P(V) METHODS FOR THE GENERATION OF CHIRAL PHOSPHORUS IN BIOACTIVE MOLECULES

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Phosphorus functional groups serve a wide array of roles in nature and in synthesis due to their ionizability and versatility. Despite their ubiquity, stereoselective methods for generating chiral at P(V) compounds remains a curiously underserved area in synthesis. While traditional oligonucleotide synthesis began with P(V) as its basis, its lack of coupling efficiency and prevalence for side reactions led to the rise of P(III) reagents in large scale synthesis. Recently, there has been a back-to-the-future-esque resurgence of P(V) methods to leverage the increased stereocontrol it grants. This presentation spotlights three ways in which modern chemists are seeking to bring P(V) platforms back into the forefront with novel chiral auxiliaries and through specialized catalysis:

SETTING STEREOCHEMISTRY VIA CHIRAL AUXILIARY

Phosphothioates:

The Baran Group targeted the synthesis of chiral phosphothioates, a crucial linker in the development of anti-sense oligonucleotides[1]. The introduction of chirality at phosphorus leads to a variation in binding affinities, and *in vivo* stabilities of these therapeutics. The three most prominently employed methods for the synthesis of phosphothioate linkages involve the use of phosphoramidites and oxathiophosphalanes, each with their own shortcomings. The P(V) platform developed by the Baran group offers a cost-effective, synthetically facile, benchtop stable reagent that improves selectivity across a variety of oligonucleotide pairs, dubbed ***ψ*** reagents. While the coupling efficiencies of ***ψ*** reagents have yet to compare to the existing P(III) methodologies, the method has demonstrated itself amenable to scale-up and automation, achieving near-complete sterocontrol with an ease unmatched by other platforms.

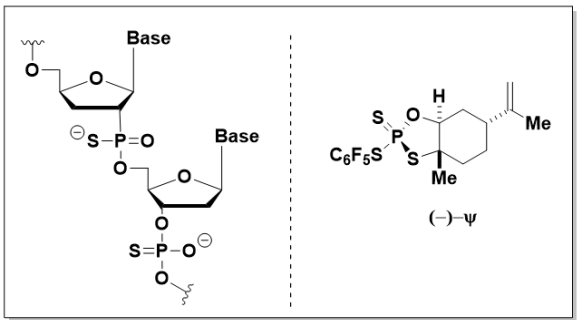

Figure 1. *(Left)*: Phosphothioate oligonucleotide linkers. *(Right):* ***ψ*** reagent.

SETTING STEREOCHEMISTRY VIA CATALYSIS

Prodrugs:

DiRocco and coworkers tackled the issue of prodrugs[2]. Prodrugs serve as precursors to biologically active therapeutics that otherwise are unable to penetrate the cell membrane. Studies have shown correlation between the stereochemistry at P in phosphoramidate prodrug oligonucleotides (ProTides) and the *in vivo* stability, effectiveness, and toxicity of the therapeutics. Traditional methods for ProTide generation are stereorandom at P and most chiral auxiliary methods are not designed to generate these compounds. These issues were addressed via dynamic kinetic resolution between two rapidly interconverting diastereomers, including nucleophile activation, leaving group activation, and transition state stabilization. A chiral bisimidazole catalyst was selected and proved capable of functioning on a variety of different substrates and potential ProTides with excellent stereocontrol.

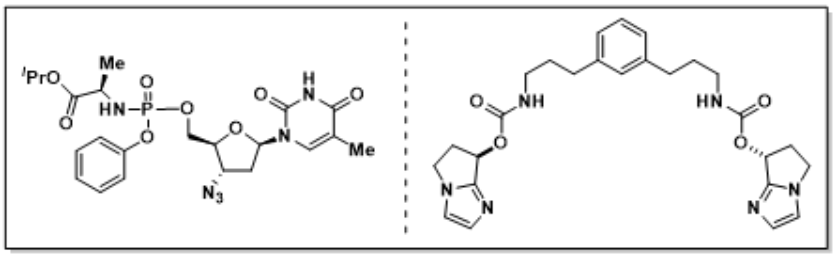

Figure 2. (*Left*) AzTTP Protide. (*Right*): Bisimidazole catalyst

Asymmetric Synthesis:

The Jacobsen group sought to expand on the relatively limited existing catalytic methods of generating stereogenic at P compounds, using commercially available urea H-bond donor catalysis to selectively generate P(V) compounds available for further substitution from aryl phosphonic dichloride[3]. The method leverages the fact that P-Cl and P-N bonds can be nucleophilically displaced under differing conditions. It was shown to work with a wide range of backbones, complex alcohol nucleophiles and nucleophiles with the potential towards further functionalization.

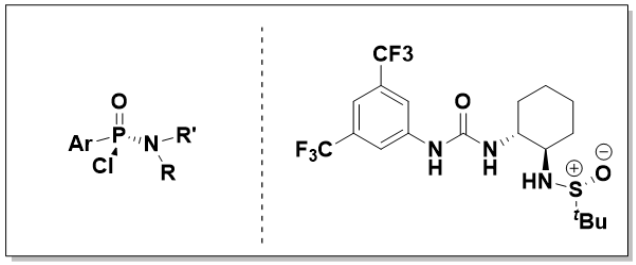

Figure 3. (*Left*): Chiral Phosphorus generated by catalyst. (*Right*) H-bond donating catalyst.

CITATIONS

[1]Knouse, K. W, et al. Unlocking P(V): Reagents for Chiral Phosphorothioate Synthesis. *Science* **2018**, *361* (6408), 1234–1238.

[2] DiRocco, D. A et al. A Multifunctional Catalyst That Stereoselectively Assembles Prodrugs. *Science* **2017**, *356* (6336), 426–430.

[3] Forbes, K. C.; Jacobsen, E. N. Enantioselective Hydrogen-Bond-Donor Catalysis to Access Diverse Stereogenic-at-P(V) Compounds. *Science* **2022**, *376* (6598), 1230–1236.