Synthesis of 5-spiroproline derivatives by organocatalytic enantioselective [3+2] cycloaddition between enals and isatinimines

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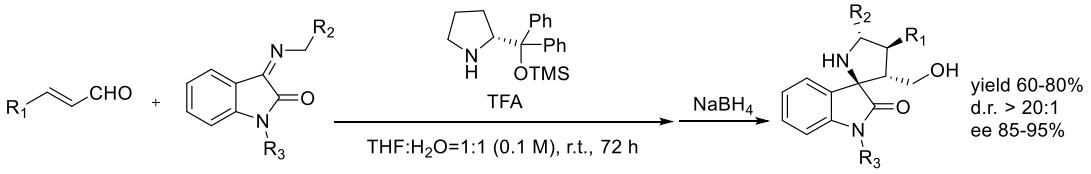
5-spiroproline derivatives, especially spiro[proline-5,3'-oxindole]s are known to show specific bioactivity such as antibacterial, antimalarial or antitubercular activities.[1] Therefore, stereocontrolled synthesis of such class of compounds is highly important. So far, they have been prepared by [3+2] cycloaddition of isatin-derived azomethine ylides. The reaction includes the formation of imines from a glycinate ester and the isatin, followed by the ylide formation and the cycloaddition. In many cases the cycloaddition occurs in a highly diastereoselective manner.[2] However, an enantioselective version of this cycloaddition has not been developed to date. Due to this situation, bioassays have been carried out only with racemates. On the other hand, there are several reports on the asymmetric synthesis of spiro[pyrrolidine-2,3'-oxindoles] by chiral amine catalysts.[3] In those papers, there is no example for the synthesis of a spiro[proline-5,3'-oxindole].

This time, our group has established the catalytic enantioselective synthesis of spiro[proline-5,3'-oxindole]s. In the presence of 20 mol% of Hayashi-catalyst, the [3+2] cycloaddition of N-alkoxycarbonylmethyl isatinimines and enals proceeded in a highly stereoselective manner. The key factor was the use of water as a co-solvent. In the absence of water, the reaction proceeded sluggishly with lower stereoselectivity.



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