LETTERS

Visible-Light-Induced Cascade Reaction of Isocyanides and *N*-Arylacrylamides with Diphenylphosphine Oxide via Radical C–P and C–C Bond Formation

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(5) Supporting Information

ABSTRACT: An effective photoredox-mediated tandem phosphorylation/cyclization reaction of diphenylphosphine oxide with three types of radical acceptors leads to $P(O)Ph_2$ -containing phenanthridines, isoquinolines, and indolin-2-ones by formation of both C–P and C–C bonds. [Ir-(ppy)₂(dtbpy)]PF₆ (1 mol %) was used as the catalyst, CsF or Cs₂CO₃ as the base, and K₂S₂O₈ as the oxidant. A series of functional groups can be tolerated at room temperature. Moderate to good yields were generated.

O rganophosphorous compounds have wide applications in organic synthesis, as phosphorus ligands, in medicinal chemistry, as π -conjugated materials, as well as in inorganic chemistry.^{1,2} Traditionally, C–P bond construction relies on orthodox nucleophilic substitutions of poisonous R₂P(O)Cl with highly reactive organometallic reagents, which lead to harsh conditions and a lack of functionality tolerance (Scheme 1a).^{1a} This problem was not overcome until Hirao and coworkers first realized phosphonation of aryl iodides or bromides under catalysis of Pd(0).³ It appears that the transition-metal-catalyzed coupling reaction of ArX (X = I, OTs, COOZ, etc.) with R₂P(O)H has been a powerful platform for C(sp²)–P bond formation (Scheme 1b-I).⁴ Yu and related groups have explored N-directed Pd(II)-catalyzed *ortho*-

Scheme 1. Construction of C-P Framework





phosphorylation reactions through C–H activation (Scheme 1b-II),⁵ and other chemists have discovered direct oxidative dehydrogenative coupling reactions (Scheme 1b-III).⁶ Fortunately, the P–H bond of phosphine oxides prefers homolytic cleavage with the mediation of Ag(I), Mn(III), or peroxides to generate P-centered radicals.⁷ Inspired by this elegant reactivity, researchers have already disclosed a series of methods to incorporate a phosphoryl group to radical acceptors (Scheme 1c).⁷ Despite the present progress in our transition-metal-mediated P-centered radical ring-closure approach, excess amounts of silver or manganese salts and higher temperature were applied, thereby resulting in a waste of transition metals and energy.

Over the past few years, visible-light-induced photoredox catalysis has grown at a dramatic pace due to the inherent green character of light, high reactivity, and good functional group tolerance.⁸ Although great efforts have been devoted to preparative methods for synthesis of a variety of molecules via a photoinduced single-electron transfer (SET) pathway, the assembly of organophosphorus compounds from readily available starting materials under a mild visible-light-mediated process still remains scarce.^{9,10} Several recent studies have shown that the P-centered radical could be generated by a reductive quenching cycle of the excited state of photocatalyst with diarylphosphine oxide.¹⁰ This might shed some light on a new pathway for visible-light-induced organophosphorous compound synthesis.

2-Arylphenylisonitrile, which can be used to construct diverse 6-substituted phenanthridines, is a good candidate for radical acceptors.^{7a,11} In 2014, Studer and co-workers first revealed an efficient protocol on preparation of 6-phosphorylated phenan-



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thridines by radical phosphorylation of isonitriles.^{7a} Nevertheless, the above transformation required an excess amount of AgOAc and high temperature. Therefore, it is promising to exploit an effective, ecofriendly, and mild phosphorylation strategy. With our continuous interest in exploitation of novel phosphorescence iridium complexes¹² and our endeavors devoted to synthesis of *N*-containing organic compounds,¹³ we herein report on visible-light-induced phosphorylation/ cyclization cascade reactions of diarylphosphine oxide with isocyanides and *N*-arylacrylamides.

We commenced our evaluation of the reaction parameters employing 1a and 2a as model substrates (Table S1). The combination of 1 mol % of Ir-I $[Ir(ppy)_2(dtbpy)PF_6]$ and 2 equiv of K₂CO₃ with irradiation by a 23 W white lightbulb in DMF under air or oxygen atmosphere for 12 h did not yield the expected compound 3aa (entries 1 and 2). Very recently, MacMillan and Jin took advantage of photogenerated sulfate radical anion to activate the inert $C(sp^3)$ -H bond with strong bond dissociation energy (BDE) through a hydrogen-atom-transfer (HAT) pathway.¹⁴ We presumed that the desired Pcentered radical might be formed following this strategy. To test this hypothesis, 3 equiv of K₂S₂O₈ was added, and as expected, the cross-coupling product 3aa was observed in a vield of 56%. A base was found to have important influence on this cascade reaction. The higher yield (82%) was obtained when Cs₂CO₃ was used (entries 3 and 4). CsF was found to be best, leading to a yield of 89% (entry 16). In addition, a series of photocatalysts, including Ir(ppy)₃, FIrpic, and Ru(bpy)₃Cl₂, were examined, and Ir-I was found to be the best choice (entries 4-7). Several other persulfates were screened as well. and $K_2S_2O_8$ was found to be the best choice (entries 4, 8, and 9). A survey of solvents demonstrated that DMF was the best choice and that moisture can decrease the yield (entries 4 and 10-15). No desired product was detected if photocatalyst or light irradiation was not applied, indicating that the photoredox system is essential (entries 23 and 24).

With the optimized conditions in hand, we investigated the scope of biaryl isocyanides. As shown in Scheme 2, substrates with substituents at the para position of the phenyl ring, such as Me, H, OMe, F, Cl, t-Bu, and CF₃, reacted efficiently to afford the corresponding products in yields ranging from 60 to 85% (3aa-ga). The examined ortho-substituted substrates led to slightly lower yields (3ha, 3ia), probably due to steric reasons. The pyridyl unit was also compatible as an electron-deficient heteroarene, and 3ja was produced in a satisfactory yield of 67%. Although the substituent changes were made at the same aryl ring as the isonitrile group in the substrates, good yields were still obtained (3la-na). Interestingly, the reaction does not occur if a strong electron-withdrawing group is located at the para position (30a,pa). However, if F substitution takes place at the *meta* position, the transformation goes well (3qa). Different phosphoryl sources were tested as well. Ideal vields were afforded if di-p-tolylphosphine oxide (2b) and tertbutyl(phenyl)phosphine oxide (2c) were employed, whereas the yield was reduced sharply if ethyl pheylphosphinate (2d) was used. No desired product was generated in the case of diethyl phosphonate (2e).

Inspired by the successful application of this strategy in preparing 6-phosphorylated phenanthridines, we decided to apply this protocol to other systems. Recent studies indicate that vinyl isocyanides are good radical acceptors as well.¹⁵ Hence, we set out to prepare less known 1-diphenylphosphoryl isoquinoline derivatives.¹⁶ To our delight, 48–70% yields





^{*a*}Reaction conditions: 1a-q (0.3 mmol), 2a-e (0.9 mmol), $K_2S_2O_8$ (0.9 mmol), CsF (0.6 mmol), Ir-I (0.003 mmol, 1 mol %), DMF (3 mL), 23 W CFL, under Ar for 12 h at rt. ^{*b*}Gram-scale preparation of 3aa in an isolated yield of 81% (see the Supporting Information).

(Scheme 3) were obtained after Cs_2CO_3 and an elongated reaction time were utilized in comparison with the optimized conditions in Scheme 2.

N-Arylacrylamide is another type of good radical receptor that has been used to synthesize bioactive oxindoles through a radical cyclization pathway.¹⁷ Next, we carried out preparation of diverse oxindoles by our practical strategy. As shown in Scheme 4, different substrates were screened. All substrates with substituents at the *para* position of the arylacrylamides reacted well (7aa-fa). Electron-withdrawing groups tend to promote the reaction (7ea,fa). The substrate containing an *N*-benzyl group also gave rise to good yield (7ia). However, N-free arylacrylamide did not work (7ha). Steric hindrance at the *ortho*-position led to reduced yields (7ga, 7ja, and 7ka).

Control reactions were executed to gain more insight into this reaction. First, 2 equiv of TEMPO was enough to quench the reaction of 2a and 6a (Scheme 5, eq 1), indicating that the reaction proceeds in a radical pathway. Second, the intermolecular kinetic isotopic effect was observed to be 1.0, suggesting that the C-H bond cleavage is not the ratedetermine step (Scheme 5, eq 2).

On the basis of the mechanistic studies and literature, a tentative mechanism is proposed in Scheme 6. The photocatalyst Ir-I(III) is activated by visible light to the excited-state Ir-I(III)*, which then reduces persulfate anion to produce Ir-I(IV), sulfate dianion, and sulfate radical anion. Thereafter, the key intermediate P-centered radical would be generated Scheme 3. Scope of Vinyl Isocyanides^a



^{*a*}Reaction conditions: 4a-f (0.3 mmol), 2a (0.9 mmol), $K_2S_2O_8$ (0.9 mmol), Cs_2CO_3 (0.6 mmol), **Ir-I** (0.003 mmol, 1 mol %), DMF (3 mL), 23 W CFL, under Ar for 20 h at room temperature.

Scheme 4. Scope of N-Arylacrylamides^a



^{*a*}Reaction conditions: 6a-k (0.3 mmol), 2a (0.9 mmol), $K_2S_2O_8$ (0.9 mmol), Cs_2CO_3 (0.6 mmol), **Ir-I** (0.003 mmol, 1 mol %), DMF (3 mL), 23 W CFL, under Ar for 20 h at room temperature.

Scheme 5. Control Experiments for Mechanism



through a HAT process between highly active sulfate radical anion and **2a** and then undergo intermolecular addition with radical acceptor **1i** to form radical intermediate **I**. Intramolecular cyclization of radical **I** subsequently produces a cyclohexadienyl-type radical **II**, which can be oxidized by **Ir**-

Scheme 6. Plausible Mechanism



I(IV) to regenerate Ir-I(III) and produce the cation intermediate III. Finally, in the presence of base, III undergoes deprotonation to yield the desired product 3ia.

In summary, by using visible-light photocatalysis, we have demonstrated a diphenylphosphinoyl radical cascade phosphorylation and cyclization reaction. The reaction can be conducted under mild conditions (room temperature, 23 W household bulb irradiation), and the photocatalyst loading is as low as 1 mol %. Our process allows convenient and direct access to three types of phosphorylated *N*-heterocycles in moderate to excellent yields. In particular, a novel series of highly substituted 1-diphenylphosphoryl isoquinolines are afforded. The further development of visible-light-promoted phosphorylation reactions is ongoing in this laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.6b02413.

Crystallographic data for compound **3na** (CIF) Procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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