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N-Heterocyclic Carbene Catalyzed Asymmetric Hydration: Direct Synthesis of α-Protio and α-Deutero α-Chloro and α-Fluoro Carboxylic Acids


Asymmetric Synthesis of α-Halo Carboxylic Acids from α,α-Dihalo Aldehydes

Significance: The enantioselective hydration of α,α-dichloro aldehydes and α-fluoro enals catalyzed by N-heterocyclic carbene 1 has been reported. α-Fluoro and α-chloro carboxylic acids 2 and 3 were obtained in good yields with high enantioselectivity. The developed reaction enables incorporation of an α-deuterium to give rise to enantioenriched α-deutero α-halo acids using D₂O as the deuterium source.

Comment: Enantioenriched α-halo carbonyls are valuable synthetic intermediates. Current approaches to these compounds rely on the asymmetric generation of α-halo aldehydes or esters. Rovis and colleagues previously demonstrated that chiral N-heterocyclic carbene catalyzes the enantioselective reaction of α,α-dichloro aldehydes and phenol leading to α-chloro aryl esters (N. T. Reynolds, T. Rovis J. Am. Chem. Soc. 2005, 127, 16406). This approach is based on the enantioselective protonation of catalytically generated chiral enolates A. Utilizing the same principle and employing water as the nucleophile instead of phenol enabled a direct approach to α-halo carboxylic acids.