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Enantioselective Synthesis of Chiral Proline Derivatives

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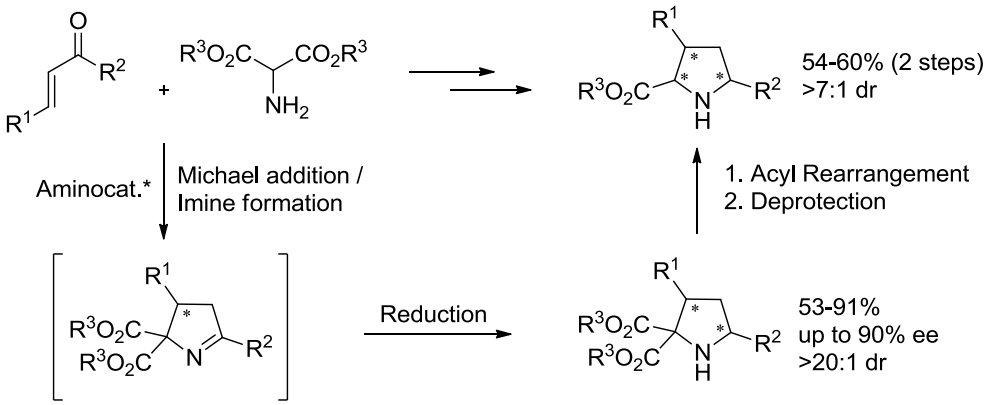
The pyrrolidine framework is present as key structure in many natural products with interesting biological and pharmaceutical activities.[1] It is also used in organic chemistry playing different roles such as ligand, organocatalyst or building block in chiral pool synthesis.[2] Furthermore, these properties are very often influenced by the configuration of the stereogenic center present in the molecule. For this reason, new and efficient routes are required to synthesize chiral proline derivatives in a stereocontrolled way. With this in mind, our group has established a good approach to this scaffold employing as key steps an organocatalytic cascade process based on a Michael addition/imine formation sequence and a novel base-promoted rearrangement reaction (Scheme 1). Therefore, the reaction between enones and aminomalonates has been studied using a chiral primary amine as catalyst, due to the known ability of the latter to activate α,β-unsaturated ketones as Michael acceptors under iminium ion formation.[3] A sequential diastereoselective reduction leads to enantiopure 1,3-disubstituted pyrrolidines in good yield and enantioselectivity, which are transformed into the desired trisubstituted proline derivatives through a base-promoted rearrangement/deprotection reactions under mild conditions.



Scheme 1

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