Tetrahedron 74 (2018) 4705–4711

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A new type of amino amide organocatalyzed enantioselective crossed aldol reaction of ketones with aromatic aldehydes

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ARTICLE INFO

Article history:
Received 12 May 2018
Received in revised form
29 June 2018
Accepted 7 July 2018
Available online 31 July 2018

Keywords:
Amino amide
Organocatalysis
Crossed aldol reaction
Ketones
Aldehydes

ABSTRACT

A new type of amino amide organocatalysts was designed and synthesized from commercially available amino acids in easy steps. Their catalytic activities were examined in enantioselective crossed aldol reaction of various acyclic and cyclic ketones with aromatic aldehydes to afford the corresponding chiral *anti*-aldol adducts with good to excellent chemical yields, diastereoselectivities and enantioselectivities (up to 99%, up to *syn*:*anti* = 1:99, up to 97% *ee*).

1. Introduction

From last decade, the process of developing chiral multifunctional organic catalysts employ in enantioselective synthesis as independent chiral sources have been a new area of focus for a scientist. Excellent catalysts possess either Lewis or Brønsted basic functionalities and a non-covalent hydrogen-bond donor group suitably positioned over a chiral scaffold have been synthesized in general use for asymmetric reactions [1]. However, it is always a difficult job to design and synthesize a new type of multifunctional organocatalysts and examine them as self-determining and eco-friendly catalysts in asymmetric synthesis. In recent years, we are exploring amino alcohols as multifunctional organocatalysts as a new class of organocatalysts with distinctive properties such as easy synthesis, stable in air, the potential for convenient alteration of the steric sites [2]. The crossed aldol reaction is known as one of the basic reaction to the creation of the β-hydroxyl carbonyl structural motif which is found in numerous biologically active natural products and drug molecules [3]. Since List, Lerner, and Barbas [4] employed the crossed aldol reaction using proline as organocatalyst, there are numerous scientific reports that have proved the tremendous functionality of the chiral crossed aldol reaction using various organocatalysts, especially asymmetric crossed aldol reaction of ketones with aromatic aldehydes [5].

Recently, we have explored a polycyclic aromatic substituted primary amino-amide type of organocatalyst **A** for an enantioselective crossed aldol reaction of ketones with isatins, based on the assumption that the primary amino group might work as both the enamine formation site and the hydrogen bonding site. And also the amide function might work as the hydrogen bonding site to the substrate [6]. Furthermore, the C–C bond at α-position and β-position in catalyst might be rotated by the difference of the species of the bulky flexible polycyclic aromatic group on the nitrogen atom of amide carbonyl site to form efficient transition state for affording satisfactory stereoselectivity. (Fig. 1) [6].

We anticipated that these types of amino amide organocatalysts

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https://doi.org/10.1016/j.tet.2018.07.016
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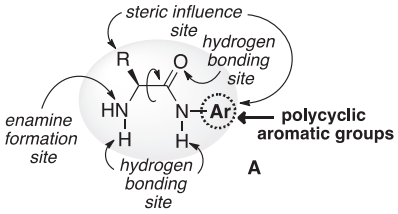


Fig. 1. The functionality of designed amino amide catalyst.

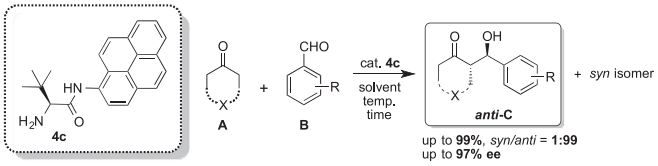
might be useful for an enantioselective crossed aldol reaction to a wide range of aromatic aldehydes with ketones except for isatins [6]. Herein, we describe that the newly prepared amino amide organocatalyst **4c** showed a highly efficient catalytic activity in the crossed aldol reaction of various cyclic ketones **A** with aromatic aldehyde **B** to afford the corresponding *anti*-aldol adducts **C** in good to excellent chemical yields and stereoselectivities (up to 99%, up to *syn*:*anti* = 1:99, up to 97% *ee*), with low-loading catalyst (5 mol %) in the presence of eco-friendly water as an additive (Scheme 1).

2. Results and discussion

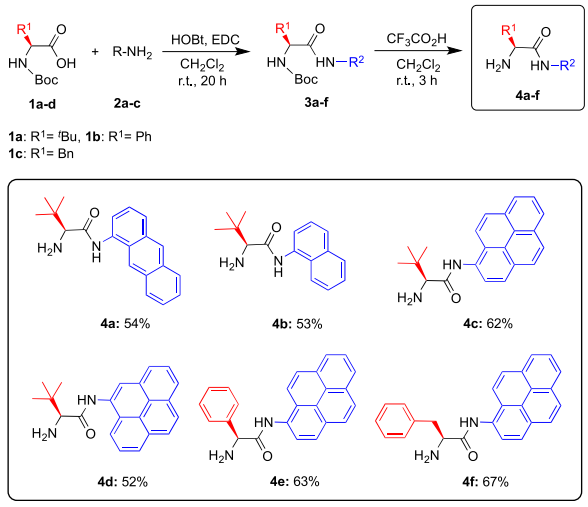
Polycyclic aromatic substituted amino amide catalysts **4a-f** were prepared easily by the condensation of the corresponding chiral *N*-Boc amino acid derivatives **1a-c** with polyaromatic amine derivatives **2a-d**, in the presence of 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC), at yields up to 67% (Scheme 2) [6,7].

Initially, we carried out the crossed aldol reaction of cyclohexanone **5** as an aldol donor and 4-nitrobenzaldehyde **6a** as an aldol acceptor with 25 mol% of organocatalyst **4a** with 2-anthracenylamide, in the presence of water at room temperature (entry 1, Table 1). Although the corresponding *anti*-aldol product **7a** as a major product was obtained with good chemical yield and relatively high diastereoselectivity, enantioselectivity was low (80%, *syn*:*anti* = 19:81, 43% *ee*). The absolute configuration and *syn*/*anti* diastereoselectivity of **7a** were identified based on comparison with literature data [8].

We next examined the catalytic abilities of all prepared catalysts **4b-f** for this reaction and the results were shown in (entries 2–6, Table 1). The catalyst **4b** with 1-naphthylamide having a *tert*-butyl group at α-position provided the corresponding *anti*-aldol adduct **7a** in good chemical yield, but with slightly increased in enantioselectivity than the result of catalyst **4a** (entry 2). On the other hand, catalyst **4c** with 1-pyrenylamide afforded the corresponding *anti*-aldol adduct **7a** with excellent chemical yield, diastereoselectivity and fairly good enantioselectivity (97%, *syn*:*anti* = 1:99, 92% *ee*, entry 3). In the case of catalyst **4d** with 4-pyrenylamide showed moderate catalytic activity (60%, *syn*:*anti* = 16:84, 45% *ee*, entry 4). Based on this result, we also examined the catalytic activity of catalysts **4e** and **4f** with 1-pyrenylamide having various substitutions at α-position. Although the *anti*-aldol adduct **7a** was obtained in good to excellent chemical yields, stereoselectivities were moderate (entries 5,6).

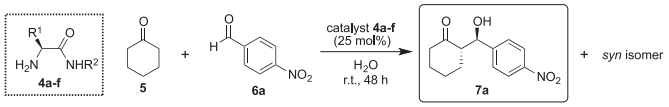


Scheme 1. Enantioselective aldol reaction using amino amide organocatalyst.



Scheme 2. Synthesis of amino amide organocatalysts **4a-f**.

Table 1
Asymmetric crossed aldol reaction of **5** and **6a** using organocatalysts **4a-f**.



entry	Catalyst **4**	Yield (%)[a]	*syn*:*anti*[b]	*anti* ee (%)[c]
1	**a**	80	19:81	43
2	**b**	67	14:86	55
3	**c**	97	1:99	92
4	**d**	60	16:84	45
5	**e**	97	11:89	65
6	**f**	81	12:88	50

[a] Isolated yields (a mixture of diastereomers).
[b] Diastereoselectivity was determined by HPLC analysis of the reaction mixture.
[c] The ee values were determined by HPLC analysis with a Daicel Chiralpak AD-H column.

These results suggested that the combination of the *tert*-butyl group at β-position and 1-pyrenyl substituent on amide group is effective for affording sufficient catalytic activity for achieving satisfactory stereoselctivity.

With these results in hand, we tried to optimize the reaction conditions using best catalyst **4c** to further improve the enantioselectivity and results were shown in (Table 2). An extensive screening of the reaction was further carried out by varying different parameters such as catalyst loading, solvent and reaction time period. First, we examined the effect of catalyst loading by varying from 25 mol% to 20 mol%, 10 mol%, 5 mol%, 2.5 mol% and 1 mol%. As a result, 5 mol% of catalyst **4c** showed the best catalytic activity and afforded the corresponding *anti*-aldol adduct **7a** with fairly good chemical yield, both excellent diastereoselectivity, and enantioselectivity (90%, *syn*:*anti* = 1:99, 96% *ee*, entry 4). Furthermore, we also carried out the reaction in distilled water and seawater using 5 mol% of catalyst **4c** (entries 7,8). Although the corresponding *anti*-aldol adduct **7a** was obtained in distilled water with fairly good chemical yield and stereoselectivities (92%, *syn*:*anti* = 1:99, 92% *ee*), the yield, as well as selectivity, was also decreased in seawater (75%, *syn*:*anti* = 10:90, 78% *ee*). The organic solvent screening was performed with different chlorinated (entries 9,10), non-polar aromatic (entries 11,12), non-polar aliphatic