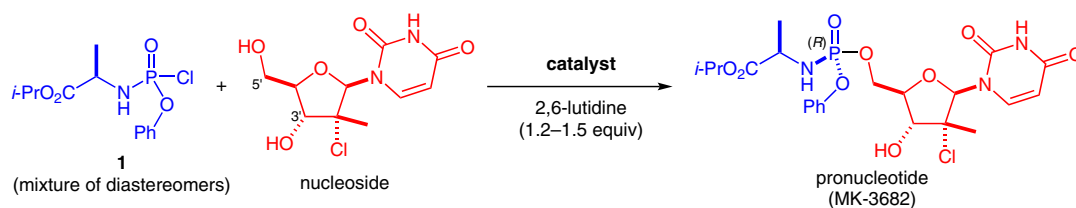


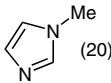
D. A. DIROCCO*, Y. JI, E. C. SHERER, A. KLAPARS, M. REIBARKH, J. DROPINSKI, R. MATHEW, P. MALIGRES, A. M. HYDE, J. LIMANTO, A. BRUNSKILL, R. T. RUCK, L.-C. CAMPEAU, I. W. DAVIES (MERCK & CO., INC., RAHWAY, USA)

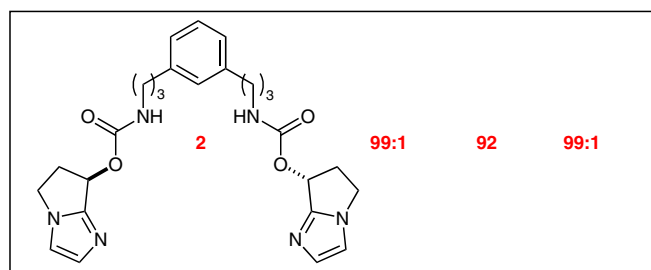
A Multifunctional Catalyst that Stereoselectively Assembles Prodrugs

Science **2017**, 356, 426–430.

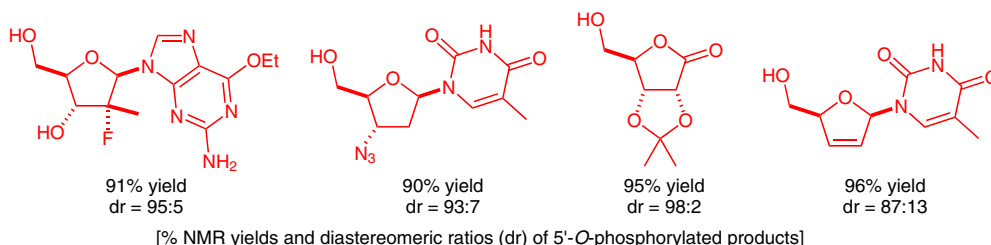
Catalytic Stereoselective Synthesis of Pronucleotides



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:



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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 DOI: 10.1055/s-0036-1590687; Reg-No.: B05317SF

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

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of the month