New Thiazolidine-Based Organocatalysts for Enantio- and Diastereoselective Aldol Reaction

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INTRODUCTION

Asymmetric organocatalysis is recognized as an efficient and versatile method for the stereoselective preparation of chiral compounds[1,2]. Over 300 reactions have been developed using organocatalyzed processes[2]. This strategy is attractive because in most cases the catalysts are nontoxic, readily available and stable. Another feature is that most reactions tolerate water and air[1,2].

In the present work, we describe the synthesis of new thiazolidine-based organocatalysts and their application in asymmetric direct aldol additions.

RESULTS AND DISCUSSION

Based on the organocatalysts recently developed by our group (**1a-c**)[3], we synthesized new thiazolidine-based compounds (**1d-f**), in order to improve their catalytic activity and selectivity (Figure 1).

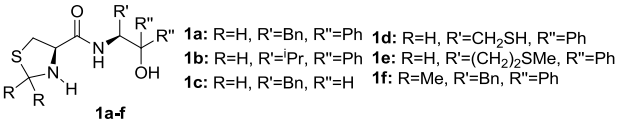


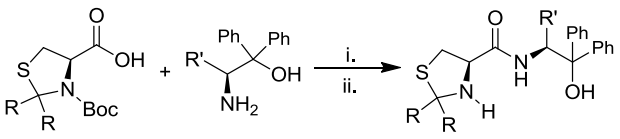
Figure 1. Thiazolidine-based organocatalysts **1a-f**.

Initially, *L*-cysteine was cyclized with paraformaldehyde or propanone leading to the thiazolidines, which were protected with Boc_2O to afford the fragments **3a-b**.

The aminoalcohols **4a-c** were obtained from *L*-aminoacid-Me-esters by double Grignard addition.

Finally, the reaction between thiazolidines **3a-b** and the aminoalcohols **4a-c**, followed by removal of the Boc group, lead to the new organocatalysts **1d-f**.

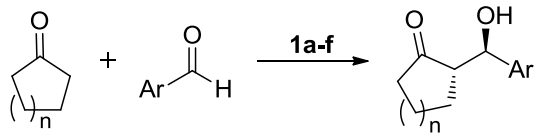
Scheme 1. Preparation of compounds **1d-f.**



Reactions conditions: (i) ClCOOEt, NMM, CH_2Cl_2, r.t., 24 h (75-85%); (ii) HCl, AcOEt, K_2CO_3, DCM, r.t., 30 min (50-80%).

Compounds **1a-f** were employed as catalysts in the asymmetric direct aldol addition between cyclic ketones and aromatic aldehydes.

Scheme 2. Asymmetric direct aldol reaction catalyzed by organocatalysts **1a-f**.



up to 99% *e.e.*
99% *d.e.*

The effect of temperature, catalyst loading, time and solvent were investigated. Using saturated aqueous media, the aldol adducts were obtained with excellent stereocontrol (up to 99% *e.e.* and 99% *d.e.*).

CONCLUSION

Three new organocatalysts derived from *L*-aminoacids were synthesized. The influence of electronic and steric characteristics of the compounds was explored and the catalytic system was optimized.

The results demonstrated that compound **1a** was the best catalyst and the aldol adducts were obtained in excellent enantiomeric and diastereomeric excesses.

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