Development of a General Organophosphorus Radical Trap: Deoxyposphonylation of Alcohols

Noah B. Bissonnette, Niels Bisballe, Andrew V. Tran, James A. Rossi-Ashton, and David W. C. MacMillan*

ABSTRACT: Here we report the design of a general, redox-switchable organophosphorus alkyl radical trap that enables the synthesis of a broad range of C(sp$^3$)–P(V) modalities. This "plug-and-play" approach relies upon in situ activation of alcohols and O==P(R$_3$)H motifs, two broadly available and inexpensive sources of molecular complexity. The mild, photocatalytic deoxygenative strategy described herein allows for the direct conversion of sugars, nucleosides, and complex pharmaceutical architectures to their organophosphorus analogs. This includes the facile incorporation of medicinally relevant phosphonate ester prodrugs.

**Phosphorus functionalities play an important role in regulating a wide range of cellular processes, including protein signaling cascades, inflammation, cellular metabolism, and gene expression. As such, organophosphorus species are widely represented in pharmaceuticals, agrochemicals, and modern materials. These predominantly P(V) motifs come in a wide variety, ranging from organic phosphates (O==P(OR)$_3$) to phosphate oxides (O==PR$_3$). While access to aryl C–P(V) species is well-established through methods utilizing Pd catalysis, aryl iodonium salts, and photoredox catalysis, methods for the formation of the corresponding alkyl C–P(V) species are underdeveloped. There is, however, demand for structurally complex P(V) species, exemplified particularly by the phosphorus prodrug motifs found in recent nucleoside-derived antivirals.

Traditional two-electron methods for the synthesis of alkyl organophosphorus species, such as the Arbuzov reaction, have historically provided access to this chemical space. However, given the use of activated electrophiles and S$_N$2 mechanism, these methods often struggle to provide access to highly functionalized or hindered P(V) species. Other methods are constrained by the requirement of reactive organometallics or feature limited scopes given the prerequisite of a π system for hydrophosphorylation. Recognizing the lack of robust synthetic methods for the construction of alkyl C–P(V) groups, we sought to develop a modular approach to directly convert alcohols to their C–P(V) congeners via radical processes. If successful, this method would (1) broadly expand access to organophosphorus chemical space through the use of abundant feedstock chemicals and (2) serve as a powerful technology for the efficient synthesis of unnatural nucleotides from sugars and nucleosides (Figure 1).

In recent years, methods that use open-shell intermediates (1) to forge X–P bonds (X = O, S, C(sp$^3$)) via radical addition to P(III) (2) have found great utility. These transformations proceed through a well-characterized P(IV) phosphoranyl radical intermediate (3), which readily under-
The potential of this method to directly interconvert the natural site of phosphorylation in sugars and nucleosides to the phosphonate derivative further motivated us to enable alcohols as the radical precursor (Figure 1).

To realize the transformation, we utilized two in situ preactivation steps on readily available starting materials (Figure 2). This modular approach would ideally enable a “plug-and-play” strategy to access many classes of \( \text{C(sp)}^3 \)–P(V) modalities. First, the alkyl radical progenitor (10) undergoes rapid (∼30 min), mild condensation with the deoxazole (11, NHC) to furnish the activated alcohol adduct (12). Simultaneously, in a separate vial, an unsymmetrical P(III) reagent (15), bearing the radical leaving group, is prepared from broadly available and inexpensive \( \text{O} = \text{P} \left( \text{R} \right) \text{H} \) precursor (13) and a benzhydrol derivative (14). This crude mixture is then directly added to the vial containing the activated alcohol, photocatalyst, and base. Upon irradiation with 450 nm light, the iridium photocatalyst’s long-lived triplet state is reached. This highly oxidizing state enables facile oxidation of 12 (\( E_{1/2}^{\text{ox}} \approx 1.0 \) V vs SCE in MeCN), and subsequent deprotonation furnishes the heterocyclic radical (16). This species generates an alkyl radical (17) and the inert, rearomatized NHC byproduct through β-scission. Next, a phosphonyl radical (18) is formed via the reversible addition of 17 to the activated P(III) species; a subsequent irreversible β-scission driven by the weak C–O bond leads to the formation of the deoxophosphorylated product (19) and a bisbenzyl radical (20). Finally, the photocatalytic cycle is closed through reductive RPC (\( E_{1/2}^{\text{red}} \approx -0.77 \) V vs SCE in MeCN), furnishing a carbanion (21). Importantly, our choice of an alkyl radical precursor serves as a key design element. P(III) motifs like phosphites, phosphonites, and phosphinites are oxidatively labile (\( E_{1/2}^{\text{ox}} \approx 1.83, 1.49 \) and 1.28 V vs Ag/Ag⁺ in MeCN, respectively). Therefore, many commonly employed, oxidatively activated alkyl radical precursors, such as BF₃ salts (\( E_{1/2}^{\text{red}} \approx 1.5 \) V vs SCE), may result in competitive, deleterious single electron transfer (SET) from P(III). By utilizing the easily oxidized NHC-activated alcohols as an alkyl radical source, we envisioned a broad tolerance of these activated P(III) radical traps, enabling the construction of a diverse array of \( \text{C(sp)}^3 \)–P(V) modalities. With this design in mind, we set out to enable the one-step deoxophosphorylation of alcohols.

Following an extensive optimization campaign (Tables S1–S5), we developed conditions to transform Boc-protected \( \text{L-phenylalaninol} \) to the corresponding diethyl phosphonate in 75% yield (Table 1, entry 1). As expected, no product was detected in the absence of light or photocatalyst (entries 2 and 3). The benzhydrol also proved to be necessary for phosphonation (entry 4), providing insight into the importance of a suitable radical leaving group. Moreover, when unactivated sources of P(III) or P(V) were utilized, no product was detected (entry 5); this finding confirms previous reports on the unproductive reactivity of standard P(III/V) species with alkyl radicals. Finally, the organic photocatalyst 4CzIPN-Bu performed comparably with the optimal iridium photocatalyst (entry 6).

With the optimized conditions in hand, we next evaluated the scope of the transformation (Figure 3). Reduced amino acids (22) and serine (23) proved to be competent substrates, furnishing medicinally relevant β-aminophosphonates in good yields (90% and 67%) from readily accessible precursors.

Figure 1. Design of a general P(III) radical trap.
Additionally, (hetero)aromatic motifs (24 and 25) and saturated heterocycles (26) were well-tolerated (70−76% yield). We were pleased to find that primary chlorides were tolerated despite the strongly basic reaction conditions (27, 81% yield). Additionally, medicinally relevant bisphosphonates could be synthesized (28, 67% yield).

A complex alcohol bearing an N-heterocycle and an easily oxidizable anilinic functionality could also be phosphorylated (29, 75% yield).

We next subjected a range of saturated N-heterocycles appended with secondary alcohols to the phosphorylation conditions, obtaining products with good to excellent efficiencies (30−33, 71−94% yield). Threonine furnished the secondary β-amino phosphonate derivative in fair yield (34, 43% yield).

Additionally, spirocyclic, bicyclic, and complex N-heterocyclic alcohols were found to be competent substrates (35−37, 46−84% yield). Gratifyingly, this transformation could be performed on a gram scale with equal efficiency (22 and 29, 94% and 78% yield).

Finally, this method was applied to a series of 3° alcohols. EPR and synthetic studies have shown that classical tertiary radicals generally do not undergo addition to P(III) species.
Figure 3. Alcohol and phosphorus scope. See Table 1 for the conditions and the Supporting Information for details and additional examples. *Assay yield. †2:1 to 1:1 dr. ‡From cubane RAE.

This phenomenon was successfully recapitulated, as tert-butanol gave no detectable product (38, 0% yield). However, when the 3° radical is tied back through a small ring or bicyclic system, its s character is increased, resulting in the formation of a stronger C−P bond and reducing the steric penalty for P(IV) formation. Indeed, 3° alcohols of this nature were converted to the desired products in good to synthetically useful yields (39−41, 30−72% yield). Although reduced efficiency is observed with some of these more challenging systems, we note that tertiary substrates cannot be accommodated by other recent phosphonylation methods, including copper-catalyzed or metallaphotoredox-based methods, highlighting a distinct advantage of a free radical trap approach. Excitingly, this platform could be generalized to other radical precursors (redox active esters (RAEs); see Figure S2) when the requisite alcohol is not readily accessible.

We next set out to explore the range of phosphorus functionalities that could be installed through this protocol, by first examining the effect of phosphite sterics: while linear and 2° phosphite esters proved to be facile substrates (43−45, 62−78% yield), tert-butyl esters were not amenable to our preactivation conditions (46, 0% yield). Gratifyingly, 1° phosphonites and 2° phosphine oxides can be transformed to 2° phosphonites and 3° phosphine oxides (47−49, 52−58% yield), highlighting the modular nature of this chemistry. Additionally, organosulfur derivatives of phosphonates, phosphonites, and phosphine oxides could be accessed using a thiobenzhydrol leaving group (42, 52% yield). Under our protocol, we were pleased to find that the established S-acylthioalkyl ester (SATE) phosphonate prodrug could be installed in a single step (53, 75% yield), obviating the need for a lengthy synthetic sequence.

We next sought to test the limits of functional group tolerance by phosphonylating a small library of sugars, nucleosides, and pharmaceuticals (Figure 4). Gratifyingly, pyranoses, ribose, and an unnatural sugar derivative were successfully converted to the hydrolytically stable congeners at the natural site of phosphorylation (54−57, 67−89% yield). Furthermore, the steroid abiraterone (58, 40% yield) bearing a heterostyrenyl motif was phosphonylated in modest yields. Pharmaceutical scaffolds, including indomethacin (59, 23% yield) and nateglinide analogs (60, 89% yield), were tolerated, illustrating the successful application of this chemistry for the modification of small-molecule drugs. Next, we targeted the direct modification of nucleosides and analogs thereof. Deoxyuridine (61, 42% yield) could be directly transformed into an unnatural nucleotide featuring an alternative site of P(V) introduction. Excitingly, the nucleoside analogue ticagrelor (62, 81% yield) could be functionalized in excellent yield despite the presence of oxidizable functionalities.

Figure 4. Phosphonylation of complex molecules. See Table 1 for the conditions and the Supporting Information for details. Assay yield. 1.4:1 dr. >20:1 dr.
(thioether and free aniline). Finally, the antiviral sofosbuvir was targeted for phosphonylation. This therapeutic features a phosphate (O–P(V)) drug at the 5′ position. Beginning with the same nucleoside diol precursor used to make the final nucleotide, we were able to selectively activate the less sterically hindered 5′ position in the presence of the more hindered 3′ hydroxyl group. Subsequent phosphonylation formed the 5′-C–P(V) analogue in a modest yet synthetically useful yield (63, 37%). This late-stage functionalization protocol offers new opportunities to explore expanded chemical space for nucleoside-derivated therapies.

In summary, we describe herein a modular platform for the deoxyphosphonylation of alcohols. The combination of mild, photocatalytic conditions, broad alkyl substrate tolerance, and the “plug-and-play” nature of activated P(III) generation enables the formation of a diverse array of alkyl−P(V) species. This platform provides the means to diversify the synthesis of medicinally relevant phosphonate esters by direct installation of the desired P(V) motifs. Importantly, this dehydroxylolation approach gives access to an expansive feedstock of radical precursors, while the complexity of the phosphites utilized can furnish valuable prodruk motifs in a single synthetic step. Furthermore, we envision that adoption of this redox-switchable benzhydrol-activated P(III) species will broadly inform the development of related transformations enabled by phosphonanyl radical chemistry.

ASSOCIATED CONTENT

* Supporting Information
  The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c00557.

  Additional experimental details, characterization, expanded substrate scope, and spectra (PDF)

AUTHOR INFORMATION

Corresponding Author
David W. C. MacMillan – Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States; Email: dmacmill@princeton.edu

Authors
Noah B. Bissonnette – Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States; orcid.org/0000-0001-6892-5040

Niels Bisballe – Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States; orcid.org/0000-0002-4476-5481

Andrew V. Tran – Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States; orcid.org/0000-0003-3855-1353

James A. Rossi-Ashton – Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/jacs.4c00557

Notes
The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor.

ACKNOWLEDGMENTS

The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (R35GM134897-04), the Princeton Catalysis Initiative, and kind gifts from Merck, Janssen, BMS, Genentech, Pfizer, and Genmab. N.B.B. thanks the Taylor family for the Edward C. Taylor Fellowship. N.B. thanks the Independent Research Fund Denmark for financial support (Grant 1056-00018B). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIGMS. The authors thank William P. Carson II for helpful scientific discussions and Rebecca Lambert for assistance in preparing the manuscript.

REFERENCES


