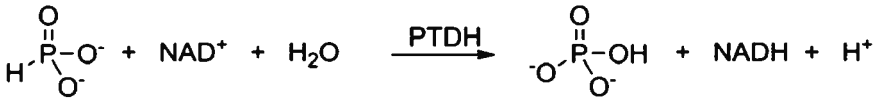
Investigations into the Role of Arg301 in Phosphite Dehydrogenase

John E. Hung and Wilfred A. van der Donk

Phosphite dehydrogenase (PTDH) catalyzes the oxidation of phosphite to phosphate with the concurrent reduction of NAD^+ to NADH. Mutants of the enzyme that have been engineered with improved stability and activity are utilized in industrial cofactor regeneration. The mechanism of the reaction involves nucleophilic attack by water or hydroxide onto the phosphoryl group, with transfer of a hydride group from phosphite to NAD^+. Given the inherently poor nature of the hydride leaving group, PTDH catalyzes highly unusual chemistry. Bioinformatic studies, combined with analysis of the crystal structure, have revealed several conserved residues that are catalytically important, including Arg301. To determine the role of this residue, pH profile, chemical rescue, inhibition, and crystallographic experiments were performed on Arg301 mutants. These experiments suggest that Arg301 plays two roles in catalysis, acting as a positively charged residue involved in electrostatic activation of the reaction and as a phosphite-binding residue preventing active site solvent access.



Enantioselective Thioaminocyclization Using a Chiral Lewis Basic Selenophosphoramide Catalyst

Hyung Min Chi and Scott E. Denmark

An enantioselective method for the thioaminocyclization of unactivated alkenes has been developed using a chiral BINAM-based selenophosphoramide Lewis base catalyst (LB*). Generation of an active chiral aryl sulfide species by coordination of the chiral selenophosphoramide catalyst to an aryl sulfur electrophile enables enantioselective formation of a thiiranium intermediate. Cyclization through the stereospecific capture of this enantio-enriched thiiranium intermediate by the pendant arylsulfonyl protected amine nucleophile gives 2,3-functionalized piperidines in high yields and up to 95:5 enantiomeric ratio.