# Stereocontrolled Radical Thiophosphorylation

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*Stereocontrolled, Phosphorus, Radical, Phosphorylation, Alkene Functionalization*

**ABSTRACT.** *The first practical, fully stereoselective P(V)-radical hydrophosphorylation is presented herein using simple, limonene-derived reagent systems. A set of reagents has been developed that upon radical initiation react smoothly with olefins and other radical acceptors to generate P-chiral products which can be further diversified (with conventional 2e⁻ chemistry) to a range of underexplored bioisosteric building blocks. The reactions have a wide scope with excellent chemoselectivity and the unexpected stereochemical outcome has been supported computationally and experimentally. Initial ADME studies are suggestive of the promising properties of this rarely explored chemical space.*

**MAIN TEXT.** The replacement of an oxygen by sulfur is a powerful strategy employed by medicinal chemists to improve biophysical properties of phosphate containing molecules. This so-called "thio effect" has proven to be clinically validated in the case of oligonucleotide therapeutics by improving cellular uptake and stability towards enzymatic degradation in the extracellular medium (Fig. 1A, left).[1-4] Although this strategy proved to be highly advantageous in the field of oligonucleotides,[1] this single-atom replacement on the phosphate backbone is underexplored in other areas of medicinal chemistry. Previous research has shown that phosphonates can act as mimics for other functional groups i.e. amides, sulfoxides, sulfones, and sulfides.[5-7] In principle, the application of the thioisosteric effect to this class of compounds could enable access to expanded chemical space with potentially desirable properties (Fig. 1A, right). Whereas replacement of *O* by *S* in the context of phosphates is generally associated with the enhanced pharmacological properties, it comes at the expense of increased structural complexity, in the form of a new stereogenic center. One practical solution to this challenge has emerged recently using P(V)-based, limonene-derived reagents leveraging the reactivity of chiral oxathiophospholanes (**Ψ**- and **Π**-reagents).[8] This reagent platform enables programmable, traceless, and stereoselective phosphorus-sulfur incorporation, making it possible to synthesize various architectures with high efficiency (Fig. 1B). The reactivity of **Ψ**- and **Π**-reagents is based solely on classical 2e⁻ logic, and as such it is limited to reactions with classical nucleophiles i.e. alcohols, amines, organometallic reagents, and phosphate anions.[9] Unlike the rapid development of stereocontrolled carbon-based radical chemistry, research into analogous *P*-centered radicals remains underdeveloped. Current methods[10,11] are based on SET,[12,13] HAT,[14-17] or $S_H2$ mechanisms[18,19] and frequently employ either toxic reagents (i.e. Se) or lack chemoselectivity.

This Communication discloses the first practical solution to stereocontrolled radical transformations on the P(V)-center (Fig. 1C), enabling access to both simple and complex *P*-containing molecules that were heretofore inaccessible in enantiopure form.

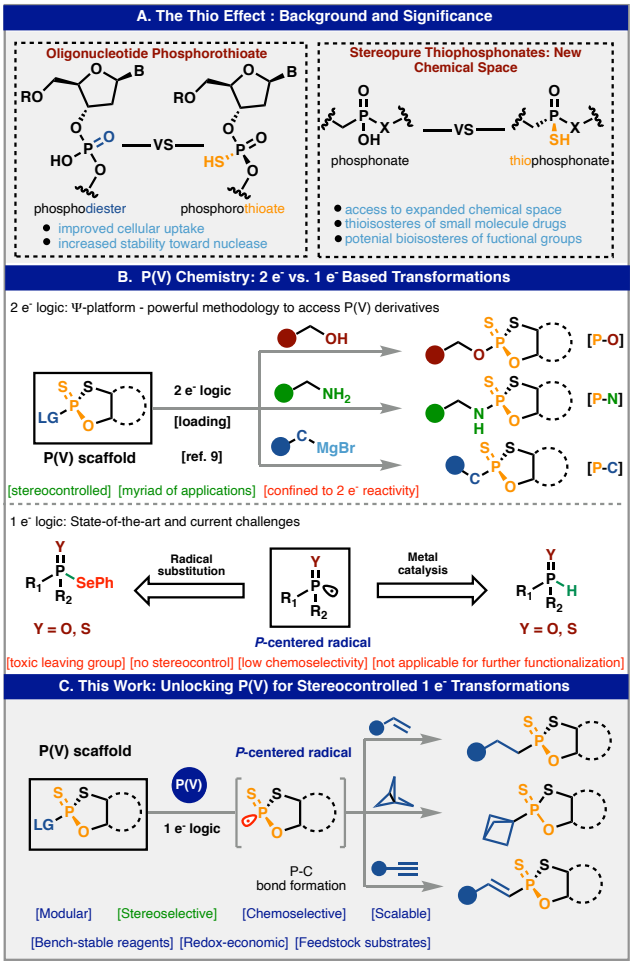



**Figure 1.** (A) The thio effect: current and potential applications. (B) P(V) chemistry: state-of-the-art. (C) This work: stereocontrolled radical hydrophosphorylation.

The starting point for this investigation was based on a singular report indicating that dialkyl selenophosphates can undergo radical substitution with Sn- or Si-centered radicals leading to a pentavalent *P* radical (Figure 2A).[18] Inspired by this finding, we wondered

if this reactivity could be translated to the **Ψ**-reagent scaffold. Due to the electrophilic nature of *P*-centered radical and given the ubiquity of alkenes as feedstock building blocks,[16] olefin hydrophosphorylation was initially explored. To our delight, initial attempts using benzeneselenol-bearing **Ψ**-reagent (**Ψ$^{Se}$**, **1**) and alkene **2**, gave the hydrothiophosphorylated product **3** in 53% yield with 10:1 d.r. With this promising lead in hand, a systematic optimization of conditions and reagent structure was pursued (Fig. 2B).

Based on the known reactivity difference in the subsequent *P*-functionalizations between **Ψ**- and **Π**-loaded reagents,[9b] the focus of the optimization was put on the previously reported **Π** scaffold **4** (useful for P-C bond formation). Due to the high toxicity associated with organoselenium compounds, P(V) reagents bearing alternative chalcogen-based functional groups were investigated (see SI). Although analogous reactivity of the P-S rather than P-Se bond has been reported only in an intramolecular scenario,[19] it was found that pentafluorothiophenol can be used as competent leaving group in this reaction, albeit in lower yield (28%, entry 1). Reduction of the double bond in the limonene backbone (reagent **dihydro-Π**, **6**) was essential from a chemoselectivity standpoint and led to a 3-fold increase in the yield of the product (entry 2). Whereas the use of a syringe pump to add radical initator and silane was essential when employing **Ψ$^{Se}$**, it can be avoided when using **dihydro-Π** with only slight decrease in yield (entry 3). Meticulous screening of temperature and solvent led to the desired hydrophosphorylation product in high yield (78%) with excellent stereocontrol (>20:1 d.r.) (entries 4-8). Choice of DCE as a solvent and lowering the temperature to 50 °C proved to be essential for high diastereoselectivity and reproducibility of the protocol (entry 8). No conversion of the starting materials was observed in the absence of radical initiator (entry 9) or in the presence of oxygen (entry 10), which supports radical nature of the reaction. Moreover, optimized conditions proved to be compatible for the analogous **dihydro-Ψ** reagent **7**, which has orthogonal reactivity to **dihydro-Π** in subsequent coupling (entry 11).

With optimized conditions in hand, the scope of the stereocontrolled alkene hydrothiophosporylation was investigated as outlined in Fig. 3. Numerous unactivated alkenes, as well as those bearing electron-withdrawing and electron-donating substituents provided products in 30-97% yields with excellent diastereoselectivities, on scales ranging from 0.1 to 3 mmol. The relatively mild conditions enabled high chemoselectivity. For example, functional groups notoriously problematic in transition metal catalyzed reactions such as Bpin (**9**) and halogens (**12**, **13**, **19**, **28**) are well tolerated. Medicinally relevant functionalities including heterocycles (**14**, **16**, **31**), and basic nitrogens (**14**, **35**) are also compatible. Even alkenes bearing redox-active moieties (i.e. *N*- hydroxylphthalimide ester; **26**, **27**) were tolerated, which are typically incompatible in many SET-based protocols. Similarly, the developed protocol expands the scope of stereocontrolled P-C bond forming reactions by tolerating functionalities not compatible with canonical 2-electron chemistry (e.g. organometallic reagents or strong bases) such as aldehyde (**20**), free hydroxyl (**25**), carbamate (**33**), and ketone (**37**). In addition, sulfide (**11**), sulfonamide (**17**), carboxylic acid (**21**), ester (**22, 33**), amide (**23, 35**), nitrile (**24**), and silyl ether (**34**) are competent functionalities. The reaction is not limited to terminal alkenes as more substituted olefins provide hydrophosphorylation products in good to excellent yields (**29**, **30**). The developed protocol can be used to install both **Π** and **Ψ** scaffolds with comparable yields (**3** *vs.* **8**; **17** *vs.* **18**).

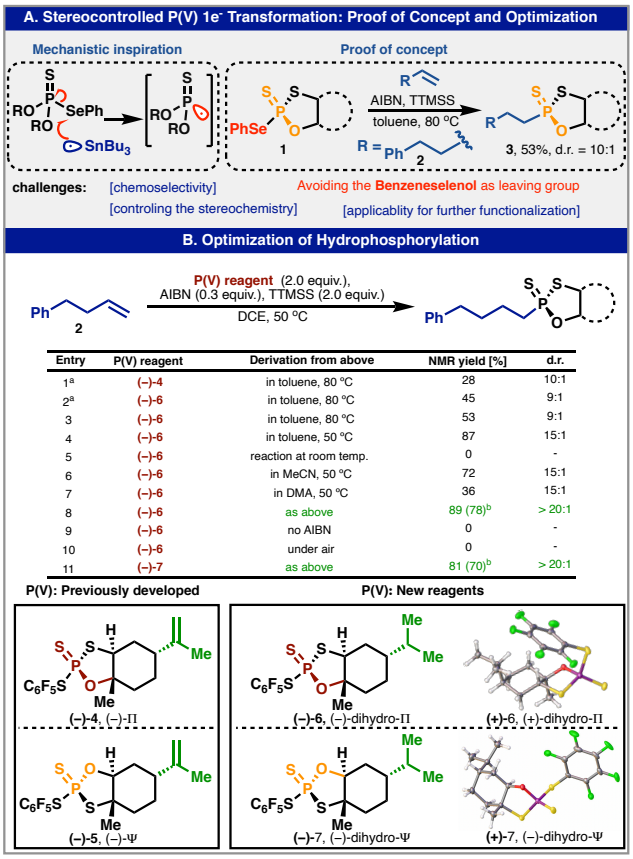



**Figure 2.** (A) Mechanistic inspiration and proof of concept. (B) Optimization details. [a]AIBN and TTMSS added via syringe pump. [b]Isolated yield.

Given the high chemoselectivity observed, multifunctionalized drug-like molecules (**33** – **37**) are viable substrates for hydrothiophosphorylation. For example, highly functionalized thiophosphate derivatives of the tyrosine kinase inhibitor Imbruvica (**35**) and the nonsteroidal anti-inflammatory drug indomethacin (**36**) were obtained in good yields. Finally, thiophosphonate isosteres of naturally occurring organic phosphates such as nucleotides (**34**) can now be easily accessed by this method.

After establishing the scope of alkene functionalization, the possibility to expand this strategy to other radicalophilic species was investigated. Unactivated and aryl-substutited alkynes provided hydrothiophosphorylation products bearing C($sp^2$)-P bonds (**38**-**42**). While unactivated alkynes led to mixture of *E*- and *Z*-isomers, aryl substituted starting materials favored formation of the *Z*-isomer. Propellane proved to be reactive towards the P-radical, leading to phosphorylated bicyclo[1.1.1]pentanes (BCP). The presented methodology could conceivably be used to prepare enantiopure analogs of these potentially useful isosteric building blocks. Moreover, non-carbon-based radical acceptors such as DBAD (di-*tert*-butyl azodicarboxylate) are viable leading to phosphorylated hydrazine derivatives via formation of P-N bond.

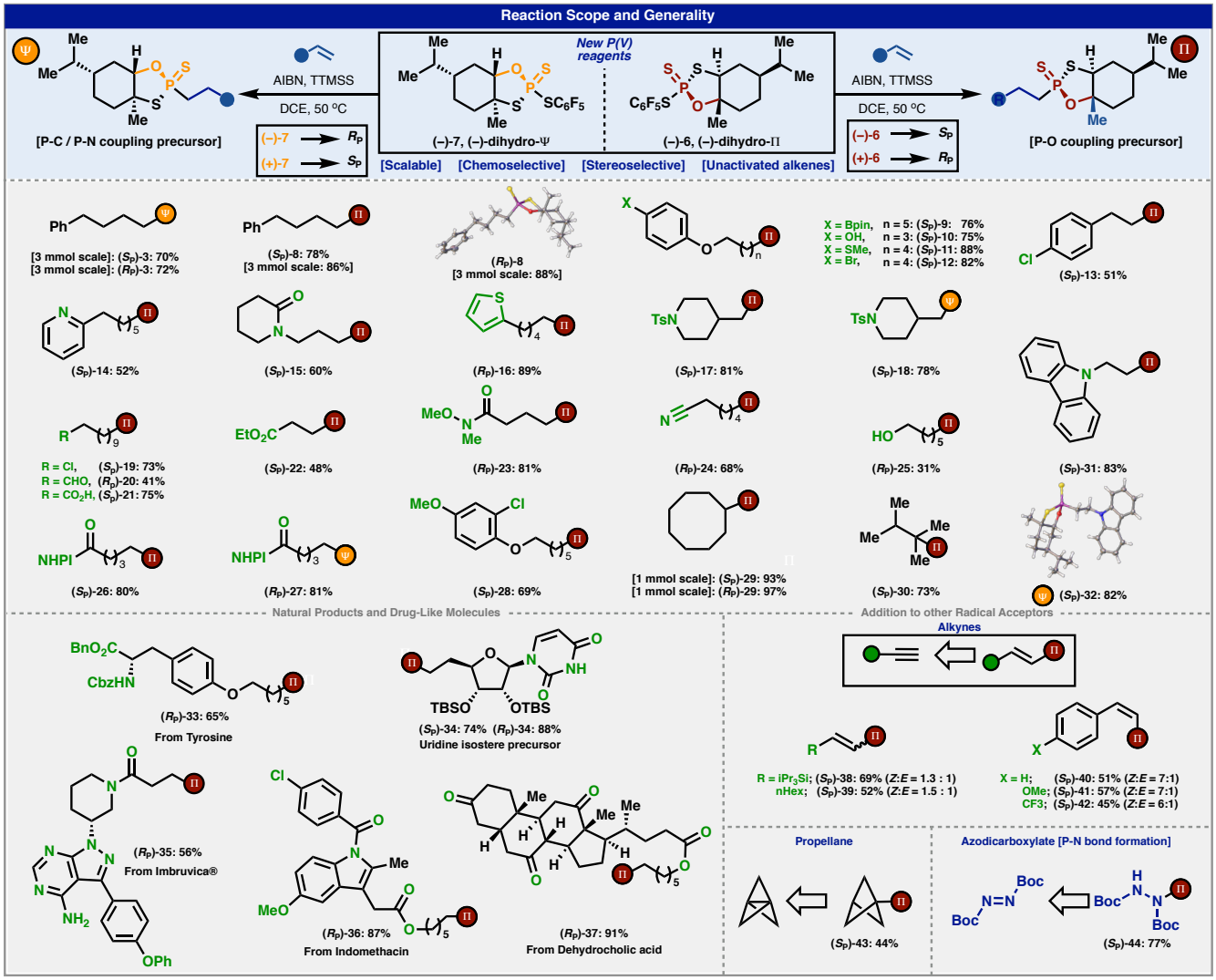



**Figure 3.** Scope investigations. All products were obtained with d.r. > 20:1. For detailed conditions see SI.

A hallmark of this reagent platform is the uniformly predictable stereochemical outcome in P-X bond formation.[9] Indeed, all the above-mentioned transformations occur with high diastereoselectivity. Net stereoretention is observed with both the **Π** and **Ψ** scaffolds as unequivocally confirmed by X-ray crystallography (see SI). The stereochemical outcome of these reaction is programmable and either configuration of the *P*-center can be accessed simply by choosing the respective enantiomer of the P(V) reagent (Fig. 3).

Fig. 4A outlines mechanistic picture of the developed reaction based on experimental observations and by analogy to previous reports of selenophospohrothioates in radical transformations.[18] Thermal fragmentation of AIBN, followed by HAT (hydrogen atom transfer) leads to formation of silyl radical, which initiates the radical chain via homolytic substitution at the leaving group of the P(V) reagent. The subsequently formed *P*-centered radical undergoes addition to the radicalophile (i.e. alkene), generating a *C*-centered radical, which regenerates a silyl radical via a HAT propagating chain.

To corroborate the hypothesis that **dihydro-Π** and **dihydro-Ψ** reagents, react via similar radical chain mechanisms, several experiments to support key steps were conducted (Fig. 4A). The deleterious effect of TEMPO (radical trap) is consistent with the radical nature of the mechanism, while exclusive formation of cyclization product **49** in the radical clock experiment supports 1e$^-$ addition to the alkene. Isolation of the silane byproduct **45** suggest formation of the *P*-centered radical via homolytic substitution at the sulfur atom. To further understand highly diastereoselective nature of the developed transformation, density functional theory (DFT) calculations were conducted. Computational analysis indicates that the epimerization barrier for P-centered radicals (generated from both **dihydro-Π** and **dihydro-Ψ** reagents) is notably high (~25 kcal/mol), which explains the stereoselective outcome of the reaction (Fig. 4B).

The utility of the developed approach ultimately arises from the ability of the hydrophosphorylation products to engage in subsequent 2e$^-$ couplings with a range of nucleophiles (Fig. 5).[9] The chiral information contained in the limonene-derived backbone can be harnessed to perform further functionalizations with excellent stereoselectivity leading to enantiopure thiophosphonate derivatives, with potential applications in medicinal chemistry. Importantly, products bearing the **Π** or **Ψ** backbone show orthogonal reactivity. For example, reaction of **Π**-based reagents with primary or secondary alcohols can be used to access previously

unexplored C-isosteres of oligonucleotides[20] (Fig. 5A). On the other hand, **Ψ**-based products can engage in couplings with organometallic reagents to form new P-C($sp$) (**54**), P-C($sp^3$) (**55**), P-C($sp^2$) (**56**), and P-N bonds (**57-59**) (Fig 5B).

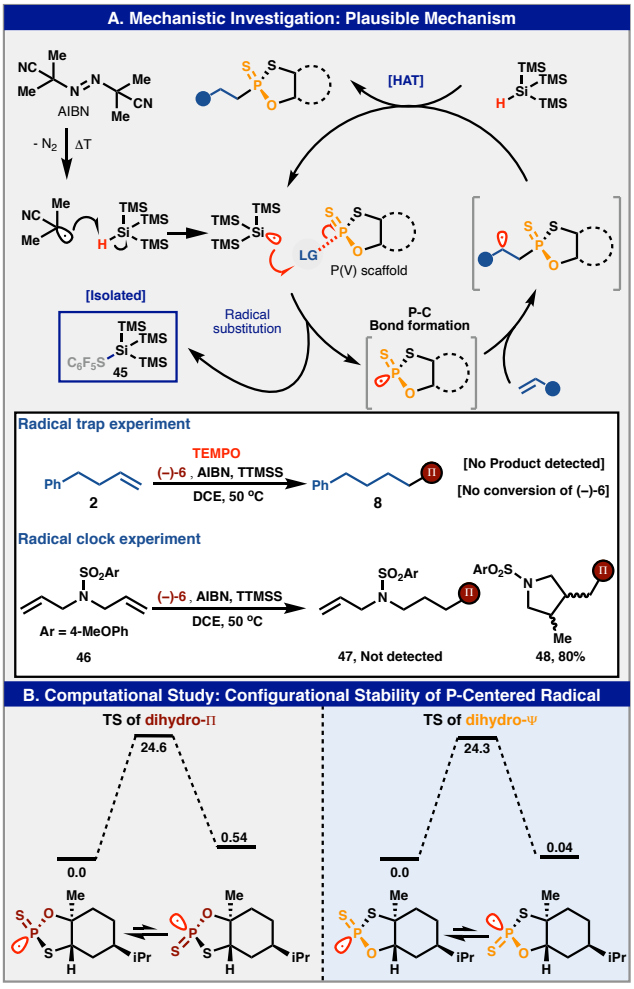
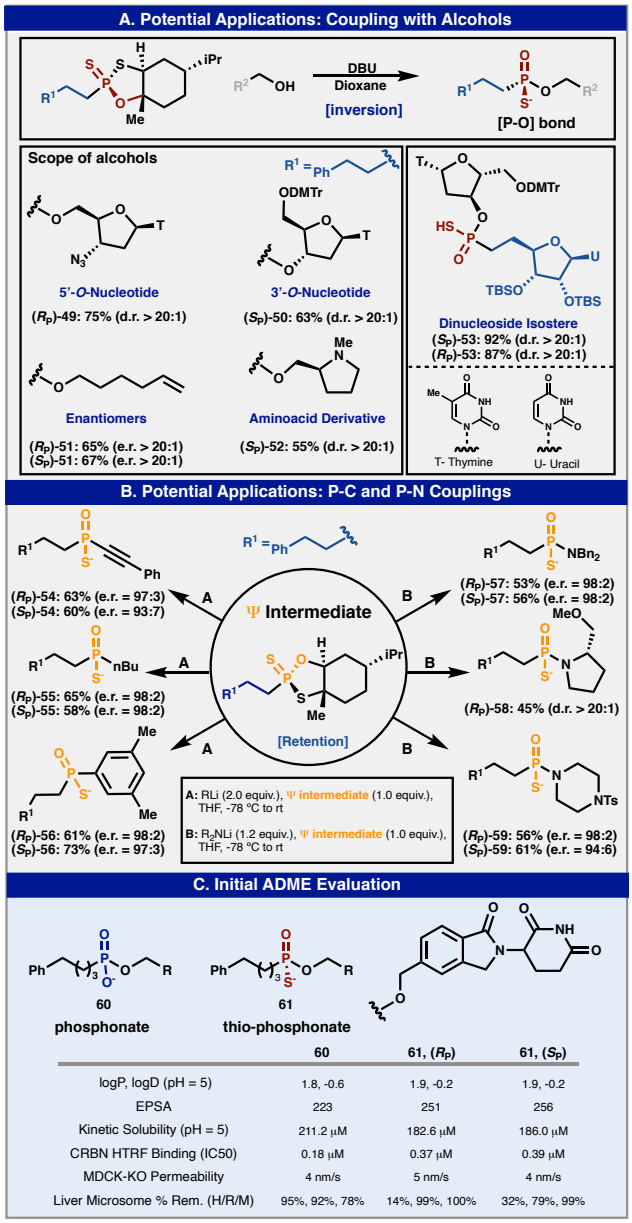



**Figure 4.** (A) Plausible mechanism. (B) Calculated epimerization barriers for *P*-centered radicals.

To probe the bioisosteric properties of these phosphonates in drug discovery, syntheses of **60** and **61** were executed with the inclusion of a substituted isoindolinone Cereblon E3 ligase binding motif, a commonly used core in the field of protein degradation.[21-23] Similar to **60**, analogs **(*R*$_P$)-61** and **(*S*$_P$)-61** showed comparable ADME profiles with polar LogPs and LogDs, high experimental polar surface areas (EPSA), kinetic solubility greater than 180 μM at pH = 5, low permeability, and moderate stability. Increasing the solubility of PROTACs has been an ongoing area of interest[23] to which inclusion of thiophosphonate-based linkers may prove beneficial. To ensure the addition of thiophosphonates did not hinder the compounds' ability to bind to Cereblon, a homogeneous time-resolved fluorescence (HTRF) assay was undertaken, confirming binding to Cereblon with $IC_{50}$ of 0.37 and 0.39 μM, respectively. Overall, incorporation of thiophosphonates offer an alternative to the phosphonate motif and may bring potential benefits to the linker design of PROTACs and in other scenarios (e.g. antibody-drug conjugates).




| | 60 | 61, ($R_P$) | 61, ($S_P$) |
|---|---|---|---|
| logP, logD (pH = 5) | 1.8, -0.6 | 1.9, -0.2 | 1.9, -0.2 |
| EPSA | 223 | 251 | 256 |
| Kinetic Solubility (pH = 5) | 211.2 μM | 182.6 μM | 186.0 μM |
| CRBN HTRF Binding (IC50) | 0.18 μM | 0.37 μM | 0.39 μM |
| MDCK-KO Permeability | 4 nm/s | 5 nm/s | 4 nm/s |
| Liver Microsome % Rem. (H/R/M) | 95%, 92%, 78% | 14%, 99%, 100% | 32%, 79%, 99% |

**Figure 5.** (A) Stereoselective formation of P-O bond using Π-based reagents. (B) Application of **Ψ**-based reagents in P-C and P-N bond formation. (C) Initial ADME evaluation.

To summarize, the rarely explored reactivity of P(V)-based radicals has been investigated and harnessed alongside conventional 2e$^-$ transforms to provide access to P-containing structures (including phosphonothioates, phosphinothioates, phosphonamidothioates) that have been heretofore inaccessible in enantiopure form. The simple, inexpensive reagent platform derived from citrus industry commodity byproducts [(+)- and (–)-limonene] has previously been utilized only in classic 2e$^-$ based chemistry. Now, this platform can be applied in stereoselective radical chemistry to open up interesting areas of bioisosteric chemical space that might find utility in drug discovery for the synthesis of both large and small molecules.

## AUTHOR INFORMATION

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Optimization: M.N, M.O
Scope and Limitations Studies: M.N, M.O, H.-J.Z
Data Analysis: M.N, M.O, H.-J.Z, Y.K
Mechanistic Studies: M.N, M.O, L.G
Biophysical Studies: B.J.S, M.S.O, A.N.C
Manuscript Writing: M.N, M.O, H.-J.Z, B.J.S., P.S.B
Funding Acquisition: P.S.B, M.A.D, M.D.E
Project administration: P.S.B

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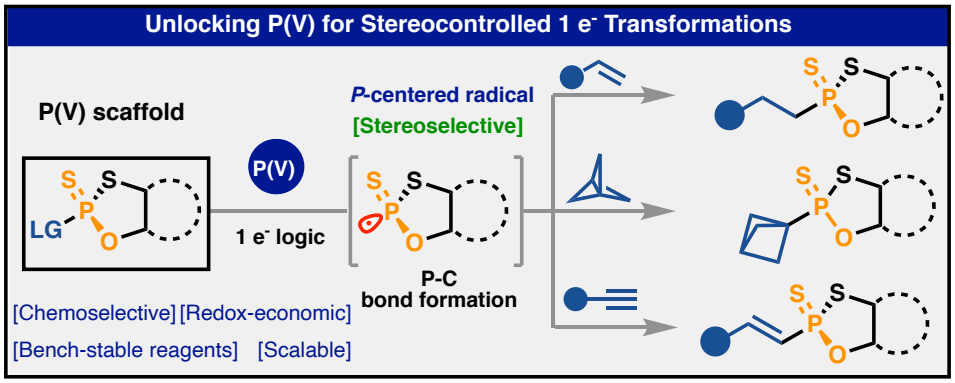
## TOC Graphic


Unlocking P(V) for Stereocontrolled 1 e- Transformations
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