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Synthesis of Phosphoramidates: A Facile Approach Based on the C−N Bond Formation via Ir-Catalyzed Direct C−H Amidation

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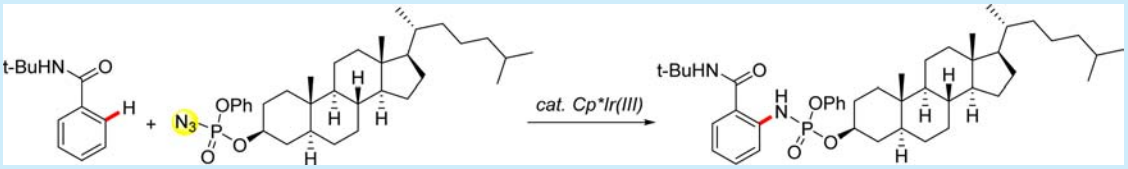
Supporting Information



ABSTRACT: A new synthetic route to phosphoramidates by intermolecular C−H amidation is presented. Substrates with assorted directing groups were activated by an iridium-based catalyst system and reacted with a number of phosphoryl azides, executing efficient phosphoramidate synthesis via C−N bond formations.

Phosphoramidates are abundant structural motifs widely present in natural and unnatural compounds of various applications. In medicine, a group of phosphoramidate molecules were found to have potent antifungal, antitumor, and anti-HIV activities.[1] Furthermore, they have been utilized as ligands[2] for metal-catalyzed organic transformations, as flame retardants,[3] and as labeling groups to improve sensitivity in mass spectroscopy.[4] In addition, their utility in organic synthesis has been validated as precursors to aziridines,[5] azetidines,[6] amines,[7] imines,[8] and heterocycles[9] (Figure 1).

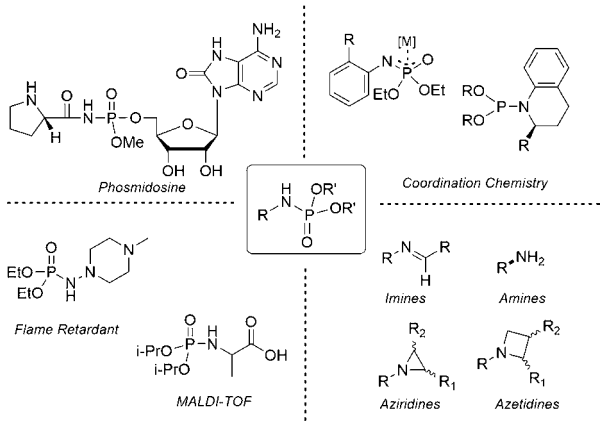


Figure 1. Examples of phosphoramidates in use.

Despite their importance, it is surprising to realize that only a handful of approaches are available toward the synthesis of phosphoramidates. While the reaction of an amine with a phosphoryl halide in the presence of a strong base has been mainly used, several methods were developed as follows. The Atherton−Todd reaction generates a reactive phosphoryl halide *in situ* from H-phosphonate and CCl_4, which reacts with an amine.[10] To avoid the use of CCl_4, the Staudinger-phosphite reaction allows the use of alkyl azides and phosphates to form phosphorimidates and subsequent hydrolysis gives the desired phosphoramidates.[11] Recently, greener procedures, dehydrogenative coupling reactions of an amine and a phosphonate,[12] and reaction of nitroarene and trialkyl phosphites were reported.[13] While this type of P−N bond formation has been widely considered, a C−N bond generation strategy has been studied only in limited cases.[14,15]

Phosphoryl azides have been utilized in the synthesis of various organo-phosphorus compounds[16] including phosphoramidates.[14b,c] Co(II)- and Ru(IV)-based metalloporphyrin catalysts were applied to the intramolecular C−H amidations of phosphoryl azides, affording cyclo-phosphoramidates. The Ru(IV) complex was also capable of triggering an intermolecular C−H amidation.[14c] However, a narrow scope of azides hindered its utility in synthesis.

Continuing our exploration on the C−H amidations with various organic azides,[16−19] we have successfully developed a C−N bond formation route to phosphoramidates. An iridium catalytic system was found to be highly active for an intermolecular amidation with phosphoryl azides. Our system could cover a wide range of substrates and phosphoryl azides under mild conditions, enabling the highly functionalized phosphoramidates with ease (Scheme 1). The detailed findings are disclosed in this letter.

To explore the amidation of phosphoryl azides, benzamide **1a** was chosen to react with diphenylphosphoryl azide **2a** in the presence of several catalysts known to promote amidations (Table 1). At first, cationic catalytic species generated *in situ* from $[Cp^*IrCl_2]_2$, $[Cp^*RhCl_2]_2$, and $[(p\text{-cymene})RuCl_2]_2$ with $AgNTf_2$ were tested as well as $Pd(OAc)_2$. Among them, only

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Scheme 1. Synthetic Routes to Phosphoramidates

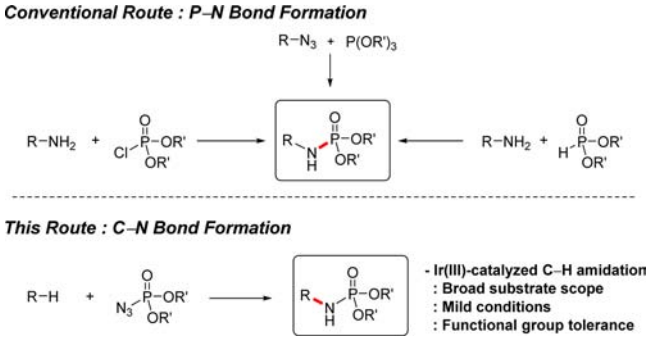
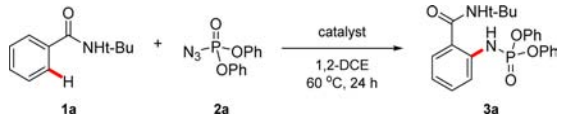


Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

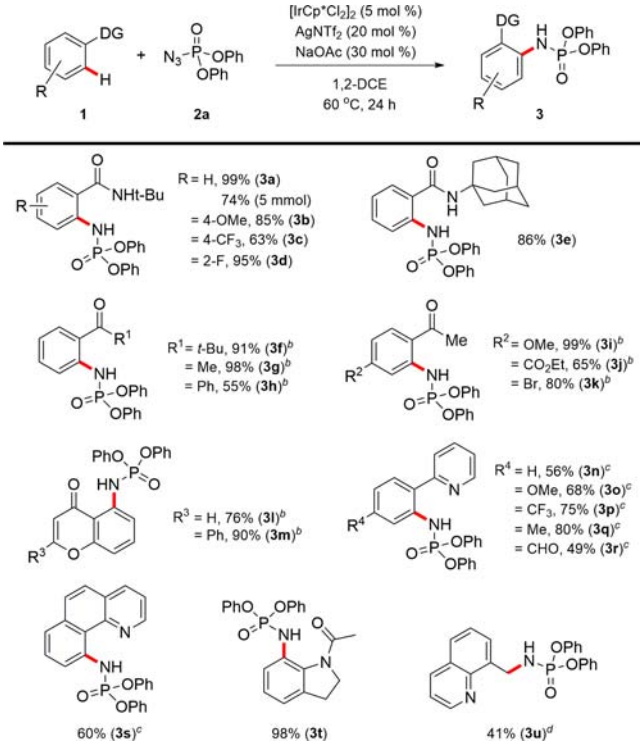
entry	catalyst	additive	yield (%)[b]
1	$[IrCp^*Cl_2]_2/AgNTf_2$	–	28
2	$[RhCp^*Cl_2]_2/AgNTf_2$	–	n.r.
3	$[Ru(p\text{-cymene})Cl_2]_2/AgNTf_2$	–	<1
4	$Pd(OAc)_2$	–	n.r.
5	$[IrCp^*Cl_2]_2/AgNTf_2$	NaOAc	99
6	$[RhCp^*Cl_2]_2/AgNTf_2$	NaOAc	<1
7	$[Ru(p\text{-cymene})Cl_2]_2/AgNTf_2$	NaOAc	n.r.
8	$Pd(OAc)_2$	NaOAc	n.r.

[a] **1a** (0.20 mmol), **2a** (0.24 mmol), catalyst 5.0 mol %, and additive (30 mol %) in 1,2-dichloroethane (1,2-DCE, 0.5 mL). [b] Yield based on ^1H NMR analysis of the crude mixture using CH_2Br_2 as the internal standard. n.r. = no reaction.

Cp*Ir(III) exhibited a measurable conversion of 28% (entries 1–4). Based on the previous report that carboxylates could assist C–H bond activations,[20] we tested an acetate additive, NaOAc. Delightfully, the Cp*Ir(III)-based catalyst with NaOAc gave a desired amidation product in quantitative yield while other catalysts remained inactive (entries 5–8).

With the optimized conditions in hand, the scope of substrates was next investigated. Substrates with various directing groups were reacted with diphenylphosphoryl azide giving rise to the corresponding phosphoramidates (Scheme 2). As expected from the previous investigation on the Ir(III)-mediated activation of benzamides,[19d,j,21] sterically bulky *N*-alkyl benzamides facilitated the amidation regardless of the electronic properties of substrates (**3a–e**). Then, we examined the reactivity of various directing groups, including both weakly and strongly chelating substrates. For ketone directing groups, it was revealed that the variation of either the steric (**3f–h**) or electronic (**3i–k**) environment did not affect the reactivity. In addition, cyclic ketones were converted to corresponding phosphoramidates in high yields (**3l–m**). Then, representative strong chelates, such as pyridyl and benzo[*h*]quinoline, were tested, verifying good functional group tolerance (**3n–s**). *N*-Acetylindoline exhibited excellent reaction efficiency (**3t**). Given that substrates needed a six-membered iridacyclic transition state to undergo slow or no C–H amidation in general,[19j–l] this exceptional efficiency in the reaction of indoline is of interest along with the utilities of selectively functionalized indolines. In addition, the present phosphoramidation could be extended into a benzylic sp^3 C–H bond in

Scheme 2. Substrate Scope of Arenes[a]

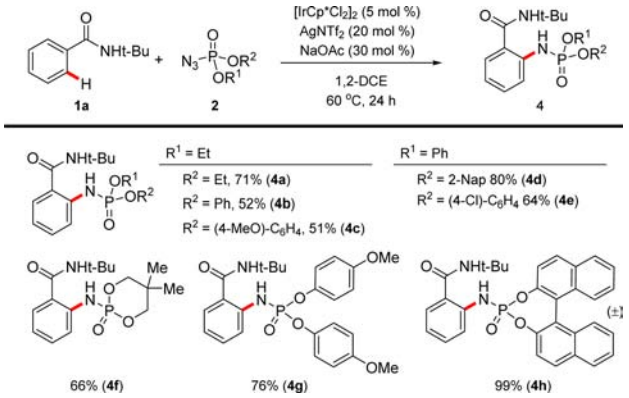


[a] **1** (0.20 mmol) and **2a** (0.24 mmol) in 1,2-DCE (0.5 mL): isolated yields. [b] Li_2CO_3 (15 mol %) and AcOH (15 mol %). [c] No additives at 80 °C. [d] NaOAc (30 mol %) at 80 °C.

reasonable yield (**3u**). A gram scale reaction proceeded smoothly without difficulty (**3a**).

Next, we turned our attention to the scope of phosphoryl azides. The optimized amidation conditions were readily applied to various phosphoryl azides as the coupling partner in the reaction with **1a** (Scheme 3). A group of phosphoryl

Scheme 3. Substrate Scope of Phosphoryl Azides[a]



[a] **1a** (0.20 mmol) and phosphoryl azides (0.24 mmol) in 0.5 mL of 1,2-DCE: isolated yields.

azides with alkyl, aryl, and binaphthyl substituents were reacted in good to excellent yields (**4a–h**). Alteration of the structural or electronic nature of the aryl groups did not significantly affect the amidation efficiency (**4b–e**).

We successfully expanded our protocol to the synthesis of phosphoramidates having biologically relevant components

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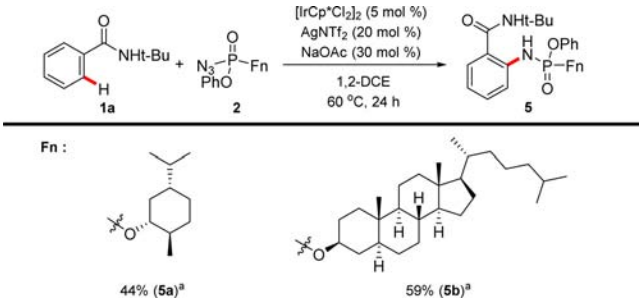
(Scheme 4). Phosphoryl azides derived from naturally occurring (−)-menthol and dihydrocholesterol were prepared

Scheme 4. Synthesis of Biologically Relevant Phosphoramidates[a]

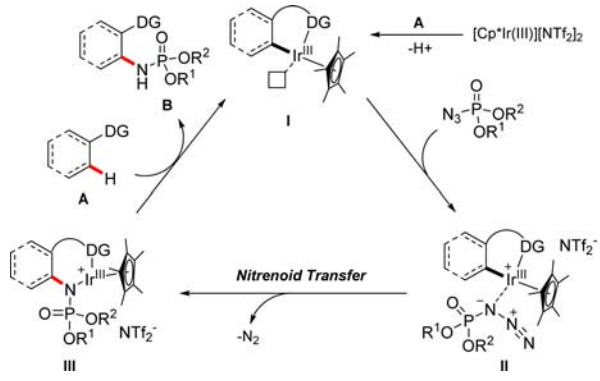


[a]**1a** (0.20 mmol) and phosphoryl azides (0.24 mmol) in 0.5 mL of 1,2-DCE: isolated yields.

and subjected to the amidation conditions in the reaction with benzamide (**1a**) to afford the corresponding phosphoramidates. Given that phosphorylated compounds have been studied extensively in biology and medicine,[22] our method would provide a tool for divergent phosphoramidate studies.

To investigate the mechanistic aspect of the present C−H amidation protocol, we conducted a kinetic isotope effect (KIE) experiment with a deuterium-labeled substrate, **1a**-d_5. A notable primary kinetic isotope effect (k_H/k_D = 2.7) was observed, suggesting that C−H bond activation is likely the rate-determining step (see the Supporting Information for details).[23] A possible phosphoramidation pathway based on this study as well as our previous investigations[19g] is depicted in Scheme 5. First, an Ir species induces C−H cleavage leading to

Scheme 5. Plausible Phosphoramidation Pathway



the formation of 5- or 6-membered iridacyclic intermediate **I**. The coordination of a phosphoryl azide is believed to form an azide-adduct **II**. Insertion of the bound azide into the Ir−C bond with concomitant release of N_2 would afford amido iridium complex **III**. In this amido group transfer process, either a stepwise nitrenoid pathway or concerted migratory insertion pathway would be possible.[24] Finally, complex **III** will be proto-demetalated to deliver the desired phosphoramidated product (**B**).

In conclusion, an efficient C−H amidation protocol for the synthesis of phosphoramidates has been developed. A facile formation of C−N bonds via Ir-catalyzed direct C−H amidation was implemented under mild reaction conditions. A broad substrate scope and excellent functional group tolerance allow various kinds of phosphoramidates to be accessed, which can find applications in medicinal and synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H, ^{13}C NMR spectra). 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.

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