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Metal-Free Azaphosphaannulation of Phosphonamides through Intramolecular Oxidative C−N Bond Formation

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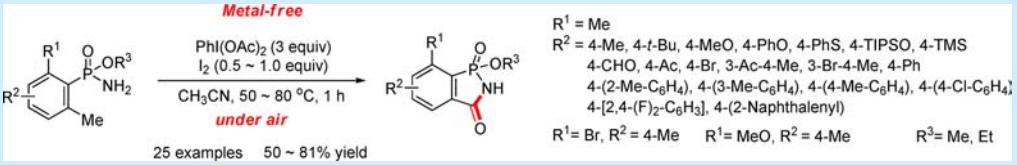
Supporting Information

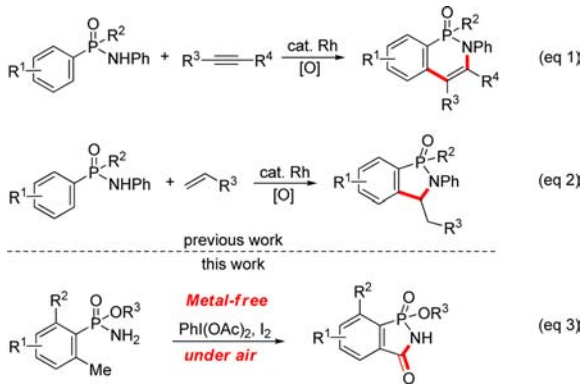


ABSTRACT: We report an efficient metal-free azaphosphaannulation of a myriad of phosphonamides through intramolecular oxidative C−N bond formation using $PhI(OAc)_2$ and iodine in acetonitrile under air, thus leading to the formation of benzazaphosphol-3-one 1-oxides, which are novel phosphorus heterocyclic privileged structures.

Selective C−H activation using a variety of transition metal catalysts with the aid of directing groups has become one of the most efficient synthetic methods for carbon−heteroatom (O and N) bond formation due to its step and atom-economical advantages, avoiding prefunctionalization of starting materials.[1] Accordingly, development of a new and efficient directing group represents an ongoing pivotal subject of research in C−H activation. Although a wide range of directing groups to facilitate position-selective C−H activation have been reported,[2] directing groups possessing phosphorus have been less exploited.[3] However, because organophosphorus compounds have been broadly used in agricultural and pharmaceutical chemistry and material science,[4] development of an efficient synthetic method for these compounds has been continuously required. In this regard, we recently investigated phosphoryl-group-directed C−H activation and demonstrated a series of C−O bond formations.[5] Encouraged by these results, we were next interested in transition-metal-catalyzed C−H activation/C−N bond formation and developed a Rh-catalyzed $C(sp^2)$−H activation/annulation (eq 1, Scheme 1) and oxidative alkenylation/aza-Michael reaction (eq 2, Scheme 1) directed by phosphonamide and phophinamide groups.[6] These results prompted us to examine the possibility of transition-metal-catalyzed $C(sp^3)$−H activation/C−N bond formation because $C(sp^3)$−H activation is more challenging and attractive than $C(sp^2)$−H. Herein, we report a streamlined metal-free azaphosphaannulation of a multitude of phosphonamides through intramolecular oxidative C−N bond formation for the synthesis of benzazaphosphol-3-one 1-oxides, which are novel phosphorus heterocyclic scaffolds and a kind of bioisosters of imide and acid anhydride (eq 3, Scheme 1).

We initiated our investigation by examining intramolecular C−N bond formation of ethyl 2,6-dimethylphenylphosphonamide (**1a**) (Table 1). Although we first used the optimum reaction conditions [$Pd(OAc)_2$, $(4\text{-MeO-}C_6H_4)_3P$, Ag_2CO_3, K_2HPO_4 in chlorobenzene][5e] for $C(sp^3)$−H activation/C−O cyclization of phosphonic acids to cyclization of **1a**, the expected

Scheme 1. Azaphosphaannulations through Phosphoryl-Group-Directed C−H Activation



$C(sp^3)$−N bonded product **3a** was not observed. Thus, synthetic methods of previously reported transition-metal-catalyzed C−N bond formation were applied to construction of the intramolecular C−N bond of **1a** (see Supporting Information). However, Rh and Cu catalysts and additives such as bases and oxidants were totally ineffective (see Supporting Information). Because there is still a great need for metal-free synthetic methods in organic synthesis,[7] we next changed our strategy for intramolecular C−N bond formation from transition metal catalysis to metal-free conditions.

First, under metal-free conditions, treatment of **1a** with $PhI(OAc)_2$ in ethyl acetate at 50 °C for 12 h unexpectedly produced the azaphosphaannulated product **2a** through oxidative C−N bond formation instead of a C−N bond, albeit in low yield (entry 1). The structure of **2a** was unambiguously determined by X-ray crystallography and HRMS (see Supporting Information). The use of additives such as NIS

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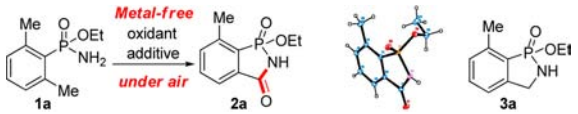
Table 1. Optimization of Azaphosphaannulation



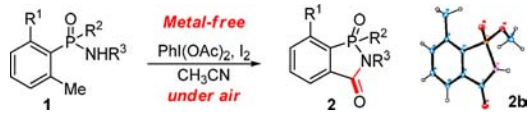
entry	oxidant (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	yield[a] (%)
1	$PhI(OAc)_2$ (3)	none	EtOAc	50	12	7
2	$PhI(OAc)_2$ (3)	NIS (0.5)	EtOAc	50	12	16
3	$PhI(OAc)_2$ (3)	Br_2 (0.5)	EtOAc	50	12	21
4	$PhI(OAc)_2$ (3)	I_2 (0.5)	EtOAc	50	12	58
5	$PhI(OAc)_2$ (3)	I_2 (0.1)	EtOAc	50	12	24
6	$PhI(OAc)_2$ (3)	I_2 (1.0)	EtOAc	50	12	60
7	$PhI(OAc)_2$ (2)	I_2 (0.5)	EtOAc	50	12	41
8	none	I_2 (0.5)	EtOAc	50	12	0
9	$PhI(OAc)_2$ (3)	I_2 (0.5)	CH_3CN	50	6	60
10	**$PhI(OAc)_2$ (3)**	**I_2 (0.5)**	**CH_3CN**	**80**	**1**	**75 (73)[b]**
11	$PhI(OAc)_2$ (3)	I_2 (0.5)	CH_3CN	100	1	65

[a]^{1}H NMR yields of **2a** using CH_2Br_2 as an internal standard. [b]Isolated yield of **2a**.

and Br_2 (0.5 equiv) slightly increased the yield (entries 2 and 3). However, in the case of the combination of $PhI(OAc)_2$ (3 equiv) and iodine (0.5 equiv), yield of the desired oxidative C−N bonded product **2a** improved up to 58% (entry 4). Iodine (0.1 equiv) afforded **2a** in 24% yield (entry 5), while 1.0 equiv of iodine gave the similar result (60%) as 0.5 equiv (entries 4 vs 6). The use of $PhI(OAc)_2$ (2 equiv) gave an inferior result (entry 7). Control reactions without $PhI(OAc)_2$ or iodine did not proceed, indicating that these reagents are essential for oxidative C−N bond formation (entries 1 and 8). Screening of temperature gave the best result at 80 °C (entries 9−11, see Supporting Information). Acetonitrile was found to be the solvent of choice (see Supporting Information). The best result for oxidative C−N bond formation was obtained, using $PhI(OAc)_2$ (3 equiv) and iodine (0.5 equiv) in acetonitrile at 80 °C, after 1 h, which gave rise to **2a** in 75% yield (isolated yield 73%) (entry 10).

On the basis of these results, we screened a variety of phosphonamides and phosphinamides **1** under the metal-free conditions (Table 2). When ethyl *N*-methyl, -phenyl,

Table 2. Scope of Phosphoamide Directing Groups[a]



entry	R^1	R^2	R^3	**1**	**2**	yield[b] (%)
1	Me	OEt	H	**1a**	**2a**	73
2	Me	OEt	Me	**1c′**		NR
3	Me	OEt	Ph	**1d′**		NR
4	Me	OEt	Ts	**1e′**		NR
5	Me	OMe	H	**1b**	**2b**	65
6	H	OEt	H	**1f′**		NR
7	Me	Ph	H	**1g′**		NR

[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), $PhI(OAc)_2$ (3 equiv), I_2 (0.5 equiv), and CH_3CN (2.0 mL), 80 °C, 1 h under air. [b]Isolated yields.

and -tosyl-2,6-dimethylphenylphosphonamides (**1c′**, **1d′**, and **1e′**) were treated with $PhI(OAc)_2$ (3 equiv) and iodine (0.5 equiv), the corresponding oxidative C−N bonded products **2** were not obtained (entries 2−4). Under the optimum conditions, methyl 2,6-dimethylphenylphosphonamide **1b** was smoothly converted to the desired product **2b** in 65% yield (entry 5; see Supporting Information for X-ray of **2b**). However, ethyl 2-methylphenylphosphonamide (**1f′**) was totally ineffective, indicating that 2,6-disubstituents are essential for the oxidative azaphosphoaannulation (entry 6). *P*-2,6-Dimethylphenyl-*P*-phenylphosphinamide **1g′** was not azaphosphaannulated (entry 7). These results suggest that the oxidative azaphosphaannulation is very sensitive to the nature of substituents attached to the phosphorus and nitrogen atoms.

Next, a number of phosphonamides **1** were examined to demonstrate the scope and limitations of metal-free azaphosphaannulation through the intramolecular oxidative C−N bond formation (Scheme 2). Reaction of ethyl 2,4,6-trimethylphenyl and ethyl 4-*tert*-butyl-2,6-dimethylphenylphosphonamides **1c** and **1d** with $PhI(OAc)_2$ and iodine produced the desired azaphosaphaannulation products **2c** and **2d** in 70% and 66% yields, respectively. Phosphonamides having 4-methoxy (**1e**) and 4-phenoxy (**1f**) groups on the phenyl ring underwent the intramolecular oxidative C−N bond formation to afford benzazaphosphol-3-one 1-oxides **2e** and **2f** in good yields. This transformation was chemoselective in that the phenylsulfenyl group (**1g**), a reacting site for oxidant, was inert. Substrate **1h** bearing a 4-triisopropylsilyloxy group on the phenyl ring was azaphosphaannulated to afford **2h** in 60% yield. The reaction turned out to be compatible with the labile 4-trimethylsilyl group (**1i**), thus leading to the formation of **2i** in 71% yield. In addition, functional groups frequently employed in synthetic chemistry were completely tolerated. For example, phosphonamides having aldehyde, ketone, or bromo groups were all smoothly azaphosphaannulated in moderate to good yields. Subjecting 3-acetyl-2,4,6-trimethylphenylphosphonamide (**1m**) to $PhI(OAc)_2$ and iodine gave rise to benzazaphosphol-3-one 1-oxide in 70% yield (**2ma**:**2mb** = 1:1.8; also see NOE in Supporting Information). We reasoned that **2mb** might be produced as the major product due to adjacent trisubstituents on the phenyl ring. Likewise, the oxidative azaphosphaannulation occurred efficiently with 3-bromo-2,4,6-trimethylphenylphosphonamide (**1n**) to deliver **2na** (26%) and **2nb** (46%). The structure of the isomers was unambiguously determined by NOE (see Supporting Information).

As an extension of this work, a wide range of phosphonamides **1** bearing biaryl moieties were employed for the

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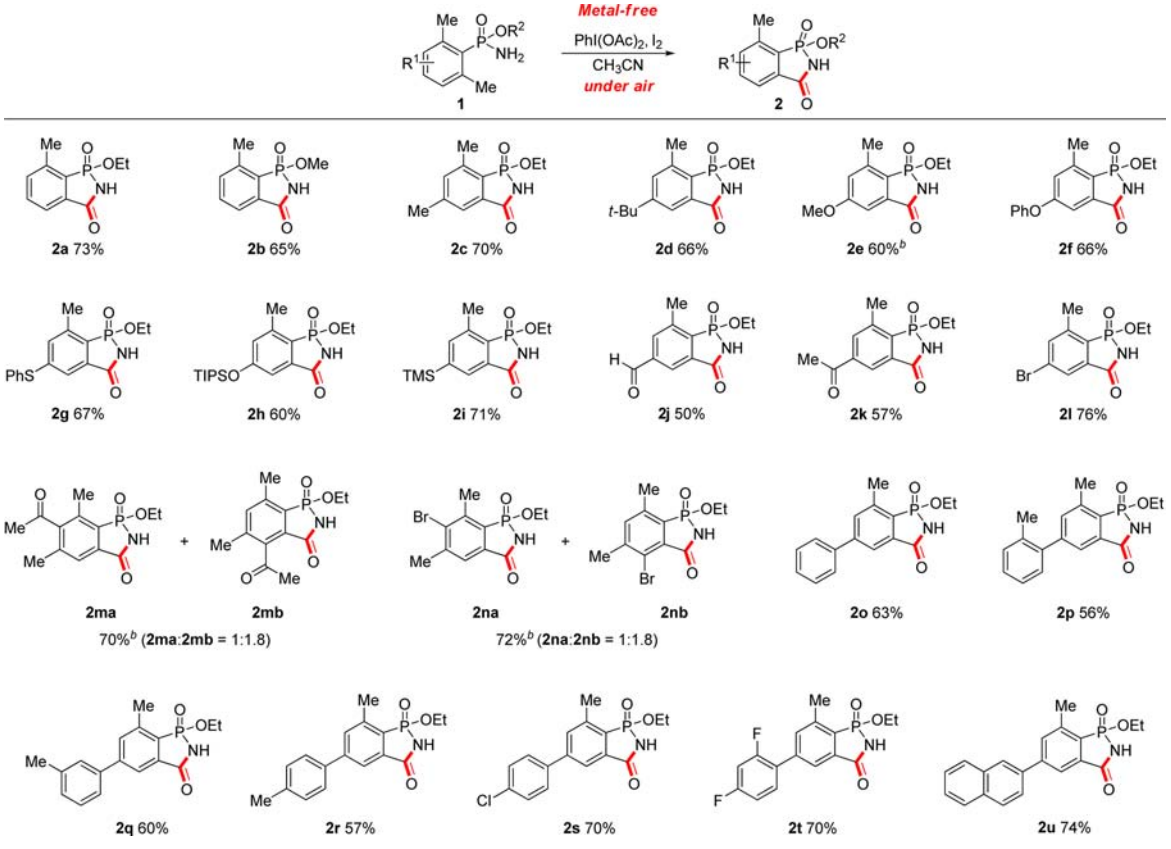
Scheme 2. Scope of Azaphosphaannulation of Phosphonamides[a]

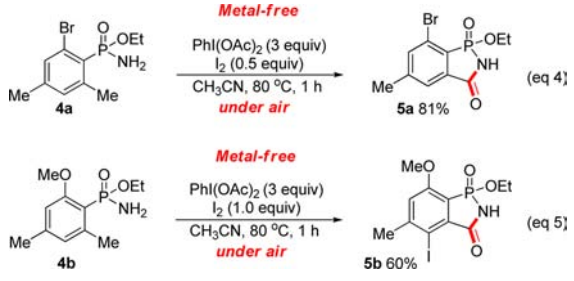


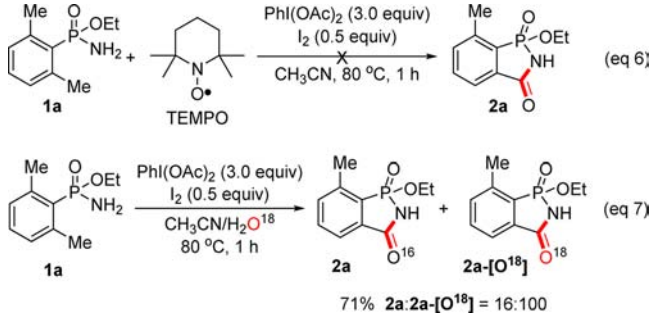
[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), $PhI(OAc)_2$ (3 equiv), I_2 (0.5 equiv), and CH_3CN (2.0 mL), 80 °C, 1 h. [b]I_2 (1 equiv), 50 °C.

optimal azaphosphaannulation. Ethyl 2,6-dimethyl-4-phenylphenylphosphonamide (**1o**) was reacted with $PhI(OAc)_2$ (3 equiv) and I_2 (0.5 equiv) in acetonitrile, thus producing the desired product **2o** in 63% yield. Biaryl phosphonamides **1p**, **1q**, and **1r** having an electron-donating methyl group on the 4-phenyl ring turned out to be compatible with the reaction conditions. Electron-withdrawing 4-chloro (**1s**) and 2,4-difluoro (**1t**) groups were tolerated on the substituted aryl ring, thus enabling a possibility for further functionalization. We were pleased to obtain **2u** from biaryl phosphonamide **1u** having a 2-naphthalenyl group at the 4-position.

Ethyl phosphonamides having different substituents at the 2,6-position worked equally well. For example, the desired product **5a** was obtained in 81% yield when 2-bromo and 4,6-dimethyl groups were substituted on the phenyl ring of phosphonamide (eq 4). Substrate **4b** bearing 2,4-dimethyl as well as 6-methoxy groups underwent the intramolecular oxidative azaphosphaannulation, producing **5b** in good yield (eq 5). The structure of **5b** was determined by NOE (see Supporting Information). Under the reaction conditions, an iodo group was introduced into the phenyl group due to the electron-rich phenyl ring.

Because the conversion of ethyl 2,6-dimethylphenylphosphonamide **1a** to the corresponding benzazaphosphol-3-one 1-oxide **2a** could be quenched in the presence of TEMPO as a free radical scavenger, a mechanism of the intramolecular oxidative C–N bond formation with $PhI(OAc)_2$ and iodine is proposed to involve a radical intermediate (eq 6). Reaction of **1a** with $PhI(OAc)_2$ and I_2 in CH_3CN (1.9 mL) and H_2O^{18} (72 μL, 20 equiv) produced **2a**-[O^{18}] (100) in 71% yield (eq 7). **2a**-[O^{18}] was detected by HRMS (see Supporting Information).





On the basis of these results and generation of sulfonamidyl radicals,[8] a plausible mechanism for the azaphosphaannulation is shown in Scheme 3. First, reaction of $PhI(OAc)_2$ with iodine provided phenyl iodide and acetyl hypoiodite (AcOI). Then, phosphonamides **1** were reacted with acetyl hypoiodite to

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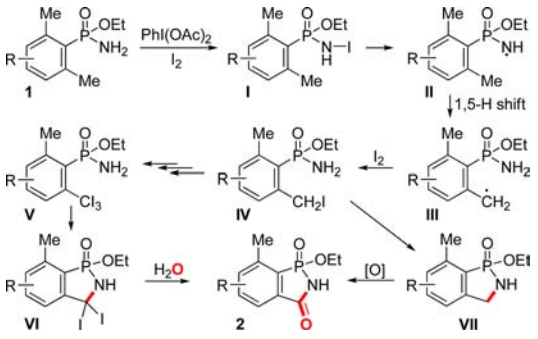
Scheme 3. A Plausible Mechanism



afford phosphonamidyl radicals **II**, which underwent a 1,5-H shift to give benzyl radicals **III**. Treatment of **III** with I_2 produced intermediates **IV**, **V**, and the cyclized **VI**. However, these intermediates were not observed in an NMR study in CD_3CN due to their instability. Hydrolysis of diiodide intermediates **VI** eventually produced benzazaphosphol-3-one 1-oxides **2**. The possibility of an initial cyclization of **IV** to **VII** and then benzylic oxidation to the desired product **2** cannot be completely ruled out at the present stage. The elucidation of the detailed mechanism of the azaphosphaannulation must wait for further study.

In summary, we have developed an efficient metal-free azaphosphaannulation of a myriad of phosphonamides through the intramolecular oxidative C−N bond formation, thus leading to the production of benzazaphosphol-3-one 1-oxides, which are novel phosphorus heterocyclic scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, X-ray crystallographic data for **2a** and **2b** (CIF), and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ DEDICATION

Dedicated to Professor Chan-Mo Yu, Sungkyunkwan University, on the occasion of his 60th birthday.

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