OL Organic Letters

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Redox-Neutral P(O)−N Coupling between P(O)−H Compounds and Azides via Dual Copper and Photoredox Catalysis

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02207 Read Online

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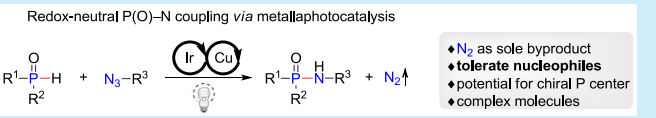
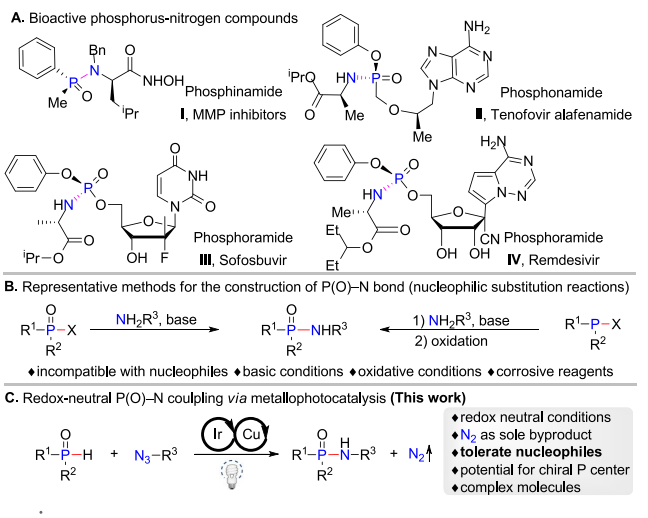
ABSTRACT: We report a redox-neutral P(O)−N coupling reaction of P(O)−H compounds with azides via photoredox and copper catalysis, providing new access to useful phosphinamides, phosphonamides, and phosphoramides. This transformation tolerates a wide range of nucleophilic functionalities including alcohol and amine nucleophiles, which makes up for the deficiency of classical nitrogen nucleophilic substitution reactions. As a demonstration of the broad potential applications of this new methodology, late-stage functionalization of a diverse array of azido-bearing natural products and drug molecules, a preliminary asymmetric reaction, and a continuous visible-light photoflow process have been developed.



Phosphorus−nitrogen compounds such as phosphinamides, phosphonamides, and phosphoramides have myriad applications in asymmetric catalysis,[1] materials science,[2] and medicinal chemistry.[3] For examples, a series of phosphinamide-based compounds, represented by compound **I**, have been recognized as potent matrix metalloproteinase (MMP) inhibitors (Scheme 1A).[4] The nucleoside phosphate and phosphonate groups masked by a chiral α-amino acid ester and an aryl motif to achieve phosphonamidated and phosphoramidated prodrugs are known as "ProTide" technology.[5] This modification not only enhances the bioactivity of parent nucleosides but also generates potent bioactivity of some parent nucleosides which are inactive because of an absence of monophosphorylation. This technology has already led to the discovery of several important drugs, such as the well-known phosphonamidated drug Tenofovir alafenamide **II** and the phosphoramidated drug Sofosbuvir **III**.[6] Very recently, Remdesivir **IV**, a phosphoramide developed by Gilead to treat Ebola viral infections, has drawn much attention since it has shown some value in treating the infection from COVID-19.[7]

Scheme 1. Phosphorus−Nitrogen Compounds



The construction of the P(O)−N bond, an essential structural unit in phosphorus−nitrogen compounds, relies heavily on the classical nitrogen nucleophilic substitution reactions (Scheme 1B). One pathway is the reaction of amines with preprepared,[8] *in situ* generated,[9] and catalytically formed phosphoryl halides[10] or their analogues[11] (left). Another alternative pathway goes through a similar nitrogen nucleophilic substitution step of phosphinyl halides with an additional oxidation step (right).[12] These processes suffered from the basic and oxidative conditions and the incompatibility with some nucleophilic functional groups. As a consequence, the construction of the P(O)−N bond was generally conducted in the first few steps in the synthesis of complex molecules.[6] In addition, such a synthesis is complicated in operation, relatively toxic and corrosive due to the use of phosphoryl and phosphinyl halides, and has poor atomic economy since a 1 equiv amount of base is necessary to neutralize the acid byproduct. Thus, atom-efficient and environment-friendly synthesis of phosphorus−nitrogen compounds are urgently needed. In continuation of our work on amination using

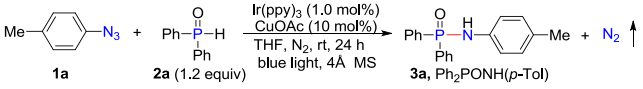
Received: July 3, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02207
Org. Lett. XXXX, XXX, XXX−XXX

organic azides as amino sources,[13] we here report a P(O)−N coupling reaction[14,15] between P(O)−H compounds and organic azides by dual copper and photoredox catalysis,[16] generating versatile phosphorus−nitrogen compounds under redox-neutral conditions (Scheme 1C).

Organic azides are used as atom-economical nitrene precursors in metal-catalyzed nitrene transfer reactions.[17] Advantages of this approach include formation of nitrogen gas as the only side product and relatively benign reaction conditions. Recently, visible-light-induced photocatalysts have also shown the ability to activate azides.[18] Based on our previous work on visible-light photocatalytic C−H amination[18g,h] and multicomponent synthesis[18i] using organic azides as nitrogen sources, we tested the reaction of *p*-tolyl azide **1a** with diphenylphosphine oxide **2a** under visible-light photocatalytic conditions (for details, see Table S1 in the Supporting Information (SI)). As shown in Table 1, the reaction provided

Table 1. Optimization of Reaction Conditions[a]



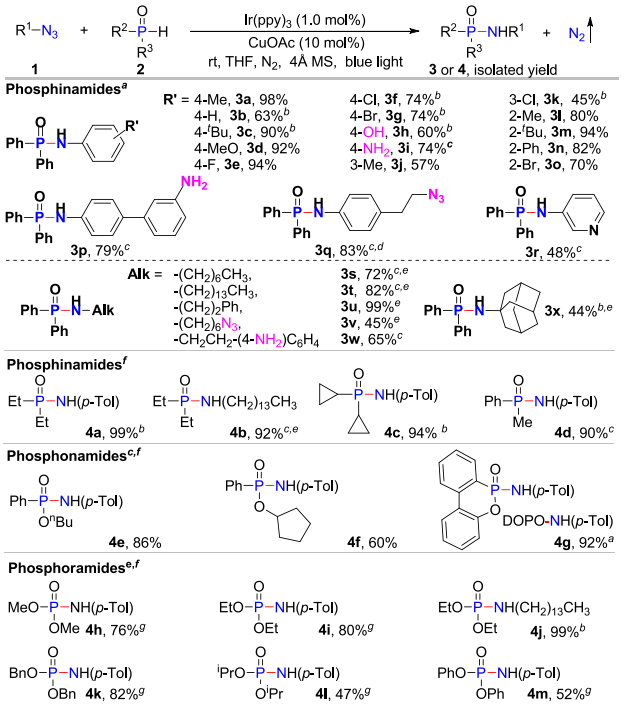
entry	variation	yield[a]
1	No CuOAc	47%
2	–	**98% (88%[b])**
3	No $Ir(ppy)_3$	15%
4	No $Ir(ppy)_3$ and CuOAc	9%
5	No blue light	0%
6	**$Cu(OAc)_2$ instead of CuOAc**	**96%**
7	**DMSO instead of THF**	**98%**

[a]0.10 mmol of **1a**; yields were assessed by crude ^{31}P NMR spectroscopy using Ph_3P as an internal standard. [b]1.0 mmol of **1a**; isolated yield.

phosphinamide **3a** in 47% yield (entry 1). A metallaphotocatalysis strategy enabling the combination of photocatalysis with transition metal catalysis has emerged, leading to various chemical transformations that are otherwise either difficult or unexpected.[16] When a catalytic amount of CuOAc was added to the reaction,[19] it produced **3a** in 98% yield (entry 2). The reaction does not proceed smoothly in the absence of $Ir(ppy)_3$ (entries 3−4), and **3a** was not produced without visible light (entry 5). Using $Cu(OAc)_2$ instead of CuOAc or DMSO instead of THF, the yield of **3a** was unchanged (entries 6 and 7). When the reaction was performed at a 1.0 mmol scale, **3a** was formed in 88% isolated yield (entry 2).

The scope and generality of the reactions were explored (Scheme 2). Aryl azide with/without a substituent in the *p*-position reacted with **2a**, providing good to excellent yields of phosphinamides **3b**−**3i**. The reactions of *m*-substituted aryl azides produced medium yields of products **3j**−**3k**. For *o*-substituted aryl azides, the possible steric hindrance has almost no effect on the yield (**3l**−**3o**), implying the advantage of this method. When the substrate contained two azido groups, the reaction of aryl azido proceeded preferentially, providing **3q** with excellent chemoselectivity. Heteroaryl azides, such as 3-azidopyridine, could give a moderate yield of phosphinamide **3r**. The reactions of linear alkyl azides produced phosphinamides **3s**−**3w** in good to excellent yields. A quaternary alkyl azide, a highly sterically hindered substrate, provided **3x** in moderate yield. Functional groups, such as methoxyl (**3d**), fluoro (**3e**), chloro (**3f**, **3k**), bromo (**3g**, **3o**), azido (**3q**, **3v**),

Scheme 2. Substrate Scope



[a]0.10 mmol of **1**, 0.12 mmol of **2**. [b]45 °C. [c]60 °C. [d]Chemoselectivity >20/1. [e]$Ir(mppy)_3$. [f]0.10 mmol of **1**, 0.30 mmol of **2**. [g]$Cu(OAc)_2$.

hydroxyl (**3h**), and even primary amino (**3i**, **3p**, **3w**), are tolerated, showing the good nucleophilic functional group compatibility. Then, dialkyl phosphine oxides containing linear ethyl or cyclopropanyl provided dialkyl phosphinamides **4a**−**4c** in excellent yields. The metallaphotocatalysis system is suitable for alkylaryl phosphine oxides, as demonstrated by the high-yielding coupling reaction of methylphenyl phosphine oxide (**4d**). The generality was further demonstrated with the coupling of alkoxylphenyl phosphine oxides, providing the phosphonamides **4e** and **4f** in good yields. In the reaction of the flame retardant DOPO (9,10-dihydro-9-oxa-10-phosphaphenanthrene 10-oxide), the phosphonamide **4g** with a cyclic phosphine structure was achieved in 92% yield. Dialkyl and diaryl phosphites were suitable substrates, as shown by the coupling reactions of dimethyl (**4h**), diethyl (**4i**, **4j**), dibenzyl (**4k**), sterically demanding diisopropanyl (**4l**), or diphenyl phosphite (**4m**), generating verstile phosphoramides in moderate to high yields.

Organic azides can be prepared in many different ways[20] and are usually treated as protected primary amines and reliable synthetic precursors (Scheme 3). For example, the cholesterol derivatives phosphinamide **6a**, phosphonamide **6b**, and phosphoramide **6c** were prepared in moderate to excellent yields from the reactions of 3*β*-cholesterylazide **5** (Scheme 3A), a synthetic precursor of the cationic cholesterol mimic 3*β*-cholesterylamine.[21,22] Similarly, the reaction of 3*β*-stigmasteylazide **7** provided 3*β*-stigmasteylphosphinamide **8** in 97% yield. Azido is a protecting group for primary amines, commonly used in peptide synthesis.[23] The catalytic P(O)−N coupling of azido-protected peptide **9** proceeded smoothly, providing phosphinamidated peptide derivatives **10a** and **10b** smoothly (Scheme 3B).[24] 5′-Phosphinamido-5′-deoxyadenosine **12** was formed in 95% isolated yield from the reaction of 5′-azido-5′-deoxyadenosine **11** (Scheme 3C), a synthetic precursor of

https://dx.doi.org/10.1021/acs.orglett.0c02207
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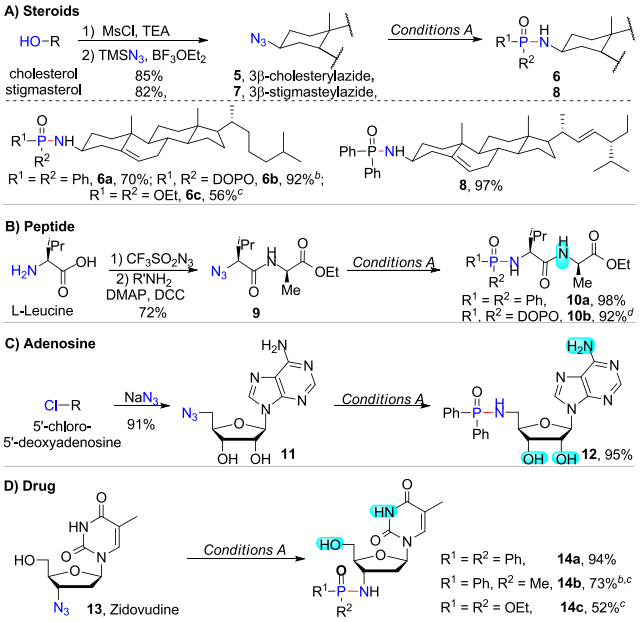
Scheme 3. Azido-Bearing Bioactive Molecules

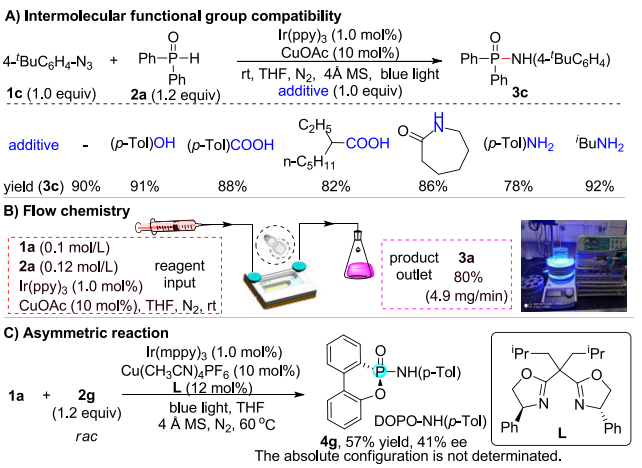


[a]Conditions A: **1** (0.1 mmol), **2** (0.12 mmol), $Ir(ppy)_3$ (1.0 mol %), CuOAc (10 mol %), 4 Å MS (50 mg), THF (1.0 mL), blue light (λmax = 470 nm), N_2, 60 °C, 24 h, isolation yield. [b]*dr* = 1/1. [c]**2** (0.3 mmol). [d]*dr* = 1.1/1.

bioactive compounds.[25] Zidovudine **13**, a thymidine analogue antiretroviral drug used to prevent and treat HIV/AIDS, is a suitable substrate, providing the phosphinamidated and phosphoramidated derivatives **14a**–**14c** in good to high yields. Nucleophilic functional groups, such as hydroxyl, amido, and primary amino groups, in **9**, **11**, and **13** failed to affect the reaction. The synthesis of P(O)–N compounds from organic azides includes advantages of high functional group tolerance, high atom economy, clean reactions, and nonoxidative and base-free conditions.

The presence of nucleophilic additives such as phenol, benzoic acid, alkyl carboxylic acid, amide, aniline, and even primary alkylamines have little impact on the P(O)–N coupling reactions (Scheme 4A), further showing the high functional-group tolerance of the method. Reactions in a continuous flow system can have numerous advantages over

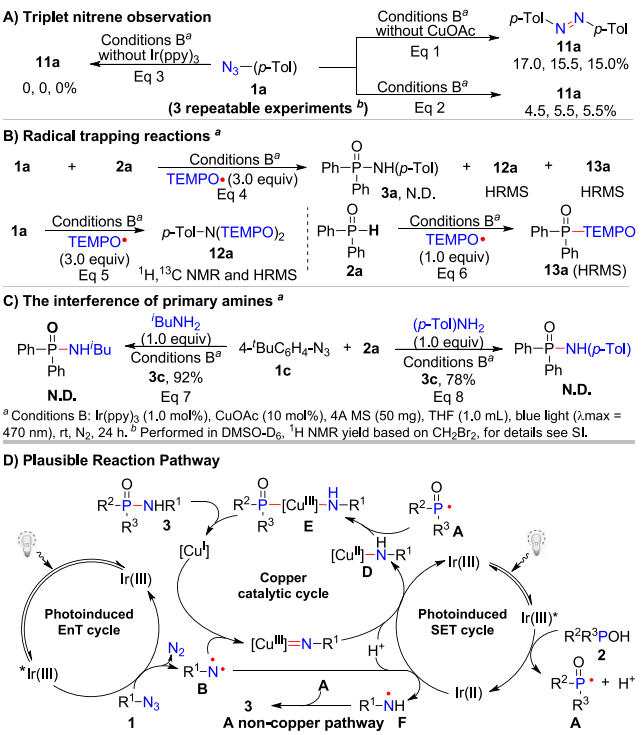
Scheme 4. Uniqueness of the Methodology



the batch reactions, especially in the field of azide chemistry.[26] After optimization of a flow microreaction (Scheme 4B; for details, see Table S2 in SI), **3a** was obtained in 80% yield at a rate of 4.9 mg/min when the flow rate was 0.2 mL/min, while the residence time was only 5 min. The P-chirogenic center of phosphorus–nitrogen compounds is very important in achieving improved bioactivity. For examples, the isomer of **I** with an *S* configuration at phosphorus was almost inactive (Scheme 1).[4] The biological activity of phosphonamidated and phosphoramidated prodrugs has often been found to be dependent on the configuration on the phosphorus atom.[7a,27] This has led companies to launch drugs mostly as single diastereoisomers, although with considerable difficulty and expense.[5,6] The asymmetric construction of the P(O)–N bond, which is theoretically difficult to achieve from the classical nitrogen nucleophilic substitution reactions, has not been developed.[28] With the copper(I) complex of **L** as the catalyst, P(O)–N coupling of DOPO afforded phosphinamide **4g** in 57% yield with 41% ee (Scheme 4C; for details, see Table S3 in SI), suggesting potential applications in asymmetric synthesis of phosphorus–nitrogen compounds and the involvement of copper species in the formation of the P(O)–N bond.

To determine the reaction mechanism, we performed a series of control experiments. According to the photodecomposition curves of azide **1a** under different conditions (Figure S1 in SI), $Ir(ppy)_3$ was shown to promote the decomposition of **1a** and the addition of CuOAc failed to improve the process. When the reaction of **1a** was performed under visible-light photocatalysis, a 16% yield of the azo compound **11a** was observed (Scheme 5, eq 1). In contrast, only a 5% yield of **11a** was observed in the presence of CuOAc (eq 2), and 0% of **11a** was detected in the absence of $Ir(ppy)_3$ (eq 3). These results indicate that $Ir(ppy)_3$ could promote the decomposition of **1a** under visible light to form a triplet nitrene

Scheme 5. Mechanistic Studies



https://dx.doi.org/10.1021/acs.orglett.0c02207
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intermediate, and CuOAc might couple to this triplet nitrene intermediate leading to the reduction of the formation of **11a**.[19] When TEMPO was added to the P(O)−N coupling reaction of **1a** and **2a** (eq 4), compound **3a** was not observed but the product **12a** containing two TEMPO units and the product **13a** with one TEMPO unit were detected. In addition, the EPR experiment shows the phosphine center radical[29] was formed under catalytic conditions (see the details in Scheme S2 in SI). Including the outcomes from the radical capture reactions of **1a** or **2a** respectively (eqs 5−6), the results suggested that the reaction system may involve the triplet nitrene intermediate[18i] and a $Ph_2PO\cdot$ radical.[29] When primary amine $^{i}BuNH_2$ or $(p\text{-Tol})NH_2$ was added (Scheme 5C), product **3a** was observed but no coupling product of **2a** and primary amine was obtained, suggesting that no primary amine intermediate was formed. Competitive reactions of **2a** with different azides were conducted (Scheme S1 in SI). The results show that *p*-chlorophenyl azide (26%) is preferred over 4-methyl phenyl azide (14%). Steric hindrance has little effect on the reaction (2-iodophenyl azide (22%) vs 4-methylphenyl azide (35%)) and 4-methylphenyl azide (57%) is much more reactive than tetradecanyl azide (0%).

A plausible mechanism with three catalytic cycles is proposed (Scheme 5D). Visible light induces $[Ir(ppy)_3]^{3+}$ to produce $[Ir(ppy)_3]^{3+*}$ which participates in two catalytic cycles: an SET process with **2** to obtain $[Ir(ppy)_3]^{2+}$ and formation of a phosphoryl radical **A** accompanied by proton dissociation, and an EnT process involving **1**, resulting in the loss of N_2 and the formation of the triplet nitrene **B**.[30] **B** is captured by Cu(I) to generate a Cu(III) nitrene intermediate **C**.[19] After undergoing the SET process and protonation,[31] **C** is converted to a Cu (II) complex **D** which is then coupled with **A** to give Cu(III) complex **E**.[32] Reductive elimination of **E** forms **3** and regenerates the Cu(I) catalyst.[33] Cu(II) species might be reduced to Cu(I) species by an excess amount of P(O)−H compound **2** under the reaction conditions,[34] which is the reason why $Cu(OAc)_2$ could also promote the reaction (entry 6, Table 1). As a minor reaction pathway, **B** can convert to nitrogen radical **F** directly via the SET process and protonation. Radical coupling of **A** and **F** leads to the formation of product **3** in the absence of CuOAc (entry 1, Table 1).

In summary, we have demonstrated a practical synthetic strategy for the redox-neutral construction of P(O)−N bond. The reaction merges the photoredox catalysis with copper catalysis and enables the coupling reactions of P(O)−H compounds and organic azides, providing verstile phosphinamides, phosphonamides, and phosphoramides with environment friendly N_2 as the sole byproduct. The use of versatile P(O)−H compounds including diphenyl-, dialkyl-, alkylphenyl-, alkoxylphenyl-, dialkoxyl-, diphenoxyl-phosphine oxides, and organic azides including aryl and alkyl azides, reveals the universal nature of the method. In contrast to classical nitrogen nucleophilic substitution reactions[8−11] and oxidative P(O)−N coupling reactions,[14] this reaction exhibited remarkable chemoselectivity and tolerates many nucleophilic functional groups such as phenol, benzoic acid, alkyl carboxylic acid, amide, aniline, and alkylamines. Late-stage functionalization of azido-bearing synthetic intermediates of bioactive compounds, potential applications in asymmetric versions, and flow chemistry through use of a microchannel device are also demonstrated. Mechanistic studies reveal that the reaction may go through visible-light-induced EnT and SET processes and a Cu(I)-catalytic cycle. It is mechanistically different from known methods and may have great potential in the synthesis of drug molecules and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02207.

Experimental details including product characterization and NMR experiments (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support by National Natural Science Foundation of China (21871131).

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