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A highly enantio- and diastereoselective direct aldol reaction in aqueous medium catalyzed by thiazolidine-based compounds

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ABSTRACT

Taking L-aminoacids as starting materials, a new set of enantiopure thiazolidine-based organocatalysts were prepared using a simple synthetic approach and successfully applied in the asymmetric direct aldol reaction between various cyclic ketones and aldehydes in a saturated aqueous medium. The aldol adducts were obtained with excellent enantioselectivity (up to >99% ee) and diastereoselectivity (dr >20:1).

1. Introduction

Asymmetric organocatalysis, which is based on use of small organic molecules in the absence of transition metals, is now a well-established research area and recognized as the third column of organic synthesis due to its versatility and efficiency. To date, more than 300 reactions and methodologies have been developed using organocatalyzed processes.[1] Since the seminal article published by List, Barbas et al.,[2] which reported the use of L-proline to catalyze the direct intermolecular asymmetric aldol reaction, this research area has experienced an exponential growth. Great effort has been devoted to the development of new organocatalysts and organocatalytic processes that can be used toward the synthesis of lead products in high yield and stereoselectivity including the synthesis of natural products and compounds with interesting biological properties.[1a–g]

The amino acid L-proline has been intensively studied and used to catalyze more than ten different reactions and has therefore achieved a 'privileged catalyst' status.[3] Consequently, over the past few years, a great deal of attention has been devoted to the use of naturally occurring amino acids in organocatalysis due to their low cost and availability in an enantiopure form.[4]

Further studies reported by Barbas et al.[2a] have shown that (*R*)-thiazolidine-4-carboxylic acids can also promote the aldol reaction with high enantioselectivity. However, the use of this type of heterocycle as a chiral modifier in organocatalysis has been rarely reported.[2,5] Despite the lack of literature precedent, during the course of our work in the field of asymmetric catalysis we have reported the successful use of thiazolidines as chiral ligands in several organometallic reactions.[6–8]

Recently, our group has developed a new class of thiazolidine-based organocatalysts, which are readily obtained from L-cysteine and successfully applied them in the direct asymmetric aldol reaction between propanone and a variety of aldehydes **3d**–**g** (Fig. 1).[9] In this context and in connection with our continuing interest in the development and application of new organocatalysts, we now report the synthesis of three new thiazolidine-based compounds **3a**–**c** (Fig. 1) in an attempt to improve the activity and selectivity of thiazolidine-based organocatalysts. We have also expanded the application of these compounds by evaluating their catalytic activity in the direct asymmetric aldol reaction between various cyclic ketones and aldehydes in an aqueous medium.

2. Results and discussion

The organocatalysts **3a**–**f** were synthesized via a short and high yielding sequence using L-amino acids as the starting materials. Most importantly, this synthetic strategy can readily generate a high degree of structural diversity, which is important for the systematic optimization of the catalysts structure.

L-Cysteine was initially reacted with formaldehyde and subsequently protected with Boc_2O to give the unsubstituted thiazolidine carboxylic acid **1a** (Scheme 1). In order to study the influence of substituents on the heterocyclic moiety, compound **1b** was also synthesized by refluxing L-cysteine in propanone followed by protection with Boc_2O.

A double Grignard addition or reduction of an aminoester afforded the desired range of aminoalcohols, which were reacted with the thiazolidine carboxylic acids **1a** and **1b** in the presence of stoichiometric amounts of $ClCO_2Et$ and NMM to give the corresponding amides **2a**–**c** (Scheme 2). In order to understand the role of the different substituents (R, R′, and R″), different amino acids were used including L-methionine and L-cysteine for compounds

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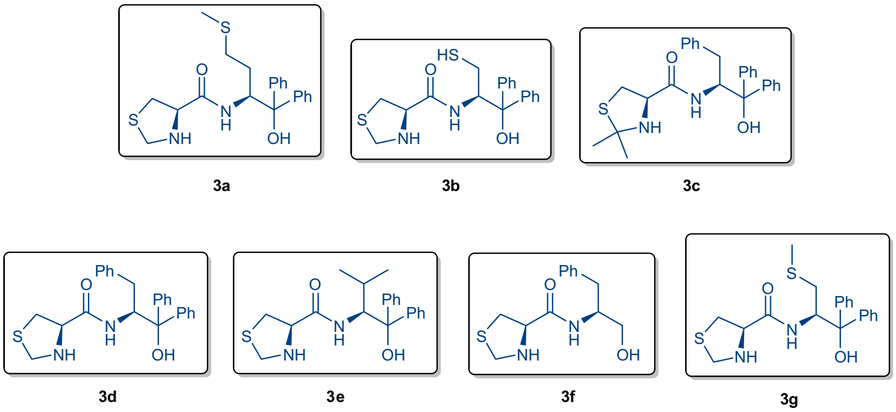
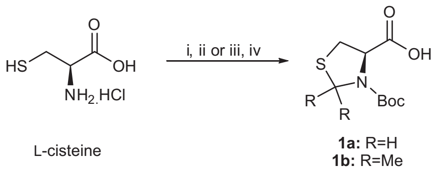


Figure 1. Thiazolidine-based organocatalysts **3a**–**g**.



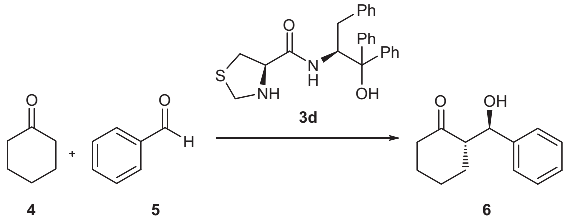
Scheme 1. Synthesis of the thiazolidine carboxylic acids **1a**–**b**. Reagents and conditions: (i) 37% HCHO, 1 M NaOH; (ii) Boc_2O, 1 M NaOH, 1,4-dioxane/H_2O (95%); (iii) Me_2CO, reflux; (iv) Boc_2O, DIPEA, MeCN (40%).

3a and **3b**, respectively, and L-phenylalanine for compound **3c**. Removal of the Boc group delivered the desired organocatalysts **3a**–**c** in good overall yield. Compounds **3d** and **3g** (Fig. 1) were synthesized using the same synthetic strategy. All spectroscopic data are in accordance with those reported in the literature.[9]

With the target compounds **3a**–**c** in hand, together with the known organocatalysts **3d**–**f**, we focused our attention toward the optimization of the aldol reaction with an aim of controlling the stereochemistry of the two stereocenters formed during the reaction. As a model reaction, we elected to investigate the aldol reaction between cyclohexanone and benzaldehyde catalyzed by compound **3d**. Organocatalyst **3d** had furnished the best results in a previously reported study[9] and the results depicted in Table 1.

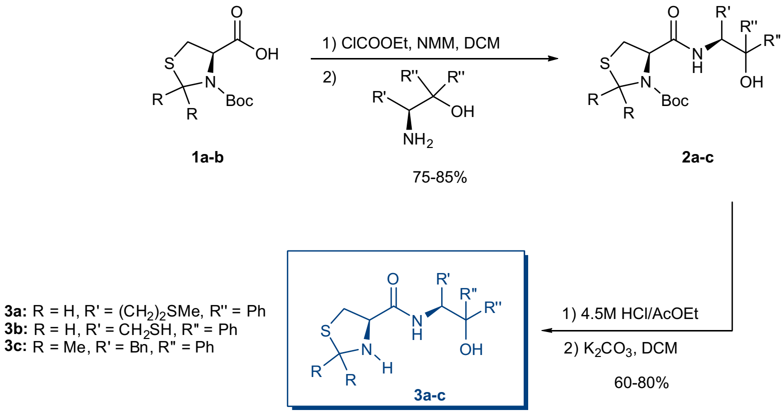
Initially, we investigated the effect of catalyst loading, reaction time, and temperature on the yield, diastereomeric ratio (dr) and enantiomeric excess (ee). As expected, lower yields were obtained with shorter reaction times (Table 1, entries 1–5). By either increasing or decreasing the catalyst loading from 10 mol %, inferior results were achieved. In the case of 5 mol % of catalyst **3d**, a dramatic decrease in the yield and ee was observed (Table 1, entries 6 and 7). Using 15 mol % of catalyst, no significant

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst (mol %)	Time (h)	Temp (°C)	Yield[b] (%)	ee[c] (%)	dr[d] (*anti*/*syn*)
1	10	24	rt	16	99	10:1
2	10	48	rt	23	99	10:1
3	10	72	rt	25	99	10:1
4	10	96	rt	58	99	10:1
5	10	120	rt	66	99	10:1
6	5	120	rt	24	92	>20:1
7	15	120	rt	55	80	>20:1
8	10	120	40	54	94	8:1

[a] Reaction performed with 1.0 mL of cyclohexanone, 1.0 mmol (0.101 mL) of benzaldehyde and 5–15 mol % of organocatalyst **3d**.
[b] Isolated yield.
[c] Determined by HPLC using chiral stationary phase.
[d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.



3a: R = H, R' = $(CH_2)_2SMe$, R'' = Ph
3b: R = H, R' = CH_2SH, R'' = Ph
3c: R = Me, R' = Bn, R'' = Ph

Scheme 2. Synthesis of organocatalysts **3a**–**c**.