Development of a General Organophosphorus Radical Trap: Deoxyphosphonylation of Alcohols

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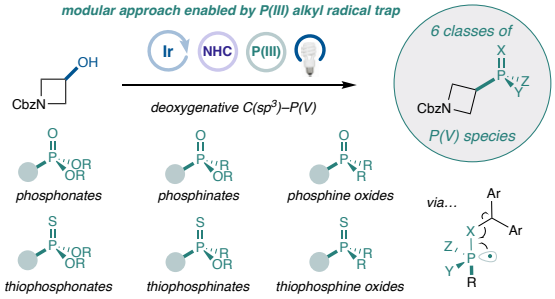


ABSTRACT: Here we report the conceptualization and design of a general, redox switchable organophosphorus alkyl radical trap enabling the synthesis of a broad range of C(sp^3)–P(V) modalities. This plug-and-play approach relies upon an *in-situ* activation of alcohols and dialkyl phosphites, two broadly available sources of molecular complexity. The mild, photocatalytic deoxygenative strategy employed here allows for the direct transformation of sugars, nucleosides, and complex pharmaceutical architectures to their organophosphorus analogs, including medicinally relevant phosphonate ester prodrugs.

The organophosphorus functionality is a ubiquitous structural motif that imparts unique properties to pharmaceuticals,[1] agrochemicals,[2] and modern materials.[3] Notably, phosphorus plays an integral role in regulating *in vivo* systems. Key cellular processes—including protein signaling cascades,[4] inflammation,[5] cellular metabolism,[6] and gene expression[7]—can be modulated by the addition or removal of a phosphate group on proteins, cofactors, and biomolecules.[8–10] Accordingly, careful introduction of P(V) motifs into small molecule therapies can leverage this *in vivo* regulatory activity, proving novel mechanisms for therapeutic intervention. Historically, organophosphorus modalities have played a key role in targeting viral replication mechanisms.[11] Small molecules designed to interfere with polymerase-mediated oligonucleotide synthesis *via* chain termination often feature an unnatural nucleotide, where the triphosphate motif that is formed *in vivo* is essential for recognition.[12] However, the direct utilization of phosphate groups in pharmaceuticals is rare.[13] This is due to the facile hydrolytic cleavage of O–P(V) species *via* phosphatases as well as the poor cell permeability caused by the anionic nature of this functional group at physiological pH.[14] Yet, these poor pharmacokinetic parameters can be overcome through a variety of strategies. Early antiviral therapies avoided these issues by dosing with the more permeable nucleoside derivative and relying upon the cells' natural kinases to form the active triphosphate state *in vivo*.[15] However, the first phosphorylation of

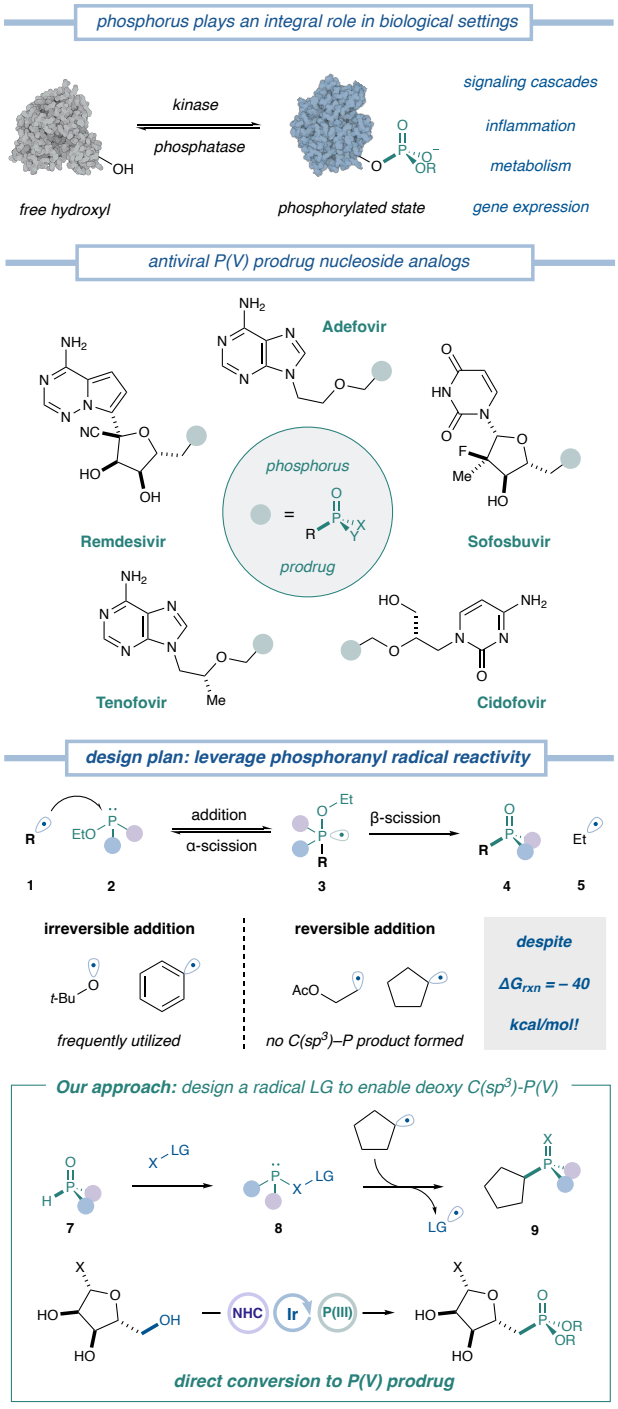


Fig. 1: Role of P(V) *in vivo* and design of a deoxyphosphonylating P(III) radical trap.

these nucleosides is much slower than the second and third, leading to high dosing requirements to reach therapeutic levels of the active drug.[16,17] Phosphonate ester prodrugs represent an alternative modern strategy that resolves some of these challenges.[18,19] These motifs feature several advantages over other approaches, including (1) a stable C–P(V) bond that resists hydrolysis, (2) a neutral charge, which improves cell permeability; and (3) lower dosing requirements achieved by eliminating the first, slow phosphorylation event.[20,21] P(V) prodrugs, such as Cidofovir, Adefovir, Tenofovir, Sofosbuvir, and Remdesivir have drastically impacted patient outcomes across may indications including HIV, HPV, hepatitis, and COVID-19 (Figure 1).[22–26]

Despite their utility, access to alkyl phosphonates (and the broader class of C(sp^3)–P(V) species) is quite limited. Traditional two-electron methods[27] for the synthesis of alkyl organophosphorus species such as the Arbuzov reaction suffer from limited scope due to high reaction temperatures (often >100 ºC).[28] In recent years, methods utilizing open-shell intermediates (**1**) to forge X–P bonds (X = O, S, or C(sp^2)) via radical addition to P(III) (**2**) at room temperature have found great utility.[29–33] These transformations proceed through a well-characterized P(IV) phosphoranyl radical intermediate (**3**);[34] this species readily undergoes β-scission, generating alkyl radical (**5**) and the desired P(V) product (**4**). However, when attempting this same transformation with more stable C(sp^3) radicals, C(sp^3)–P product (**4**) is not formed. This curious phenomenon is further complicated by the fact that the key alkyl phosphoranyl radical intermediate (**3**) can be detected at appreciable concentrations by EPR (electron paramagnetic resonance) spectroscopy.[35] Furthermore, the net transformation is significantly exothermic ($\Delta G \approx$ – 40 kcal/mol).[36] However, instead of forming product formation *via* β-scission, this intermediate decomposes through α-scission, regenerating the starting phosphite and alkyl radical. Owing to 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.[37] Instead, alternative free radical methods have emerged including addition of phosphorus centered radicals to π-systems[38,39] and transition metal catalyzed cross coupling methods.[40,41] Although these transformations represent significant inroads towards 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 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 HAT or disproportionation or (b) β-scission to form phosphonate. Linking both of these pathways is a rapid equilibration between the free alkyl radical P(III) pair (**1** and **2**) and the phosphoranyl radical (**3**). Through careful design of an activated P(III) species, we sought to modulate the relative rate of β-scission, shifting equilibrium towards the desired C(sp^3)–P(V) pathway. More particularly, we reasoned that β-scission could be favored through the design of an activated P(III) species (**8**) containing a suitable radical leaving group (LG) through weakening of the C–O bond.[35] Upon reversible radical capture, this expedited β-scission would enable an irreversible trapping event to form the desired phosphonate (**9**). Given the integral role of the organophosphorus motif in nucleoside analogs, we were particularly interested in using alcohols as radical precursors.[42–47] If successful, this would constitute as a powerful method to interconvert the natural site of phosphorylation in sugars and nucleosides to the phosphonate derivative (Figure 1). Furthermore, alcohols are broadly available sources of structural complexity,[48] enabling access to new organophoshorus chemical space.

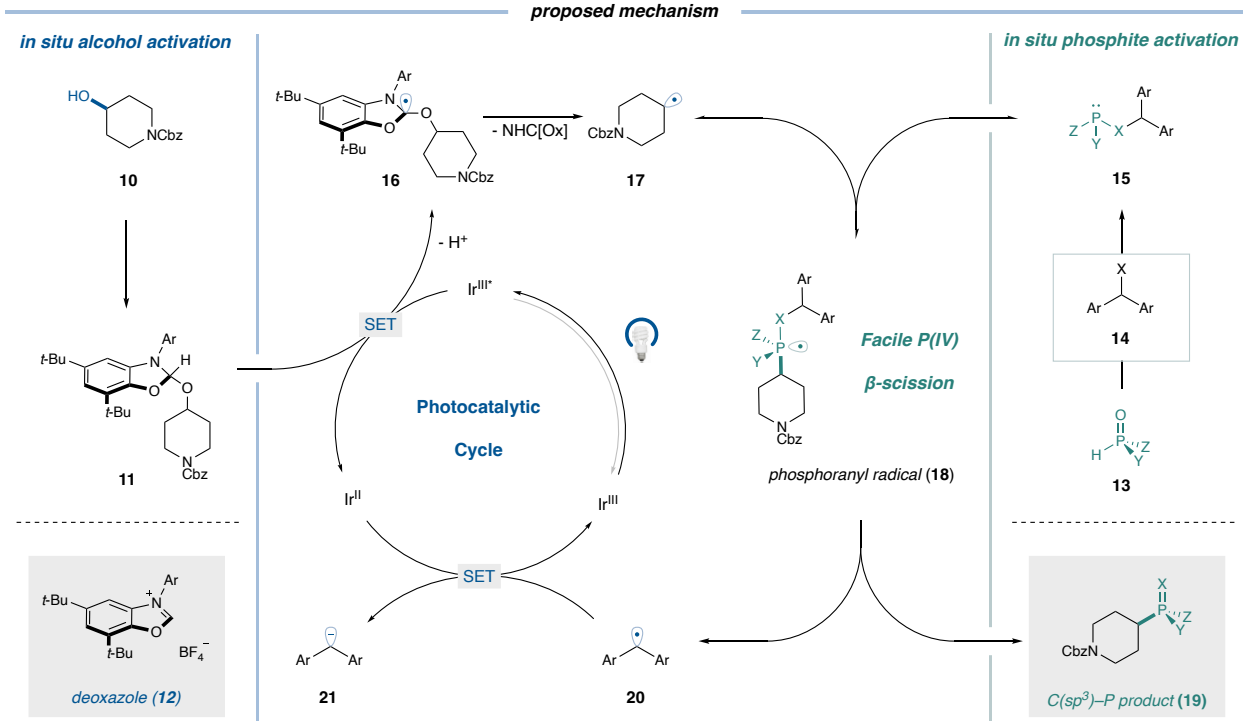
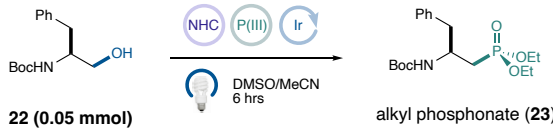


Fig. 2: Proposed mechanism. Deoxazole Ar = *p*-CF_3Ph.

To realize this transformation from readily available starting materials, we envisioned performing two *in situ* pre-activation steps. This 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**) can undergo a rapid (~30 min), mild condensation with the deoxazole or "NHC" reagent (**12**) to furnish the NHC-activated alcohol adduct (**11**).[42] Simultaneously, in a second vial, an unsymmetrical P(III) reagent (**15**), bearing the radical leaving group, can be prepared from broadly available and inexpensive O=P(R)$_2$H motifs (**13**) and a benzhydrol derivative (**14**).[49] This crude mixture is then directly added to the vial containing the activated alcohol, iridium catalyst, and base. Upon irradiation with blue light (450 nm), the iridium catalyst undergoes excitation and subsequent intersystem crossing to reach a long-lived triplet state.[50,51] This highly oxidizing triplet state enables facile oxidation of **11** ($E_{1/2}^{ox}$ = 1.0 V vs SCE in MeCN) and subsequent deprotonation by a suitable base furnishes NHC radical (**16**).[42] This species is primed to undergo β-scission, forming alkyl radical (**17**) and the inert, aromatized NHC byproduct. 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 enables the formation of the deoxyphosphonylated product (**19**) and a bisbenzylic radical (**20**). This radical then undergoes reductive radical polar crossover ($E_{1/2}^{red}$ ≈ –0.77 V vs SCE in MeCN)[52] furnishing a carbanion (**21**) and closing the photocatalytic cycle in a redox neutral manner. Importantly, the readily oxidizable NHC adduct should enable the use of activated phosphites, phosphonites, and phosphinites ($E_{1/2}^{ox}$ = 1.83 V, 1.49 V and 1.28 V, respectively, all vs Ag/Ag^+ in MeCN),[53] providing a modular platform for which to access a broad array of P(V) products while avoiding deleterious P(III) oxidation to the corresponding radical cation. With this design plan in mind, we set out to develop conditions to enable the deoxyphosphonylation of alcohols.



22 (0.05 mmol)

alkyl phosphonate (**23**)

entry	*control*	*assay yield*
1	full reaction	75%
2	no light	0%
3	no photocatalyst	<1%
4	no leaving group	<1%
5	$P(OEt)_3$ instead of activated P(III)	0%
6	$P(OEt)_3$ instead of activated P(III), open to air (18 g needle)	0%
7	$HP{=}O(OEt)_2$ instead of activated P(III)	0%
8	$HP{=}O(OEt)_2$ instead of activated P(III), open to air (18 g needle)	0%

Fig. 3: Optimized conditions and controls.

After an extensive optimization campaign, we were pleased to arrive at conditions (see standard reaction setup) to

transform Boc protected L-phenylalaninol (**22**) to the corresponding diethyl phosphonate (**23**) in 75% yield (Figure 3, entry 1). Pleasingly, in the absence of irradiation or photocatalyst, no product was detected (entry 2-3). Additionally, omitting the benzhydrol shut down the phosphonylation (entry 4), providing key mechanistic insight into the importance of a suitable radical leaving group. Finally, when unactivated sources of P(III) or P(V) were utilized, no product could be detected (entries 5-8), recapitulating the unproductive reactivity of standard P(III) species with alkyl radicals.

With optimized conditions in hand, we next set out to evaluate the scope of this new method (Figure 4). Reduced amino acids (**24**) and serine (**25**) proved to be competent substrates, furnishing medicinally relevant β-aminophosphonates[54] in good yields (90% and 67%, respectively) from readily accessible precursors. Additionally, heterocyclic (**26**) and aromatic motifs, including those bearing cross coupling handles (**27**), were well tolerated (70% and 76% yield, respectively). We next turned our attention to saturated heterocycles which also proved to be effective substrates (**28** and **29**, 75% and 72% yield, respectively). We were pleasantly surprised that 1º chlorides (**30**, 55% yield) were tolerated despite strongly basic reaction conditions. A complex alcohol bearing N-heterocycles and easily oxidized anilinic functionalities could also be phosphonylated (**31**, 71% yield), illustrating functional group tolerance. Next, a range of saturated N-heterocycles were subjected to phosphonylation, yielding product with good to excellent efficiencies (**32**-**35**, 82-98% yield). The amino acid threonine could be utilized, forming the 2º β-amino phosphonate derivative in fair yields (**36**, 43% yield). Pleasingly, spirocyclic, bicyclic, and complex N-heterocyclic alcohols were competent substrates (**37**-**39**, 43-85% yield).

Finally, this transformation was applied to a range of 3º alcohols. It is well precedented through EPR and synthetic studies[37] that classical, strain free 3º radicals do not undergo addition to P(III) species. This phenomenon was successfully recapitulated, as *tert*-butanol gave no detectable product (**40**, 0% yield). However, when the 3º radical is tied back, through either small rings or bicyclic systems, its *s*-character is increased, resulting in the formation of a stronger C–P bond and the steric penalty for P(IV) formation is reduced.[55,56] Indeed, cyclopropyl 3º alcohols (**41**, 47% yield) and strained bicyclic systems including adamantane (**42**, 10%), generated product

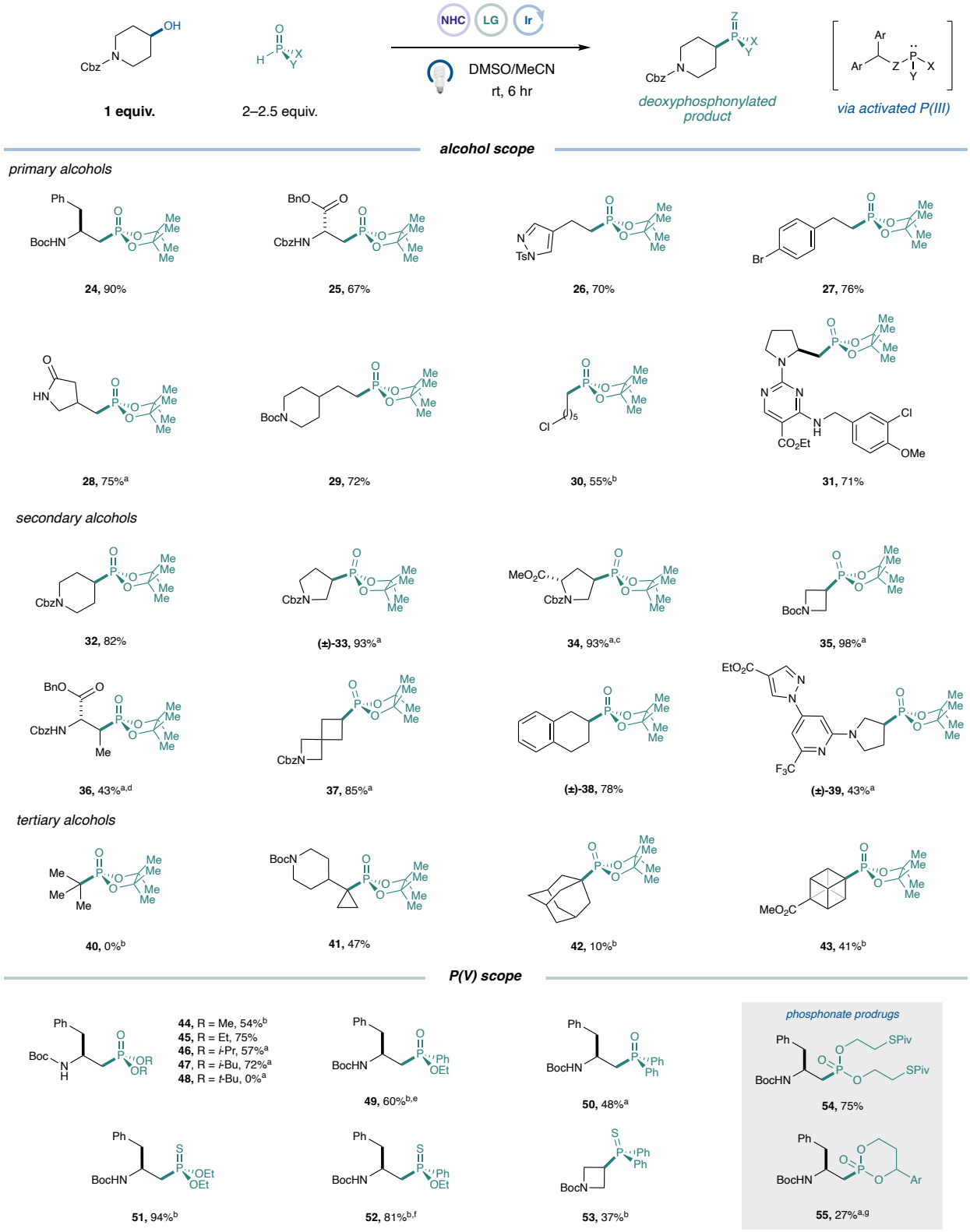


Fig. 4: Alcohol and phosphorus scope. See standard reaction setup for details. [a]Assay yield on 0.5 mmol scale. [b]Assay yield on 0.05 mmol scale. [c]2.1:1 dr. [d]1.1:1 dr. [e]1.2:1 dr. [f]1:1 dr. [g]Ar = *m*-ClPh.

in modest to synthetically useful yields. Despite the reduced efficiency of these challenging substrates, classical methods for synthesizing alkyl phosphonates (i.e., Arbuzov via S_N2) as well as recent reports (metallophotoredox[41] or copper catalyzed[40]) are not amenable to 3º substrates, illustrating the distinct advantage of a free radical trap approach. We accredit the success—albeit modest—of these substrates to the careful design of our radical leaving group. Additionally, we were pleased to observe that this platform could be generalized to other radical precursors (redox active esters, RAE) when the requisite alcohol is not readily accessible or stable. By simply altering the benzhydrol utilized in the phosphite activation and employing an oxidative radical polar crossover ($E_{1/2}^{ox}$ = 0.35 V vs SCE in MeCN),[57] a redox neutral cycle led to the formation of cubane phosphonate from the RAE (**43**, 41% yield).

Having evaluated the scope of this transformation with respect to the alcohol coupling partner, we next turned our attention to examining the range of phosphorus functionality that could be installed using this method. First, we examined the effect of phosphite sterics on this transformation; while linear and 2º phosphite esters proved to be facile substrates (**44**-**47**, 54-75% yield), 3º esters were not amenable to our preactivation conditions (**48**, 0% yield). Gratifyingly, 1º phosphonites and 2º phosphine oxides can be transformed to 2º phosphonites and 3º phosphine oxides (**49** and **50**, 60 and 48% yield, respectively), highlighting the modular nature of this chemistry. Additionally, organosulfur derivatives of phosphonates, phosphonites and phosphine oxides were also accessed by simply using a thiobenzhydrol leaving group (**51**-**53**, 37-94% yield). Excitingly, established prodrug phosphonates including *S*-acylthioalkyl ester (SATE)[58] and HepDirect, a liver selective phosphonic acid prodrug motif,[59] could be installed in a single step (**54** and **55**, 75% and 27% yield, respectively). Typically, these prodrug motifs are synthesized through a laborious multistep sequence, often relying on forcing conditions (strong acid/base or elevated temperatures) to hydrolyze simple phosphonates only to then generate the desired prodrug phosphonate *via* addition to an electrophilic sidechain.[60]

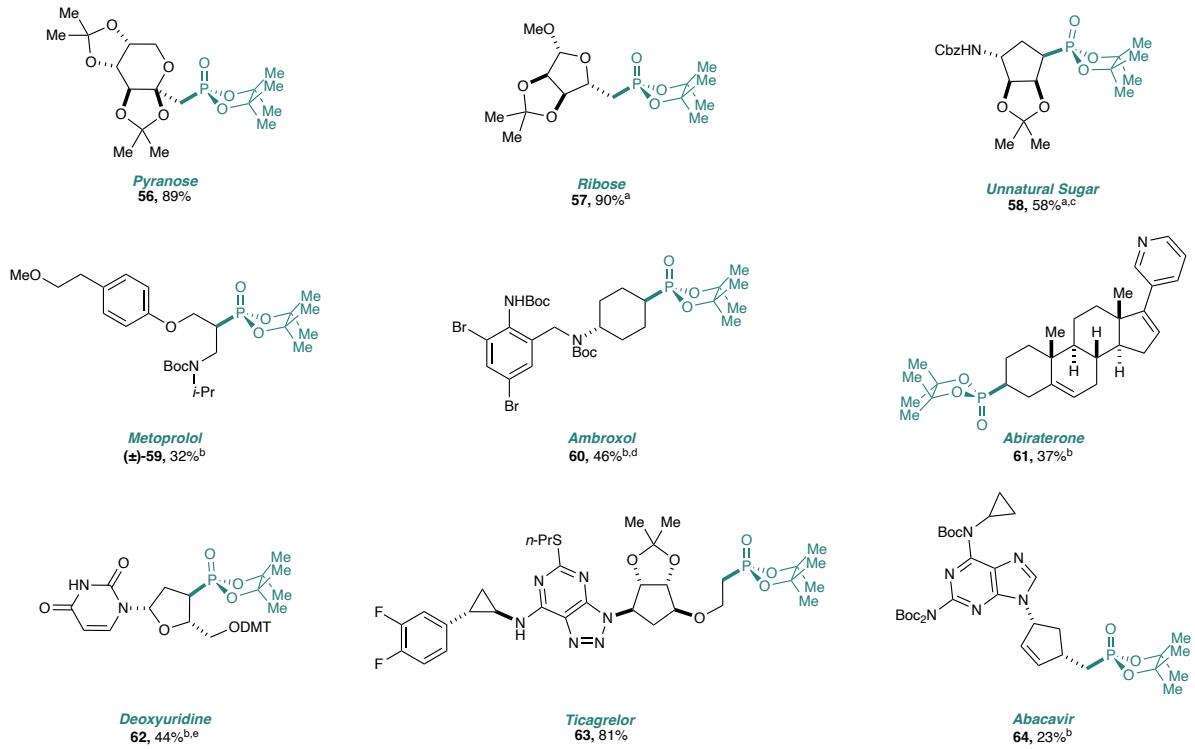


Fig. 5: Phosphonylation of sugars, nucleosides, and pharmaceuticals. See standard reaction setup for details. [a]Assay yield on 0.5 mmol scale. [b]Assay yield on 0.05 mmol scale. [c]1.6:1 dr. [d]2.5:1 dr. [e]>10:1 dr.

Having applied this transformation to a range of alcohol containing small molecule fragments, we sought to test the limits of functional group tolerance by phosphonylating a small library of sugars, nucleosides, and pharmaceuticals. Gratifyingly, protected pyranoses (**56**), furanoses (**57**), and unnatural sugar derivates (**58**) were successfully converted to the hydrolytically stable congeners at the natural site of phosphorylation (58-90% yield). Furthermore, pharmaceutical scaffolds including Metoprolol (**59**, 32% yield) and Ambroxol (**60**, 46% yield) were well tolerated, illustrating the successful application of this chemistry for the modification of small molecule drugs. The steroid Abiraterone (**61**, 37% yield), bearing a heterostyrenyl motif, was phosphonylated in modest yields. As a final application of free radical phosphonylation in a medicinal chemistry setting, we targeted the direct modification of nucleosides and analogs thereof. Deoxyuradine (**62**, 44% yield) could be directly transformed into an unnatural nucleotide featuring an alternative site of P(V) introduction. Excitingly, the nucleoside analog Ticagrelor (**61**, 81% yield) could be functionalized in excellent yield despite the presence of oxidizable

functionalities including a thioether and free aniline. Additionally, the antiviral Abacavir (**62**, 23% yield) was derivatized in synthetically useful yield. Abacavir undergoes phosphorylation at this position *in vivo* to generate the active form of the drug;[61] thus, this transformation allows for the preparation of a hydrolytically resistant phosphonate derivative in a single step.

In summary, the combination of these mild, photocatalytic conditions, broad alkyl substrate tolerance, and the 'plug-and-play' nature of activated P(III) generation allows for the formation of a diverse array of alkyl-P(V) species. This modular platform provides the means to diversify the synthesis of medicinally relevant phosphonate esters by direct installation of the desired P(V) motifs. Uniquely, this dehydroxylation approach gives access to an unrivaled feedstock of radical precursors, while the complexity of the phosphites utilized can furnish valuable prodrug motifs in a single synthetic step. Furthermore, we envision the utilization of this redox switchable benzhydrol activated P(III) species will broadly inform the development of related transformations enabled by phosphoranyl radical chemistry.

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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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STANDARD REACTION SETUP

General Procedure A: 1º/2º Alcohol Activation and Deoxyphosphonylation

To an oven dried 8 mL vial charged with an X shaped stir bar was added alcohol (if solid, 0.5 mmol, 1 eq.) and NHC-5 (278.9 mg, 0.6 mmol, 1.2 eq.). The vial was purged and backfilled with N_2 3x then, dry TBME (5 mL) was added *via* syringe against the flow of N_2. Alcohol (if liquid, 0.5 mmol, 1 eq.) was added by syringe against the flow of N_2. The heterogeneous mixture was stirred vigorously for 2 minutes then pyridine (47.5 mg, 48.5 µL, 0.6 mmol, 1.2 eq.) was added dropwise. The mixture was stirred at room temperature for ~30 minutes under nitrogen.

Next, the TBME suspension of activated alcohol was transferred to a 5 mL syringe under air. A syringe filter was installed, and the suspension was filtered into a new 40 mL vial. Quantitative transfer of the activated alcohol was ensured by washing the condensation vial with ~1.25 mL of TBME followed by filtration through the same syringe filter (2x). TBME was carefully removed under rotary evaporation (~250 mbar to 100 mbar, 35 ºC) resulting in a pale-yellow oil until there were no clear changes in the oil's volume. The oil was dried on high vacuum for ~5 minutes. During this time, a voluminous white/yellow solid formed indicating complete removal of TBME. (It is recommended to apply high vacuum slowly as this solid is prone to "bumping.") $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (5.6 mg, 0.005 mmol, 1 mol%), and CsOAc (96.0 mg, 0.5 mmol, 1.0 eq.) were added to the 40 mL vial containing the dried, activated alcohol. To this 40 mL vial, 2.5 mL of dry DMSO was added, and the mixture was sparged for 10 min and left under N_2 until the phosphite activation was completed. Upon completion, the entirety of the MeCN solution containing the activated P(III) compound in the 4 mL vial was added (with a 0.1 mL wash with dry MeCN) and the 40 mL vial was sealed with molten parafilm. Next the mixture was irradiated in the M2 PennOC integrated photoreactor (450 nm LED module, 100% intensity, 1000 rpm stirring, max fans) for 6 hours.

After irradiation, the mixture was transferred to a separatory funnel and diluted with 30 mL of EtOAc. The organics were washed with water (4x10 mL). The combined aqueous washes were back extracted with EtOAc (1x15 mL). The combined organics were then dried over sodium sulfate, filtered, and concentrated. The crude oil was purified by column chromatography, furnishing pure alkyl phosphonate.

General Procedure B: 3º Alcohol Activation

To an oven dried 8 mL vial charged with a X shaped stir bar was added alcohol (if solid, 0.5 mmol, 1 eq.) and NHC-5 (277.9 mg, 0.6 mmol, 1.2 eq.). The vial was purged and backfilled with N_2 3x. Then, dry TFT (5 mL) was added via syringe against the flow of N_2. Alcohol (if liquid, 0.5 mmol, 1 eq.) was added by syringe against the flow of N_2. The heterogeneous mixture was stirred vigorously for 2 minutes then cooled to -25ºC using a dry ice/acetone bath. After the mixture was

cooled, pyridine (47.5 mg, 48.5 µL, 0.6 mmol, 1.2 eq.) was added dropwise. The mixture was vigorously stirred while slowly warming to room temperature over 2 hours.

Next, the TFT suspension of activated alcohol was transferred to a 5 mL syringe under air. A syringe filter was installed, and the suspension was filtered into a new 40 mL vial. Quantitative transfer of the activated alcohol was ensured by washing the condensation vial with ~1.25 mL of TFT followed by filtration through the same syringe filter (2x). TFT was carefully removed under rotary evaporation (~150 mbar to 10 mbar, 35 ºC) resulting in a pale-yellow oil until there were no clear changes in the oil's volume. The oil was dried on high vacuum for ~5 minutes. During this time, a voluminous white/yellow solid formed indicating complete removal of TBME. (It is recommended to apply high vacuum slowly as this solid is prone to "bumping.") $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (5.6 mg, 0.005 mmol, 1 mol%), and CsOAc (96.0 mg, 0.5 mmol, 1.0 eq.) were added to the 40 mL vial containing the dried, activated alcohol. To this 40 mL vial, 2.5 mL of dry DMSO was added and the mixture was sparged for 10 min and left under N_2 until the phosphite activation was completed. Upon completion, the entirety of the MeCN solution containing the activated P(III) compound in the 4 mL vial was added (with a 0.1 mL wash with dry MeCN) and the 40 mL vial was sealed with molten parafilm. Next the mixture was irradiated in the M2 PennOC integrated photoreactor (450 nm LED module, 100% intensity, 1000 rpm stirring, max fans) for 6 hours.

After irradiation the mixture was transferred to a separatory funnel and diluted with 30 mL of EtOAc. The organics were washed with water (4x10 mL). The combined aqueous washes were back extracted with EtOAc (1x15 mL). The combined organics were then dried over sodium sulfate, filtered, and concentrated. The crude oil was purified by column chromatography furnishing pure alkyl phosphonate.

General Procedure C: Phosphite activation for 1º alcohol substrates

Concurrently, to an oven dried 4 mL vial charged with a stir bar was added 2-pyridyldiphenylphosphine (289.6 mg, 1.1 mmol, 2.2 eq). The vial was purged and backfilled with N_2 3x, then MeCN (0.8 mL) was added. The mixture was stirred for 1 minute then DIAD (222.4 mg, 216.5 µL, 1.1 mmol, 2.2 eq.) was added dropwise against the flow of N_2. The resulting orange solution was stirred for 15 minutes at room temperature then $X_2(P{=}O)H$ compound (1.0 mmol, 2.0 eq.) was added by syringe (if liquid) or the entirety of the orange solution was transferred to a new 4 mL vial under N_2 containing the solid phosphite and a stir bar. The resulting solution was stirred for ~30 minutes at room temperature as the mixture changed color from light orange to a light yellow (Note: typically, the NHC condensation was run during this 30 min stirring period.) The entire solution was transferred to a vial under N_2 charged with 3-chloro-4-((4-cyanophenyl)(hydroxy)methyl)benzonitrile (295.6 mg, 1.1 mmol, 2.2 eq.) and a stir bar with a 0.1 mL wash of dry MeCN to ensure full transfer. The solution was then stirred for 1 hr at room temperature. Afterwards, the activated phosphite was directly utilized in General Procedure A.

General Procedure D: Phosphite activation for 2/3º alcohol substrates

Following the same procedure as General Procedure C but utilizing 2.75 eq of 2-pyridyldiphenylphosphine (362.0 mg, 1.38 mmol, 2.75 eq), DIAD (278.0 mg, 270.7 µL, 1.38 mmol, 2.75 eq.), 3-chloro-4-((4-cyanophenyl)(hydroxy)methyl)benzonitrile (369.46 mg, 1.38 mmol, 2.75 eq.) and 2.5 eq of $X_2(P{=}O)H$ compound (1.25 mmol, 2.5 eq.).

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