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Enantiopure azetidine-2-carboxamides as organocatalysts for direct asymmetric aldol reactions in aqueous and organic media

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ABSTRACT

A family of enantiopure azetidine-2-caboxamides was asymmetrically synthesized, and was examined as organocatalyst in direct aldol reactions. A well chosen chiral azetidine-2-caboxamide was found to smoothly catalyze the direct aldol reaction of various benzaldehydes with acetone in brine, and β-hydroxy ketones were produced with enantiomeric excess up to 96%. The reaction of benzaldehydes with cyclic ketones also led to the formation of anti-products in diastereomeric ratio up to 99:1 and enantiomeric excess up to 99%.

1. Introduction

Because of the remarkable biological activities of azetidines, the interest in the four-membered constrained aza-heterocyclic compounds in organic syntheses and pharmaceutical chemistry has increased dramatically over the years.[1,2] Although numerous efficient methodologies have been developed to assemble the strained ring systems,[3] it is still difficult to synthesize enantiopure forms with general approaches.[4] The difficulty renders it uncommon to integrate enantioenriched azetidine scaffold in the framework of chiral catalysts. As early as in 1998, Zwanenburg and co-workers successfully applied *N*-alkyl azetidine-2-tertiary alcohols in asymmetric boron catalyzed Diels–Alder reactions.[5] The same group also demonstrated enantioselective diethylzinc addition to aldehydes using the similar azetidine-derived chiral ligands.[6] Meanwhile, chiral C_2-symmetric 2,4-disubstituted azetidines were developed by Shi and co-workers, and were examined in the catalytic asymmetric induction reactions.[7] Recently, we highlighted a three-step, one-pot protocol for a facile and practical preparation of enantiopure *N*-ferrocenylmethyl azetidine-2-ylmethanol, which served as a general ligand for asymmetric addition of various organozinc species (alkylzinc, arylzinc, and alkynylzinc) to the prochiral aldehydes with excellent enantioselectivities.[8] As illustrated in these examples, azetidine-based chiral ligands usually afforded improved asymmetric induction compared with pyrrolidine- or aziridine-based counterparts. As a result, the enantiopure four-membered aza-heterocyclic scaffold should be introduced into the building block arsenal for chiral catalysts, and await broad application and further elaboration.

Compared with its higher homologues, such as pyrrolidine and piperidine, azetidine has found little application as an effective aminocatalyst.[9] In infantile era of organocatalysis, List and co-workers brought out the concept of enamine catalysis of the proline-catalyzed direct asymmetric aldol reaction.[10] In this pioneer work, L-azetidinecarboxylic acid showed similar catalytic ability, but gave an inferior stereoselectivity of 40% ee comparing with 76% ee of L-proline. Interestingly, the higher homologue, pipecolic acid was ineffective for the reaction. Barbas III and co-workers also demonstrated the unique catalytic ability of L-azetidinecarboxylic acid in the asymmetric Mannich-type reaction.[11] The azetidine-based catalyst afforded a major *syn*-product with an enantioselectivity of 80% ee, while its pyrrolidine counterpart induced *anti*-selectivity. Enders and co-workers developed an efficient asymmetric syntheses of 3-substituted azetidine-2-carboxylic acids and 2-substituted azetidine-3-carboxylic acids, but neither of these amino acids produced

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matchable enantioselectivity in aldol reaction as simple L-proline.[12] In some other cases, L-azetidinecarboxylic acid could produce similar asymmetric induction comparable to that of L-proline.[13] Moreover, Greck and co-workers described the asymmetric α-amination of carbonyls, in which L-azetidinecarboxylic acid induced better enantioselectivity than L-proline.[14]

The proline amides are believed to be one type of the most effective organocatalysts for stereoselective direct aldol reaction.[15] The Gong's and Singh's research group have independently developed L-proline amino alcohol amides as catalysts for direct aldol reactions.[16,17] Substitution the pyrrolidine scaffold in proline amides with azetidine would lead to a kindred family of organocatalysts. The study of enantiopure azetidine amides would pose a useful complement to the five-membered-aza-heterocycle-dominated aminocatalysis, and gain deeper insight as well as broader perspective in the organocatalysis. In this paper, we reported the practical asymmetric syntheses of a series of chiral azetidine-2-caboxamides (Fig. 1, **1**, **2**, and **3**), and the studies of these compounds in the asymmetric catalysis of direct aldol reaction.

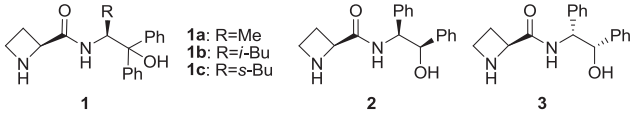


Fig. 1. Azetidine-2-carboxamides used for direct aldol reactions in this study.

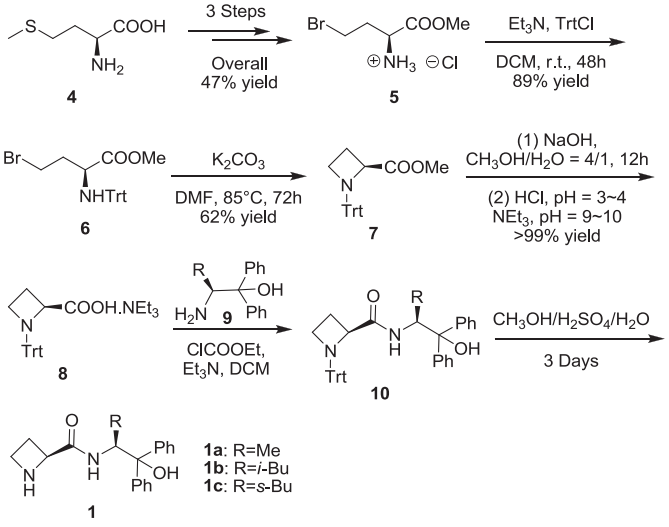
2. Results and discussion

2.1. Preparation of azetidine-based novel organocatalysts

The synthetic route leading to chiral azetidine-2-carboxamides (**1**, **2**, and **3**), was based on our previously developed approach to the enantiopure azetidine-2-carboxylate (Scheme 1).[8b]

Starting from the cheap and commercially available L-(+)-methionine **4**, which contained the source of chirality, the methyl L-2-amino-4-bromobutanoate **5** was obtained in the overall yield of 47% after three-steps. After the treatment of compound **5** with triethylamine and triphenylmethyl (trityl, or Trt) chloride in dichloromethane at room temperature for two days, the amino group was protected with trityl to afford the compound **6** in 89% yield. The aza-heterocyclic compound **7** was directly constructed from acyclic compound **6** via intramolecular nucleophilic substitution. The cyclization was carried out at an elevated temperature of 85 °C for 3 days with the efficiency of 52% yield.

The carboxylic acid was obtained after the hydrolysis of the methyl ester **7**, and was stabilized in the form of triethylamine salt **8**. The salt could react with various 2-aminoethanol **9** in the presence of stoichiometric amount of ClCOOEt and triethylamine to give the corresponding amides **10**. Upon the de-protection of *N*-trityl group under acidic condition, the chiral azetidine-2-carboxamides **1** were produced in decent yields. Following the similar route, the chiral amides **2** and **3** were also synthesized.

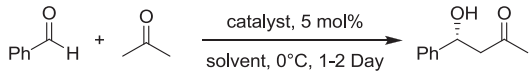


Scheme 1. Representative asymmetric synthetic route of chiral azetidine-2-carboxamide **1**.

2.2. The direct asymmetric aldol reaction of acetone with aldehydes catalyzed by azetidine-2-carboxamide 1a

The aldol reaction of benzaldehydes with acetone was used as a model reaction to test the catalytic efficiency of various azetidine-2-carboxamides (Table 1). The organocatalyst **1a**, which contains methyl as steric hindrance group on 2-aminoethanol moiety, was submitted to the model reaction in brine at room temperature (26 °C), and received 47% yield and 93% ee (Table 1, entry 1). The dehydration of aldol adduct was observed, and (*E*)-4-phenylbut-3-en-2-one was isolated as a major side product. Decreasing the reaction temperature to 0 °C would increase the yield to 71% by suppression of dehydration process (Table 1, entry 2). When azetidine amide **1b** or **1c**, which bears larger steric hindrance group on the side arm, was used as catalyst, decreased enantioselectivity was observed (Table 1, entries 3 and 4). The observation was contrary to our expectation. In Singh's work, the pyrrolidine counterpart of **1b** was found as the optimal catalyst.[17e] Similar effect was also observed with chiral amides **2** and **3** (Table 1, entries 5 and 6). Keeping **1a** as the optimal catalyst, when other organic solvents were screened, both reaction yield and stereoselectivity were decreased (Table 1, entries 7–12). When the catalyst loading was decreased from 5% mol to 3%, 2%, or even 1% mol, the catalytic efficiency was diminished, and decreased yield as well as extended reaction time was observed (not shown in Table 1).

Table 1
Direct aldol reaction of benzaldehyde with acetone catalyzed by **1**–**3**[a]



Entry	Catalyst (mol %)	Solvent	Yield (%)[b]	ee (%)[c,d]
1[e]	**1a**	Brine	47	93
2	**1a**	Brine	71	93
3	**1b**	Brine	72	84
4	**1c**	Brine	67	86
5	**2**	Brine	49	69
6	**3**	Brine	63	53
7[f]	**1a**	Neat	45	90
8	**1a**	*i*-PrOH	55	92
9	**1a**	MeOH	40	26
10	**1a**	CH_2Cl_2	57	87
11	**1a**	$CHCl_3$	53	90
12	**1a**	THF	42	69

[a] Unless specified, aldehyde **11a** (1 mmol), acetone **12** (5 mmol), and catalyst (5 mol %) were dissolved in solvent (2 mL, 0.5 M) and stirred at 0 °C for 1–2 days.
[b] Isolated yield calculated based on benzaldehyde.
[c] The ee values were determined by HPLC using the Chiralcel AD column.
[d] The absolute configuration of **13a** was assigned as *R* by comparison of retention times of known compounds.
[e] The reaction was carried out at the room temperature of 26 °C.
[f] The reaction was carried out in neat acetone with a concentration of 0.5 M.