Catalytic Stereoselective Synthesis of Pronucleotides

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.

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.