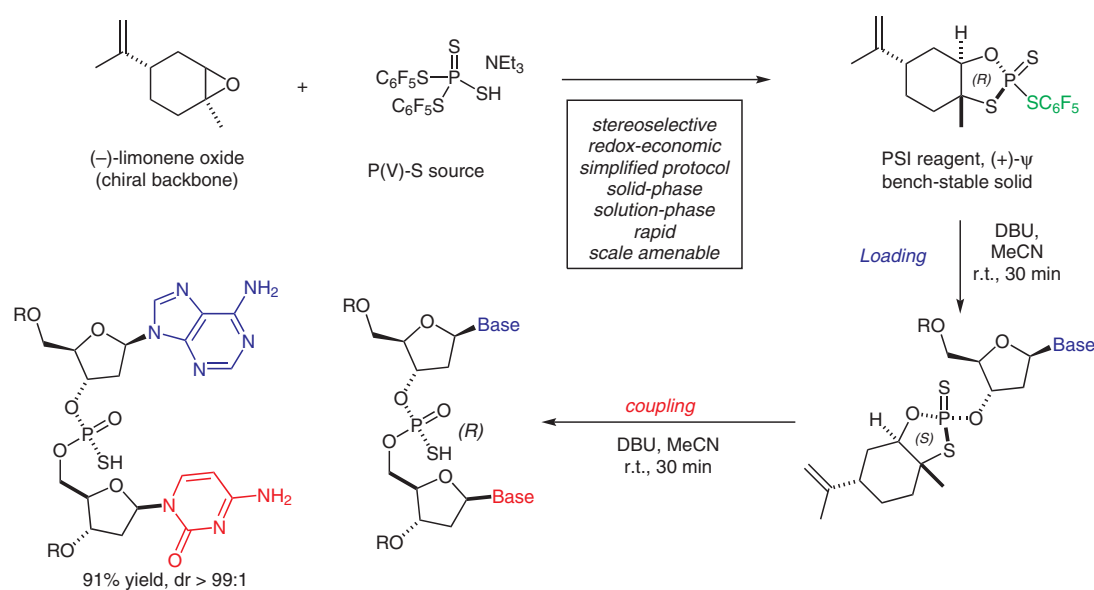


K. W. KNOUSE, J. N. DEGRUYTER, M. A. SCHMIDT\*, B. ZHENG, J. C. VANTOUROPT, C. KINGSTON, S. E. MERCER, I. M. McDONALD, R. E. OLSON, Y. ZHU, C. HANG, J. ZHU, C. YUAN, Q. WANG, P. PARK, M. D. EASTGATE\*, P. S. BARAN\* (THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, BRISTOL-MYERS SQUIBB, NEW BRUNSWICK AND PRINCETON, AND BRISTOL-MYERS SQUIBB RESEARCH AND DEVELOPMENT, WALLINGFORD, USA)

Unlocking P(V): Reagents for Chiral Phosphorothioate Synthesis

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## Stereoselective Synthesis of Phosphorothioate Nucleotides



**Significance:** Antisense oligonucleotide (ASO)-based and cyclic dinucleotide (CDN)-based therapeutics represent an area of current significant interest, as highlighted by the recent approval of the ASO spinraza as a sole treatment for spinal muscular atrophy (E. W. Ottesen *Transl. Neurosci.* **2017**, *8*, 1). A key element in the design of these molecules is the replacement of native phosphodiester linkages with phosphorothioate (PS), wherein one of the nonbridging oxygen atoms is replaced with a sulfur atom. This modification, known as the ‘thio effect’, provides more metabolic stability and improves the cellular uptake of the compounds. However, it also leads to an increase in structural complexity, as each phosphorus atom becomes a stereogenic center. The current report describes a reagent-based scalable strategy to assemble phosphorothioate nucleotides in a stereocontrolled manner.

**SYNFACTS Contributors:** Victor Snieckus, Paul Richardson (Pfizer)  
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**Comment:** In contrast to previously reported methods for the assembly of nucleotides, this method proceeds through P(V)-based reagents. The reagent  $\psi$  is derived from limonene (both enantiomers are readily available) through epoxidation and ring-opening. Assembly of the nucleotides is achieved through loading of the first nucleoside to form a stable oxothiophospholane adduct by using DBU as an activator without the need for rigorous exclusion of air and moisture. The next nucleoside in the sequence can then be added under identical conditions to deliver the dinucleotide as a single diastereomer in excellent yield with the stereochemistry defined by the enantiomer used in the  $\psi$  reagent. The method is further extended to the synthesis of CDNs, as well as to the solid phase synthesis of oligonucleotides.

Category

Synthesis of Heterocycles

Key words

cyclic dinucleotides

oligonucleotides

phosphorus(V) reagents

phosphorothioates

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