ORGANIC LETTERS

2007
Vol. 9, No. 21
4247−4249

Design of Organocatalysts for Asymmetric Direct Syn-Aldol Reactions

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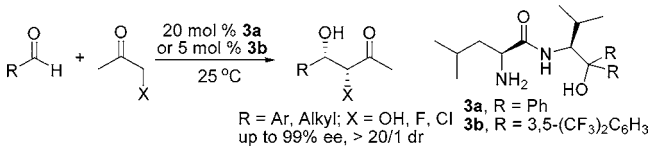
Received July 26, 2007

ABSTRACT



Two new organocatalysts 3a and 3b, derived from L-leucine and (*S*)-*β*-amino alcohols that were prepared from L-valine, were designed and afforded the direct syn-aldol reactions of a wide scope of aldehydes with various ketones with an excellent diastereomeric ratio of up to >20/1 and enantioselectivities of up to 99% ee.

Direct asymmetric aldol reactions, which provide straightforward access to optically active *β*-hydroxy carbonyls, are highly useful in organic synthesis[1,2] and thus have received much research interest.[2] As a result, great advances have been made in asymmetric direct aldol reactions, in particular, in those using organic molecules as catalysts.[3,4] Of diastereo- and enantioselective organocatalytic direct aldol reactions, anti-selective variants have been obtained with impressive results.[3,4] However, there have been a limited number of syn-selective organocatalytic asymmetric direct aldol reactions available for a spectrum of aromatic aldehdye acceptors and highly activated aldehydes.[5] The design of new organocatalysts with high enantio- and diastereoselectivities for a wide scope of substrates to serve as donors and acceptors of syn-direct aldol reactions therefore remains an important challenge. Herein, we will report a new type of organocatalyst (Figure 1) for highly enantioselective syn-direct aldol reactions.

Our previous studies[6] have shown that the direct aldol reaction using a butanone donor catalyzed by proline amides

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10.1021/ol701798x CCC: $37.00
Published on Web 10/04/2007

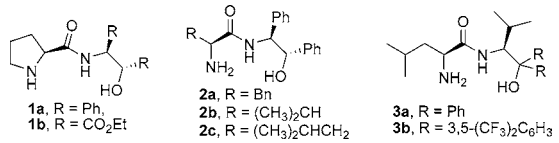
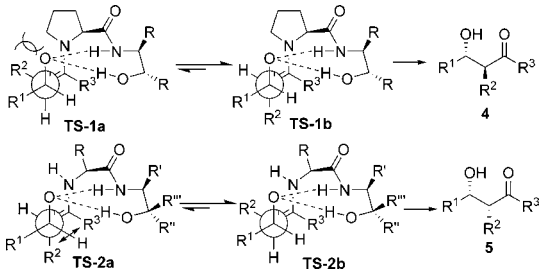


Figure 1. Organocatalysts in this study.

1 provided anti-selective aldol adducts with an excellent diasetereomeric ratio (>99:1 dr).[6c] The high diastereoselectivity can be explained by transition states, shown in **TS-1a** and **TS-1b** (Scheme 1). **TS-1a**, which adopts a Z-enamine

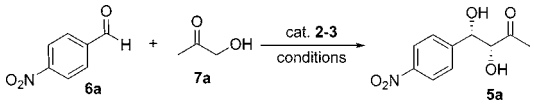
Scheme 1. General Strategy for the Design of New Organocatalysts for Syn-Aldol Reactions



structure and principally generates syn-aldol adducts, is less favorably formed than **TS-1b**, which adopts an E-enamine structure and generates anti-aldol products, because of the steric repulsion between R^2 and the pyrrolidine ring in the Z-enamine of **TS-1a**. To achieve a syn-aldol reaction, the reaction should proceed via a transition state similar to type **TS-1a**, and thus the Z-enamine should be predominately formed.[5a] Antibodies and primary amine-based organic molecules may catalyze the nucleophilic addition of an acyclic ketone by forming a Z-enamine in some cases,[5,7] resulting in a diastereoselectivity distinct from that observed with secondary amine catalysts.[5] According to the model that Barbas proposed for a primary amino acid-catalyzed syn-aldol reaction[5a] and the mode of carbonyl activation by double hydrogen bonds,[6] we think that the direct aldol reactions involving acyclic ketone donors catalyzed by **2** and **3** probably proceed via transition state **TS-2b** to give syn-aldol products **5** because the steric interaction between R^2 and R^3 makes **TS-2a**, which generates an anti-aldol adduct, less favorable than **TS-2b**.

We first examined a direct aldol reaction of hydroxyacetone with *p*-nitrobenzaldehyde catalyzed by 20 mol % **2a** in CH_2Cl_2. To our delight, the reaction proceeded smoothly at 25 °C to give *syn*-**5a** in high yield (89%) with fairly good diastereo- and enantioselectivities (4/1 dr, 67% ee for *syn*-**5a**, Table 1, entry 1). Under these conditions, organic molecules **3a** and **3b**, which are derived from L-leucine and (*S*)-*β*-amino alcohols that are prepared from L-valine,[10] afforded superior diastereo- and enantioselectivities to their structural analogues (entries 4 and 5).[11] A survey of solvents indicated that THF was a suitable solvent for the aldol reaction catalyzed by **3a**. In THF, **3a** delivered 96% ee and 19/1 dr for aldol adduct **5a** (entry 6). The enantioselectivity could be further improved to 98% ee at 0 °C (entry 7). Interestingly, *m*-xylene is the solvent of choice for the **3b**-catalyzed reaction (entries 8−10). Notably, the presence of 5 mol % **3b** is sufficient to afford the reaction in high yield (92%), with an excellent stereochemical outcome (19/1 dr, 96% ee, entry 10).

Table 1. Screening of Catalysts and Optimization of Reaction Conditions[a]



entry	cat. (mol %)	solvent	temp (°C)	yield (%)[b]	dr (syn/anti)[c]	ee (%)[d]
1	**2a** (20)	CH_2Cl_2	25	89	4/1	67
2	**2b** (20)	CH_2Cl_2	25	77	4/1	61
3	**2c** (20)	CH_2Cl_2	25	91	4/1	71
4	**3a** (20)	CH_2Cl_2	25	95	5/1	86
5	**3b** (20)	CH_2Cl_2	25	99	7/1	89
6	**3a** (20)	THF	25	95	19/1	96[e]
7	**3a** (20)	THF	0	82	19/1	98[f]
8	**3b** (20)	*m*-xylene	25	92	12/1	94[g]
9	**3b** (20)	*m*-xylene	0	96	19/1	96[h]
10	**3b** (5)	*m*-xylene	25	92	19/1	96

[a] The reaction mixture of *p*-nitrobenzadehyde (**6a**), hydroxyacetone (**7a**), and catalytic amounts of catalyst was stirred for 12 h unless indicated otherwise. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The ee of the syn diastereomer was determined by HPLC. [e] Stirred for 36 h. [f] Stirred for 96 h. [g] Stirred for 24 h. [h] Stirred for 48 h.

The optimal protocol was expanded to aldol reactions of hydroxyacetone with a variety of aromatic and aliphatic aldehydes (Table 2). The aldol reactions promoted by 5 mol % **3b** afforded syn-diols in high yields (80−97%) with high diastereomeric ratios (10/1->20/1 dr) and excellent enantioselectivities (91−98% ee). Generally, the electron-withdraw-

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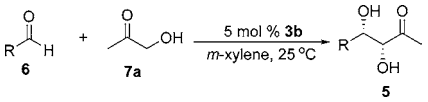
(11) For the reaction catalyzed by organic molecules structurally similar to **2a-c** and **3a-b**, see Table S1 in Supporting Information.

(12) For organocatalytic asymmetric anti-aldol reactions of fluoroacetone with aldehydes, see (a) Zhong, G.; Fan, J.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 5681. (b) Xu, X.-Y.; Wang, Y.-Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2007**, *18*, 237. (c) Chen, X.-H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Chem.—Eur. J.* **2007**, *13*, 689.

Table 2. Asymmetric Syn-Aldol Reactions of Hydroxyacetone with Aldehydes[a]



entry	5	R	time (h)	yield (%)[b]	dr (syn/anti)[c]	ee (%)[d]
1	**5a**	4-$NO_2C_6H_4$	12	92	19/1	96
2	**5b**	4-CNC_6H_4	36	86	19/1	96
3	**5c**	4-$MeO_2CC_6H_4$	36	95	13/1	95
4	**5d**	3-$NO_2C_6H_4$	24	97	16/1	96
5	**5e**	3-BrC_6H_4	48	95	13/1	96
6	**5f**	2-$NO_2C_6H_4$	24	92	>20/1	98
7	**5g**	2-ClC_6H_4	48	91	16/1	97
8	**5h**	2-FC_6H_4	36	90	10/1	94
9	**5i**	2-BrC_6H_4	36	91	19/1	96
10	**5j**	3,5-$F_2C_6H_3$	48	90	13/1	95
11	**5k**	3,5-$Br_2C_6H_3$	48	82	16/1	94
12	**5l**	3,5-$(CF_3)_2C_6H_3$	48	97	10/1	96
13	**5m**	3-Cl-4-FC_6H_3	60	86	10/1	94
14	**5n**	1-$BrC_{10}H_6$	48	80	16/1	91
15	**5o**	*c*-C_6H_{11}	60	68	>20/1	98[e]
16	**5p**	*i*-Pr	60	45	>20/1	98[e]

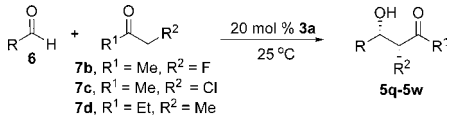
[a] See Supporting Information for the exact reaction procedure. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The ee of the syn diastereomer was determined by HPLC. [e] Catalyzed by 20 mol % **3b**.

ing group on the aldehyde facilitates the reaction proceeding to completion. Interestingly, the substituents of benzaldehydes, regardless of their size and electron nature, have little effect on the enantioselectivity (entries 1−13). Importantly, aliphatic aldehydes smoothly underwent reactions to give syn-aldol adducts **5o** and **5p** with excellent diastereo- and enantioselectivities (entries 15 and 16).

The aldol reactions of various ketones such as fluoroacetone, chloroacetone, and 3-pentanone were examined in the presence of 20 mol % **3a** (Table 3). Fluoroacetone underwent the direct aldol reaction to afford predominantly *syn*-α-fluoro-*β*-hydroxy ketones **5q-s**, which so far have been reached only by antibody catalysis,[7] with diastereomeric ratios ranging from 5/1 to >15/1 and excellent enantioselectivities (entries 1−4). In contrast, the secondary amine-based organocatalysts provided predominantly anti diastereomers.[12] The aldol reactions involving chloroacetone also favorably generated syn-aldol adducts[13] with enantioselectivities of up to 93% ee (entries 5−7). Notably, 3-pentanone, a much less reactive donor, smoothly underwent the aldol reaction to afford the syn product with 4/1 dr and 80% ee (entry 8).

(13) For organocatalytic asymmetric anti-aldol reactions of chloroacetone with aldehydes, see He, L.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang Y.-Z.; Gong, L.-Z. *Tetrahedron* **2006**, *62*, 346.

Table 3. Asymmetric Syn-Aldol Reactions of Acyclic Ketones with Aldehydes[a]



entry	5	R	7	time (h)	yield (%)[b]	dr (syn/anti)[c]	ee (%)[d]
1	**5q**	4-$NO_2C_6H_4$	**7b**	48	76	5/1	94[e]
2	**5q**	4-$NO_2C_6H_4$	**7b**	120	45	13/1	99[f]
3	**5r**	2-$NO_2C_6H_4$	**7b**	72	82	>15/1	98[e]
4	**5s**	3-$NO_2C_6H_4$	**7b**	48	79	6/1	93[e]
5	**5t**	4-$NO_2C_6H_4$	**7c**	40	81	2.5/1	89[g]
6	**5u**	4-$CO_2MeC_6H_4$	**7c**	72	61	2/1	93[g]
7	**5v**	4-CNC_6H_4	**7c**	72	64	2/1	88
8	**5w**	3-$NO_2C_6H_4$	**7d**	48	82	4/1	80[h]

[a] See Supporting Information for the exact reaction procedure. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The ee of the syn diastereomer was determined by HPLC. [e] The reaction was performed in CH_2Cl_2 (0.5 mL). [f] Catalyzed by 5 mol % **3b** in *m*-xylene (1 mL). [g] The reaction was performed in Et_2O (0.5 mL) with chloroacetone (0.5 mL). [h] Reaction with 20 equiv of ketones under neat conditions.

In summary, we have designed a type of organocatalyst, which was prepared from primary amino acids and *β*-amino alcohols, for the catalytic syn-selective direct aldol reactions of aldehydes with hydroxy-, fluoro-, and chloroacetones and 3-pentanone. We found that organic molecules **3a** and **3b**, derived from L-leucine and (*S*)-*β*-amino alcohols that were prepared from L-valine, offered superior diastereo- and enantioselectivities. The presence of 5 mol % catalyst **3b** significantly catalyzes the direct aldol reactions of a wide range of aromatic and aliphatic aldehydes with hydroxyacetone to give syn-diols with excellent dr (10/1->20/1) and enantioselectivities ranging from 91 to 98% ee. The direct aldol reactions of aldehydes with either fluoro- and chloroacetones or 3-pentanone proceeded in the presence of 20 mol % **3a** to afford predominantly syn products with high enantioselectivities.

Acknowledgment. We are grateful for financial support from NSFC (20472082 and 20325211) and the Chinese Academy of Sciences.

Supporting Information Available: Experimental procedures, spectra data, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701798X