

P ≡− Ad	+ CN_CO ₂ Et	[Cu] (10 mol%) ligand (10 mol%) CNCO2Et K2CO3 (0.6 equiv)	
1a	2a , 2 equiv	solvent 100 °C, 18 h	P —∕ 3a ^{Ad}
entry	[Cu]	ligand	yield (%) ^[b]
1	Cul	dppm	62
2	CuBr	dppm	92
3	CuCl	dppm	8
4	CuOTf•1/2C ₆ H ₆	dppm	68
5 ^[c]	CuBr	dppm	33
6	CuBr	dppe	33 ^[d]
7	CuBr	dppp	25
8	CuBr	PPh3 ^[e]	39 ^[f]
9	CuBr	dtbpy	38 ^[f]
10	-	dppm	0
11	CuBr	-	15 ^[d]
12 ^[g]	CuBr	dppm	0
	P2Et PPh2 PPh2 Pf	Ph ₂ PPh ₂ Ph ₂ PPh ₂	
3a'	dppm dpp	be dppp	dtbpy

[a] All reactions of **1a** (0.20 mmol) with **2a** (0.40 mmol) were carried out in the presence of Cu salt (0.020 mmol), a ligand (0.020 mmol), and K_2CO_3 (0.12 mmol) in 1,4-dioxane (2 mL) at 100 °C for 18 h. [b] Isolated yield. [c] 5 mol% of CuBr and 5 mol% of dppm were used. [d] 10:1 mixture of **3a** and **3a'**. [e] 20 mol% of PPh₃. [f] 12:1 mixture of **3a** and **3a'**. [g] Without K₂CO₃.

The detailed molecular structure of **3a** was determined by X-ray crystallographic analysis,^[12] and an ORTEP drawing is shown in Figure 1. To the best of our knowledge, single crystal X-ray analyses on non-anellated 1,3-azaphospholes have not been reported, although some theoretical studies have revealed structures of 1,3-azaphospholes.^[13] Comparison of the bond lengths and angles of the obtained X-ray structure with those of calculated structures indicates that the structure of **3a** is in consistent with 1*H*-1,3-azaphosphole rather than 3*H*-1,3-azaphosphole. Furthermore, the short N1–O1' bond length suggests existence of an intermolecular hydrogen bonding between N1-H22 moiety and O1' atom.



Figure 1. ORTEP drawing of **3a**. Selected bond lengths (Å) and angles (°): P1-C1, 1.715(2); P1-C3, 1.7757(19); N1-C1, 1.337(3); C2-C3, 1.392(3); N1-C2, 1.379(2); N1-O1', 2.827(2); C1-N1-C2, 114.85(16); P1-C1-N1, 112.97(14); N1-C2-C3, 112.10(17); C1-P1-C3, 89.92(9); P1-C3-C2, 110.14(13); N1-H22-O1', 154.93 (11).

Table 2. Reactions of 1a with isocyanoacetates (2).[a]



[a] All reactions of **1a** (0.20 mmol) with **2** (0.40 mmol) were carried out in the presence of CuBr (0.020 mmol), dppm (0.020 mmol), and K₂CO₃ (0.12 mmol) in 1,4-dioxane (2 mL) at 100 °C for 18 h. [b] 0.40 mmol of **1a** and 0.20 mmol of hexane-1,6-diyl bis(isocyanoacetate) was used.

Under the optimized reaction conditions, the use of various isocyanoacetates was investigated. Typical results are shown in Table 2. Isocyanoacetates bearing primary, secondary, and tertiary alkyl ester moieties were successfully converted into the corresponding 1,3-azaphospholes in excellent yields (**3b-g**). Introduction of functionalized benzene rings and naphthalene ring was also successful to give **3h-o** in high yields. Noteworthy is that the alkene and alkyne moieties were well tolerant in the present reaction system to afford **3p** and **3q** because these functional groups



have been usually involved in the metal-mediated cyclization reactions with isocyanides.^[10,11] A double cyclization reaction of hexane-1,6-diyl bis(isocyanoacetate) was also successful to give **3r** in 42% yield without the formation of the corresponding monocyclization product. We also tested other isocyanides bearing phenyl ester, amide, alkyl ketone, aryl ketone, sulfonate, phosphonate and simple alkyl moieties instead of the ester moiety, however, no desired products were obtained in all cases.^[14]

Next, we investigated reactions with other phosphaalkynes. Typical results are shown in Table 3. A phosphaalkyne bearing 3,5dimethyladamantyl group was transformed successfully to give 3s in 67% yield. Introduction of phenyl (3t), alkoxyphenyl (3u-x), alkylphenyl (3y-ac), and biphenyl (3ad) groups to the phosphaethyne skeleton gave the corresponding products in high yields. The reaction of 3,3,3-triphenyl-1-phosphaprop-1-yne also afforded the corresponding tetraarylmethane-type product (3ae) in 20% yields, respectively. We also tested the use of trimethylsilylphosphaethyne, however, no desired 1,3-azaphosphole was observed. This is probably due to the thermal instability of trimethylsilylphosphaethyne^[15] under the current heating conditions.

Table 3. Reactions of phosphaalkynes (1) with 2a.[a]



[a] All reactions of 1 (0.20 mmol) with **2a** (0.40 mmol) were carried out in the presence of CuBr (0.020 mmol), dppm (0.020 mmol), and K_2CO_3 (0.12 mmol) in 1,4-dioxane (2 mL) at 100 °C for 18 h.

To obtain information on reactive copper species, preparation of some copper complexes was investigated (Scheme 2). At first, we carried out the reaction of CuBr with 1 equiv of dppm in 1,4-



Investigated reactions of CuBr with 1 equiv of dppm in the presence of 0.5 equiv and 1 equiv of isocyanoacetate 2a. In these reactions, the corresponding dimetallic copper complexes bearing mono- and bis-isocyanide coordination (5 and 6) were obtained in 89% and 60 % yields, respectively (Scheme 2b and 2c). Detailed molecular structures of 4, 5, and 6 were determined by X-ray crystallographic analysis.^[12]



Scheme 2. Preparation of copper complexes.

IR measurements of **5** and **6** were carried out to reveal the nature of coordinated isocyanoacetate **2a**. Absorbance signals attributable to the C–N stretching of **2a** on **5** and **6** were observed at 2188 and 2186 cm⁻¹, respectively. These values are higher than that of free isocyanoacetate **2a** (2164 cm⁻¹). In copper-isocyanide complexes, the isocyanides have been known to work as not only σ -donor but also π -acceptor toward the Cu atom.^[16] The high frequency shift of the IR signals of **5** and **6** indicates that back-donation is weak in these complexes and **2a** is activated with electrophilic manner to promote deprotonation of the copper-isocyanide complexes leading the formation of Cu-enolate complexes (vide infra).

To explain the relationship between copper complexes 4, 5 and 6, we carried out the following stoichiometric reactions (Scheme 2d). At first, the reaction of trimetallic complex 4 with 0.5 equiv of isocyanoacetate 2a (0.5 equiv based on the Cu atom of 4) gave mono-isocyanide complex 5 in 65% yield. Furthermore, 5 was further treated with 0.5 equiv of 2a (0.5 equiv based on the Cu atom of 5) to give bis-isocyanide complex 6 in 83% yield. These results clearly indicate that all copper complexes 4, 5, and 6 are possible species in the reaction system, but 6 may be a dominant species under the catalytic reaction conditions containing an excess amount of isocyanoacetate 2a.

To examine the reactivity of the isolated complexes 4, 5, and 6, the following catalytic and stoichiometric reactions were examined (Scheme 3). At first, we carried out catalytic reactions of 1a with 2a in the presence of 4, 5, and 6 as catalysts under the typical reaction conditions (Scheme 3a). In all cases, a similar catalytic activity was



observed. Next, we investigated the stoichiometric reaction of **6** with 3 equiv of **1a**, where corresponding 1,3-azaphosphole **3a** was obtained in 73% yield based on **2a** ligands in **6** (Scheme 3b). These results of the catalytic and stoichiometric reactions indicate the dimetallic complex **6** is involved as a catalytic active species. Separately, we confirmed that the dimetallic structure is maintained during the catalytic reaction. The mass spectrum of ESI-MS analysis on the reaction mixture of the catalytic reaction showed signals of m/z = 1201 and 975, which correspond to dimetallic species such as $[Cu_2Br(dppm)_2(2a)_2]$ (cationic part of **6**) and $[Cu_2Br(dppm)_2]$ (part of **5** or **6**), respectively. In contrast, no signals derived from monometallic Cu-dppm fragments such as [Cu(dppm)] were observed from a reaction mixture.



Scheme 3. Stoichiometric and catalytic reactivity of copper complexes.



Scheme 4. Plausible reaction pathway.

Based on the experimental results, a plausible reaction pathway is shown in Scheme 4. At first, coordination of isocyanoacetate 2 to a dimeatallic copper species forms copper-isocyanoacetate complex (A). Subsequent deprotonation of A gives the corresponding copperenolate complex presumably as a mixture of B and B'. Then, the reaction of B or B' with phosphaalkyne 1 proceeds to form the corresponding copper complex (C). Finally, protonolysis of C gives

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Figure 2. Reaction pathway examined by B3LYP-D3 level DFT calculations. Relative free energies ΔG^{296K} (kcal mol⁻¹) are in parentheses.

The pathway from **B** to **C** shown in Scheme 4 was examined by using B3LPY-D3 level DFT calculations (Figure 2) (For the computational details, see Supporting Information). The structure of dimetallic copper-enolate complex (I) suggests that a copper center accepts the bridging bromide and provides a vacant site to the other copper center. The coordination of 1-adamantylphosphaethyne 1a to the vacant site in I is followed by a nucleophilic attack of the enolate carbon to phosphaalkyne to afford the six-membered ring complex III (II \rightarrow TS_{II-III} \rightarrow III). The relative Gibbs free energy (ΔG^{298K}) of the transition state **TS**_{II-III} is 15.2 kcal mol⁻¹. Then, the P-C bond formation gives the complex IV via the transition state **TS**_{III-IV}. The ΔG^{298K} of **TS**_{III-IV} and **IV** are 7.0 and -8.7 kcal mol⁻¹, respectively. The addition of phosphaalkyne to enolate in the opposite direction occurs via the same mechanism $(II' \rightarrow TS_{II'-III'})$ \rightarrow III' \rightarrow TS_{III'-IV'} \rightarrow IV'), although the initial complex II' and the transition state $TS_{III'-IV'}$ are lower in free energy than II and TS_{III-IV} , respectively. On the other hand, we found other transition states that undergo direct [3+2] cyclization without coordination of phosphaalkyne to the copper $(TS_{[3+2]\text{-}A},\ TS_{[3+2]\text{-}B},\ TS'_{[3+2]\text{-}A},\ and$ TS'_{[3+2]-B}). In these cases, the activation barriers (19.8 - 23.9 kcal mol⁻¹) are higher than that of TS_{II-III} , and the orientation of the P=C bond is not selective because of the small difference in free energy between $TS_{[3+2]-A}$ and $TS_{[3+2]-B}$ or between $TS'_{[3+2]-A}$ and $TS'_{[3+2]-B}$. Thus, the bimetallic copper structure with a vacant site enables the coordination of both isocyanide and phosphaalkyne toward the same



copper center and the formation of energetically unfavorable 1,3azaphosphole ring is achieved (V_A is higher in free energy than V_B by 4.6 kcal mol⁻¹).

Finally, we examined further synthetic applications of 1,3azaphosphole **3a** (Scheme 5). Treatment of **3a** with NaH and subsequent propionyl chloride gave the *N*-acylation product (7) in 81% yield. In this case, no *P*-acylation product was observed. On the other hand, reduction of ester moiety was succeeded by the reaction of **3a** with LiAlH₄ to afford the corresponding alcohol (8) in 65% yield.



Scheme 5. Transformations of 1,3-azaphosphole 3a.

In summary, we have developed a new synthetic method to construct 1,3-azaphospholes by the reactions of phosphaalkynes with isocyanoacetates in the presence of copper-dppm complex as a catalyst. Metal-catalyzed cycloaddition reactions of phosphaalkynes with nitrogenous counterparts offered an efficient strategy to construct the phosphorous- and nitrogen-containing heterocycles. Additionally, DFT calculations revealed the detailed reaction pathway and the origin of selectivity. We believe the present study has opened up a new aspect of synthetic utilization of phosphaalkynes as building blocks of phosphorous- and other heteroatom containing heterocycles.

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A novel copper-catalyzed synthetic method is described for phosphorous- and nitrogen-containing heterocycles such as 1,3-azaphospholes. Cycloaddition reactions of various isocyanoacetates with phosphaalkynes in the presence of copper bromide, dppm, and potassium carbonate afford the corresponding 1,3-azaphospholes in high yields with a complete selectivity. Some dppm-bridged dicopper complexes work as active species for the formation of 1,3-azaphospholes.



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