Silver-Catalyzed Asymmetric Aldol Reaction and Michael Reaction of Activated Isocyanides

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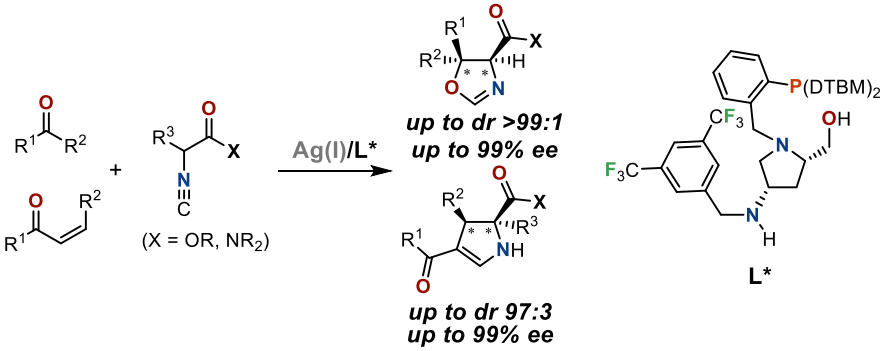
Asymmetric aldol reactions are powerful carbon-carbon bond formation reactions. Especially, the asymmetric aldol reactions of isocyanoacetic acid derivatives proceed with successive cyclization to produce chiral oxazolines, which can be transformed into β-hydroxy-α-amino acids by hydrolysis. While the reactions using aryl ketones or sterically accessible dialkyl ketones were reported,[1] the reaction using sterically and electronically unbiassed ketones was elusive.

Our original chiral prolinol-phosphine ligands enable promotion and stereocontrol of aldol reactions with aldehydes by forming multiple hydrogen bonds with the carbonyl group of the substrates.[2] The newly developed ligands bearing a secondary amino group showed excellent performance in the asymmetric aldol reactions of isocyanoacetoamides with various ketones. In particular, bulky dialkyl ketones such as pinacolone were competent giving the products in highly diastereo- and enantioselective manner. Furthermore, the same catalytic system can be applied to the asymmetric Michael reactions of α-substituted isocyanoacetates with α,β-unsaturated ketones, affording the cyclized products with high stereoselectivity.

Computational analysis suggested that multiple hydrogen bonds and dispersive interactions between the ligand and substrates contribute to stabilization of the transition states to increase the reactivity and stereoselectivity.



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