General Platform for Divergent Construction of Phosphorus-Modified DNA/RNA Backbones

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Phosphorus-containing biomolecules, including nucleotides, cyclic dinucleotides, and related cofactors, play central roles in signaling, immunity and enzyme regulation. Despite their biological importance, the highly anionic and polar nature of canonical phosphate linkages severely limits the therapeutic potential of nucleotide-based modalities by restricting membrane permeability, metabolic stability, and systemic delivery. Charge-neutral phosphorus backbones offer a promising solution, yet their development is hindered by synthetic challenges, limited structural diversity and incompatibility with oligonucleotide assembly workflows.

In this work, we present a unified platform that enables the direct modification of phosphorus centers within oligonucleotide backbones. Building on recent advances in organophosphorus radical chemistry, our strategy allows the engagement of diverse reaction partners with phosphorus centers under mild conditions, overcoming selectivity challenges typically encountered in complex nucleotide substrates. The synthetic concept opens access to previously inaccessible and unprecedented phosphorus linkages without relying on sensitive and unstable reagents or extensive protecting-group manipulations.