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Communication

Development of a General Organophosphorus Radical Trap: Deoxyphosphonylation of Alcohols

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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_2)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,[1] inflammation,[2] cellular metabolism,[3] and gene expression.[4−7] As such, organophosphorus species are widely represented in pharmaceuticals,[8] agrochemicals,[9] and modern materials.[10] These predominantly P(V) motifs come in a wide variety, ranging from organic phosphates (O═P(OR)$_3$) to phosphine oxides (O═PR_3). While access to aryl C−P(V) species is well-established through methods utilizing Pd catalysis,[11] aryl iodonium salts,[12,13] and photoredox catalysis,[14] 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.[15−19]

Traditional two-electron methods[20] for the synthesis of alkyl organophosphorus species, such as the Arbuzov reaction,[21] have historically provided access to this chemical space. However, given the use of activated electrophiles and S_N2 mechanism, these methods often struggle to provide access to highly functionalized or hindered P(V) species.[22] Other methods are constrained by the requirement of reactive organometallics or feature limited scopes given the prerequisite of a π system for hydrophosphonylation. 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[23] 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^2)) via radical addition to P(III) (**2**) have found great utility.[14,24−28] These transformations proceed through a well-characterized P(IV) phosphoranyl radical intermediate (**3**),[29] which readily undergoes β-scission to generate alkyl radical (**5**) and the desired P(V) product (**4**). However, attempts to extend this transformation to more stable alkyl radical species have been unsuccessful, despite the fact that the key alkyl phosphoranyl radical intermediate (**3**) can be detected at appreciable concentrations by electron paramagnetic resonance (EPR) spectroscopy[30] and the net transformation is significantly exothermic ($\Delta G \approx -40$ kcal/mol).[31] Interestingly, instead of achieving product formation via β-scission, the P(IV) intermediate decomposes through α-scission, regenerating the starting phosphite and alkyl radical. As a result of this mechanistic limitation, no general method for the construction of C(sp^3)−P(V) species via phosphoranyl radical fragmentation has been described in the literature.[32] Alternative free radical methods have emerged, including addition of phosphorus-centered radicals to π systems,[33,34] carbocation formation by radical polar crossover (RPC) followed by S_N1 trapping,[35,36] and transition-metal-catalyzed cross-coupling methods.[37,38] Although these transformations represent significant inroads toward the formation of C(sp^3)−P(V) species, we hypothesized that the development of a general P(III) alkyl radical trap and subsequent merger with photoredox conditions would enable access to a novel organophosphorus chemical space.

Specifically, we viewed this problem through the lens of the Curtin−Hammett principle, wherein the alkyl radical is terminated through one of two irreversible pathways, namely, (a) undesirable decomposition via either hydrogen atom transfer or disproportionation or (b) β-scission to form the desired phosphonate. Connecting these pathways is a rapid

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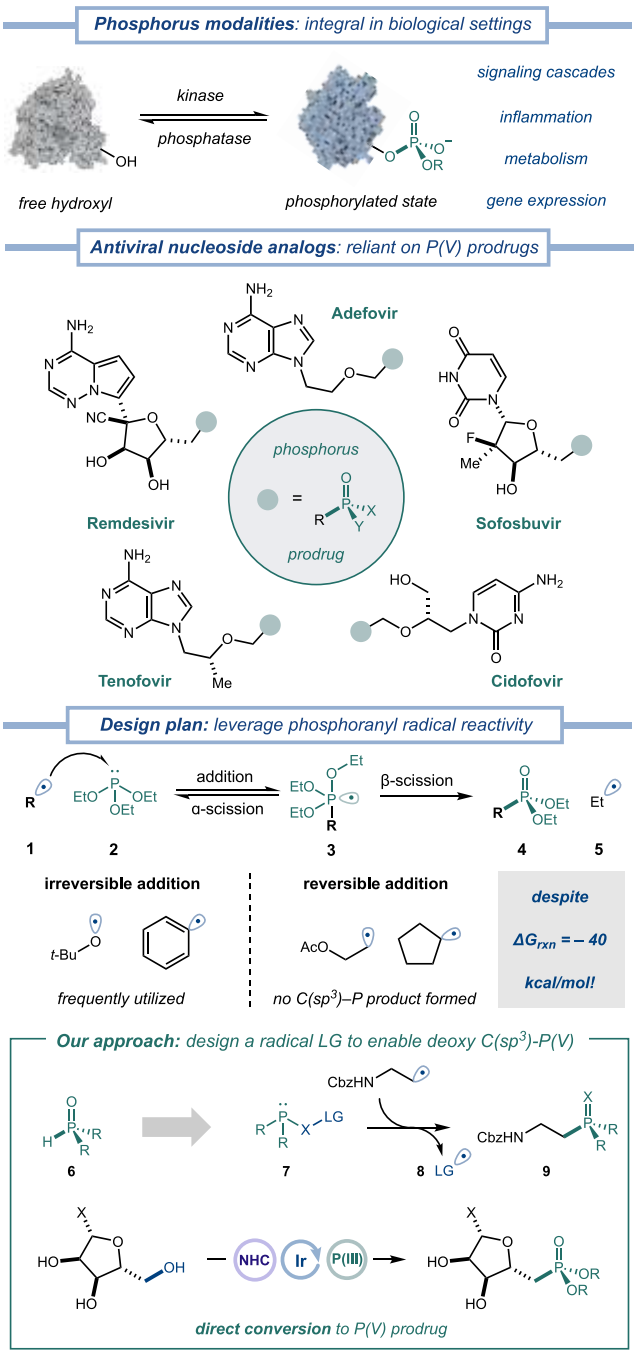

Figure 1. Design of a general P(III) radical trap.

equilibration between the free alkyl radical/P(III) pair (**1** and **2**) and the phosphoranyl radical (**3**). We sought to modulate the relative rate of β-scission with the goal of favoring the desired C(sp^3)−P(V) formation. Specifically, we envisioned utilizing an activated P(III) species (**7**), generated *in situ* from **6**, that would be equipped with a suitable radical leaving group (LG) through a weakened C−O bond.[30] Upon reversible radical capture, expedited β-scission would enable an irreversible trapping event via loss of **8**, thereby delivering phosphonate (**9**).

These phosphonates are often found within antiviral therapeutics,[39] particularly those that target polymerase-mediated viral replication.[40] Their hydrolytic stability and increased membrane permeability can improve pharmacokinetic profiles[41−43] and may lower dosing requirements.[44,45] 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).[46−51]

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 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**).[46] Simultaneously, in a separate vial, an unsymmetrical P(III) reagent (**15**), bearing the radical leaving group, is prepared from broadly available and inexpensive O═P(R)$_2$H precursor (**13**) and a benzhydrol derivative (**14**).[52] 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.[53,54] This highly oxidizing state enables facile oxidation of **12** ($E^{ox}_{1/2}$ ≈ 1.0 V vs SCE in MeCN), and subsequent deprotonation furnishes the heterocyclic radical (**16**).[46] This species generates an alkyl radical (**17**) and the inert, rearomatized NHC byproduct through β-scission. Next, a phosphoranyl 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 deoxyphosphonylated product (**19**) and a bisbenzylic radical (**20**). Finally, the photocatalytic cycle is closed through reductive RPC ($E^{red}_{1/2}$ ≈ −0.77 V vs SCE in MeCN),[55] 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 ($E^{ox}_{1/2}$ = 1.83, 1.49 and 1.28 V vs Ag/Ag$^+$ in MeCN, respectively).[56] Therefore, many commonly employed, oxidatively activated alkyl radical precursors, such as BF_3K salts ($E^{ox}_{1/2}$ = 1.5 V vs SCE),[32] 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 C(sp^3)−P(V) modalities. With this design in mind, we set out to enable the one-step deoxyphosphonylation of alcohols.

Following an extensive optimization campaign (Tables S1−S5), we developed conditions to transform Boc-protected 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 phosphonylation (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.[29] Finally, the organic photocatalyst 4CzIPN-*t*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[57] in good yields (90% and 67%) from readily accessible precursors.

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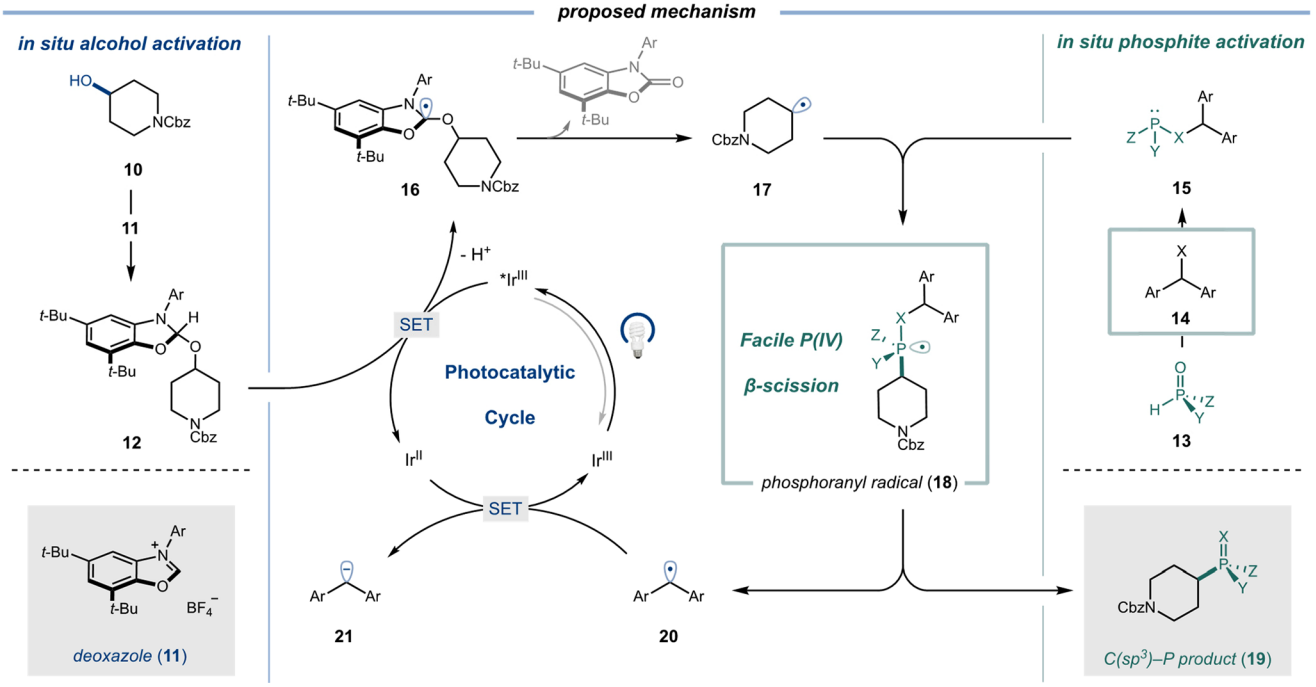
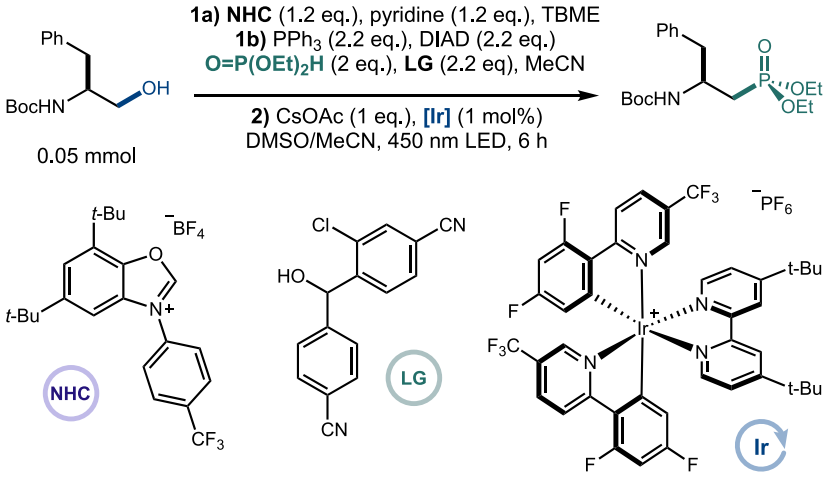


Figure 2. Proposed mechanism. Deoxazole Ar = *p*-CF_3Ph.

Table 1. Optimized Conditions and Controls



entry	deviation	assay yield (%)
1	none	75
2	no light	0
3	no photocatalyst	<1
4	no leaving group	<1
5	$P(OEt)_3$ or $O{=}P(OEt)_2H$ instead of activated P(III)	0
6	4CzIPN-*t*Bu (2 mol %) instead of Ir	74

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).[58] A complex alcohol bearing an N-heterocycle and an easily oxidizable anilinic functionality could also be phosphonylated (**29**, 75% yield). We next subjected a range of saturated N-heterocycles appended with secondary alcohols to the phosphonylation 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[32] have shown that classical tertiary radicals generally do not undergo addition to P(III) species.

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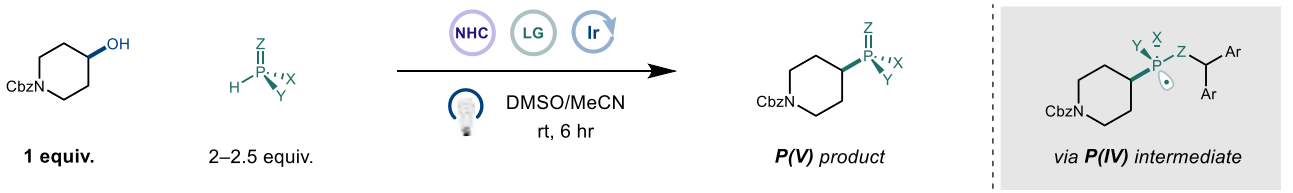
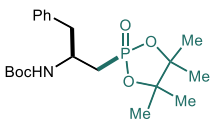
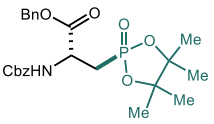


alcohol scope

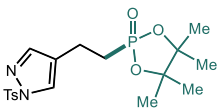
primary alcohols



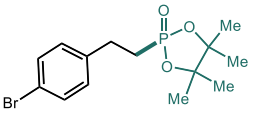
22, 90%
Gram-scale: 94%



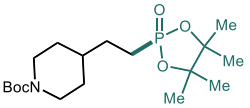
23, 67%



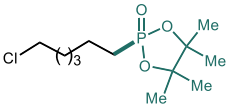
24, 70%



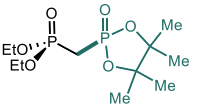
25, 76%



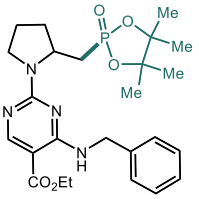
26, 72%



27, 81%[a]

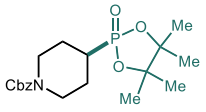


28, 67%[a]

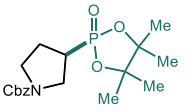


29, 75%
Gram-scale: 78%

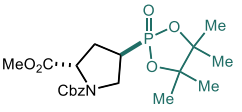
secondary alcohols



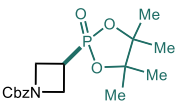
30, 82%



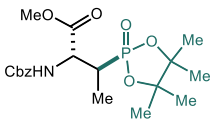
(±)-31, 94%



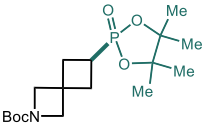
32, 71%[b]



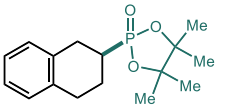
33, 72%



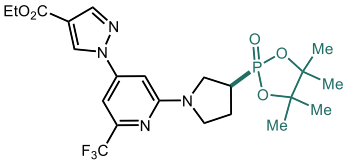
34, 43%[a,b]



35, 84%

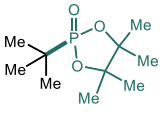


(±)-36, 78%

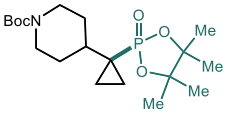


(±)-37, 46%

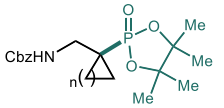
tertiary alcohols



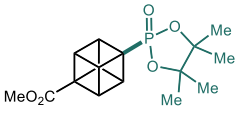
38, 0%[a]



39, 47%

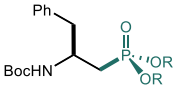


40 (n=1), 72%
41 (n=2), 30%

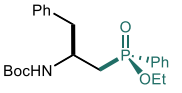


42, 52%[c]

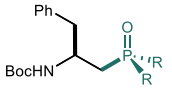
P(V) scope



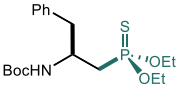
43, R = Et, 75%
44, R = *i*-Bu, 78%
45, R = *i*-Pr, 62%
46, R = *t*-Bu, 0%[a]



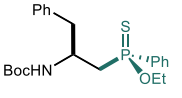
47, 58%[b]



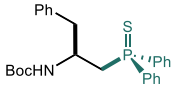
48, R = Ph, 54%
49, R = Me, 52%[a]



50, 68%



51, 81%[b]



52, 63%

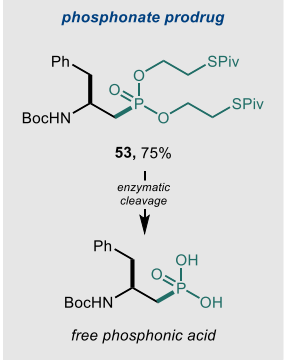


Figure 3. Alcohol and phosphorus scope. See Table 1 for the conditions and the Supporting Information for details and additional examples. [a]Assay yield. [b]2:1 to 1:1 dr. [c]From cubane RAE.

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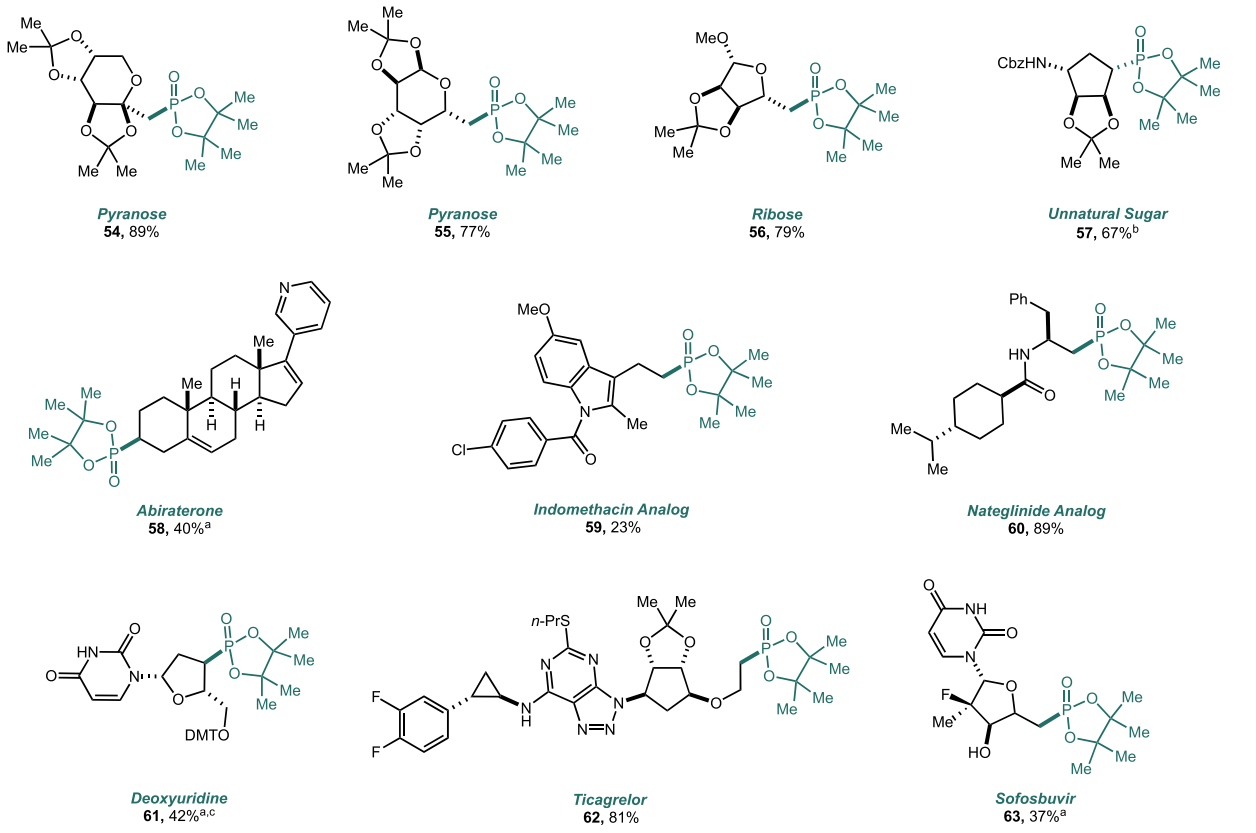

Figure 4. Phosphonylation of complex molecules. See Table 1 for the conditions and the Supporting Information for details. [a]Assay yield. [b]1.4:1 dr. [c]>20:1 dr.

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.[59,60] 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[37] or metallaphotoredox-based[38] 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. By simply altering the benzhydrol utilized in the phosphite activation to employ an oxidative RPC ($E^{ox}_{1/2}$ = 0.35 V vs SCE in MeCN),[61] a redox-neutral cycle generated cubane phosphonate from the RAE (**42**, 52% yield).

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 (**50**−**52**, 63−81% yield). Finally, we turned our attention to P(V) prodrugs. Typically, these motifs are synthesized through laborious multistep sequences, often relying on forcing conditions (strong acid/base or elevated temperatures).[62] Under our protocol, we were pleased to find that the established *S*-acylthioalkyl ester (SATE)[63] 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

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(thioether and free aniline). Finally, the antiviral sofosbuvir was targeted for phosphonylation. This therapeutic features a phosphate (O−P(V)) prodrug at the 5′ position.[18] 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.[50] 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-derived 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 dehydroxylation approach gives access to an expansive feedstock of radical precursors, while the complexity of the phosphites utilized can furnish valuable prodrug 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 phosphoranyl 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)

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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.

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