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An Umpolung Strategy towards Catalytic Stereoselective Synthesis of Chiral Amines

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Abstract

Chiral enantiopure amines are increasingly common structural features of small molecule therapeutics with vicinal diamines and amino alcohols a potent subset. The development of new catalytic enantioselective protocols to prepare these stereodiads is therefore an important goal. A powerful strategy towards these motifs would leverage a carbon–carbon bond formation between the two heteroatom-substituted carbons while simultaneously setting the stereochemistry at both; however, this synthetic disconnection exhibits electronic dissonance as both carbons are naturally electrophilic. To address this challenge, we have developed a strategy that reverse the polarity of one carbon through the design of 2-azadienes and azatrienes as enamine umpolung reagents. These unsaturated building blocks serve as pronucleophiles for reductive couplings with ketones and imines that deliver amino alcohols and diamines, respectively. A suite of copper-based chiral catalysts promote these reactions with high levels of chemo-, regio-, diastereo-, and enantioselectivity.