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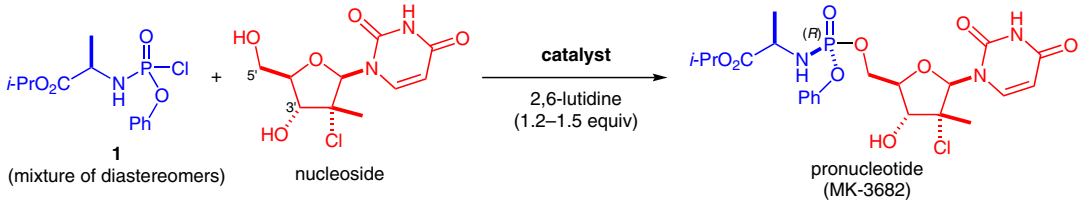
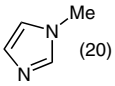
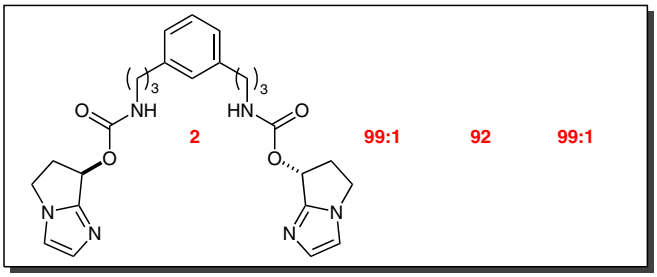
A Multifunctional Catalyst that Stereoselectively Assembles Prodrugs
Science **2017**, *356*, 426–430.

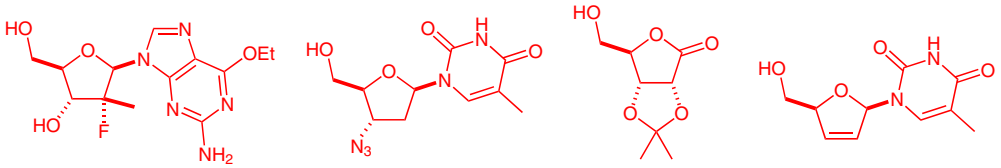
Catalytic Stereoselective Synthesis of Pronucleotides



catalyst (mol%)	5'/3'-OH	Yield (%)	P(*R*)/P(*S*)
none	n.d.	3	55:45
 (20)	96:4	49	52:48



Selected further nucleoside substrates:



91% yield, dr = 95:5 | 90% yield, dr = 93:7 | 95% yield, dr = 98:2 | 96% yield, dr = 87:13

[% NMR yields and diastereomeric ratios (dr) of 5'-*O*-phosphorylated products]

Significance: DiRocco and co-workers report a diastereoselective synthesis of pronucleotides from the corresponding nucleosides by a dynamic kinetic resolution of chlorophosphoramidate **1**. Whereas the reaction with *N*-methylimidazole as catalyst proceeds with almost no stereoselectivity toward the newly formed stereogenic center on phosphorus, a dimeric, chiral, imidazole-based catalyst with additional hydrogen-bonding sites furnished a series of pronucleotides in good yields and good to excellent stereoselectivities.

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Comment: Pronucleotides are important compounds for the treatment of viral diseases and cancer. The derivative MK-3682, for instance, is a hepatitis C viral RNA polymerase inhibitor, currently undergoing late-stage clinical trials. Because different absolute configurations of the P-based stereogenic center can significantly alter the drug's potency and toxicity, stereoselective generation thereof is of great importance. Herein, the authors report the first catalytic, stereoselective access to compounds bearing P-based stereogenic centers.

Category
Organo- and Biocatalysis

Key words
pronucleotides
P-based stereogenic centers
nucleosides
medicinal chemistry