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syn-Selective and Enantioselective Direct Cross-Aldol Reactions between Aldehydes Catalyzed by an Axially Chiral Amino Sulfonamide

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Category

Organo- and Biocatalysis

Key words

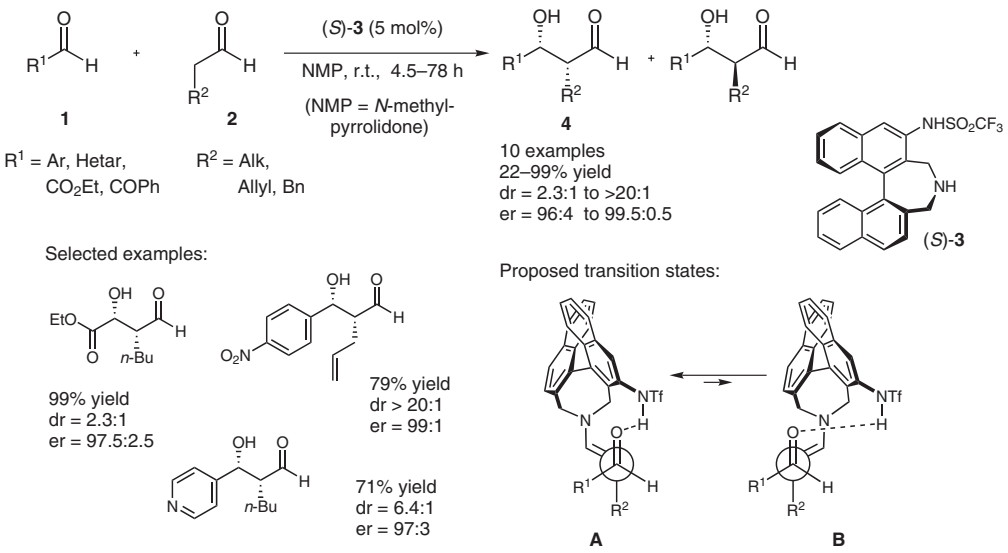
cross-aldol reaction

***syn* selectivity**

axial chirality

amino sulfonamides

syn-Selective Direct Asymmetric Cross-Aldol Reaction



Significance: A highly *syn*-selective asymmetric direct cross-aldol reaction between two different aldehydes has been developed. By employing 5 mol% of the axially chiral amino sulfonamide (*S*)-**3**, *syn*-aldol products **4** resulting from mostly electron-poor acceptor **1** and aliphatic donor aldehydes **2** are obtained in moderate to good yields along with high diastereo- (*syn/anti* ratio up to >20:1) and excellent enantioselectivities (er up to 99.5:0.5). The authors rationalize the stereochemical outcome with the help of proposed transition states **A** and **B**. In contrast to the *anti*-enamine **B**, the *syn*-enamine geometry in **A** allows for effective hydrogen bonding activation of the acceptor aldehyde by the acidic proton of the triflamide moiety. This favors the reaction to proceed via the *syn*-enamine intermediate and explains the observed *syn* selectivity.

Comment: The described method represents one of the rare examples of *syn*-selective direct cross-aldol reaction proceeding via an enamine intermediate (e.g., C. F. Barbas, III and co-workers *J. Am. Chem. Soc.* **2007**, *129*, 288-289). With respect to the *syn/anti* selectivity, the use of axially chiral amino sulfonamide (*S*)-**3** complements the proline-catalyzed version of both the direct asymmetric cross-aldol and the Mannich reaction, recently reported by the same group (*J. Am. Chem. Soc.* **2005**, *127*, 16408-16409). The drawback of multi-step catalyst synthesis is compensated not only by low catalyst loading but also by 95% catalyst recovery after column chromatography. A more general substrate scope with regard to the acceptor aldehyde might be desirable.

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