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Efficient Organocatalytic Cross-Aldol Reaction between Aliphatic Aldehydes through Their Functional Differentiation

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Supporting Information

ABSTRACT: A chemo- and stereoselective asymmetric direct cross-aldol reaction between aliphatic aldehydes and α-chloroaldehydes has been developed as a method for the formation of the sole cross-aldol adduct with both enantio- and diastereocontrol, and either *anti*- or *syn*-aldol adducts were obtained in good to excellent stereoselectivities by use of proline or a novel axially chiral amino sulfonamide as catalyst.

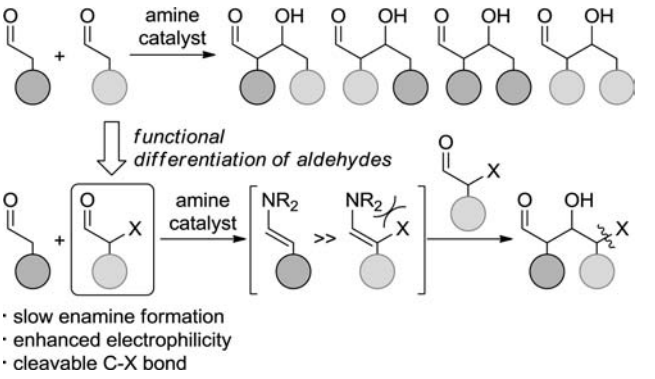
The aldol reaction has long been recognized as one of the most fundamental tools for the construction of new carbon−carbon bonds.[1] In this area, the cross-aldol reaction between two different aldehydes has remained an elusive challenge because of undesired side reactions including homoaldol reaction and multiple addition of nucleophilic species such as the enolate and the enamine to the aldol product.[2−14]

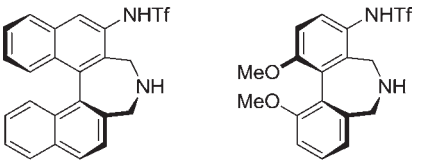
In organocatalytic cross-aldol reaction of aldehydes through the enamine intermediate first reported by MacMillan et al.,[13a,15] the cross-aldol adduct could be obtained in a highly stereoselective fashion without prior formation of activated enolate species.[13,14] However, most such reactions required the use of sterically hindered aliphatic aldehydes, from which the enamine intermediates are rather difficult to be formed, or aromatic aldehydes as electrophile. In the direct aldol reaction between simple aliphatic aldehydes, both aldehydes can perform the double role of nucleophile and electrophile, and consequently, two cross-aldol adducts and two homoaldol adducts would be possible major products with each having four stereoisomers (Scheme 1). Accordingly, the development of chemo- and stereoselective asymmetric direct cross-aldol reactions between aliphatic aldehydes represents a highly desirable and challenging goal.

To differentiate the two aldehydes in terms of their role in the reaction, we introduced a halogen group at the α-position of acceptor aldehydes as shown in Scheme 1.[13d] The formation of the enamine intermediate of the sterically hindered α-haloaldehyde and an amine catalyst would be suppressed. Moreover, the α-haloaldehyde, which is electronically activated by the α-halo group, would be expected to react predominantly with the enamine intermediate over the other aliphatic donor aldehyde. Finally, the halogen group on the cross-aldol adduct can be removed under reductive conditions.

Herein, we wish to report the development of chemo- and stereoselective asymmetric direct cross-aldol reaction between aliphatic aldehydes and α-chloroaldehydes[13r,16] as a method for the formation of the sole cross-aldol product with both enantio- and diastereocontrol.

Scheme 1. Cross-Aldol Reaction between Aliphatic Aldehydes through Enamine Catalysis





(*S*)-**1** (*S*)-**2**

We first examined the reaction between 3-methylbutanal and racemic 2-chloro-3-phenylpropanal in the presence of 30 mol % of L-proline in DMF at 0 °C (Table 1, entry 1). When the extracted reaction mixture was treated with $LiAlH_4$ in THF,[13r] the corresponding *anti*-diol *anti*-**3** derived from the desired cross-aldol adduct was obtained in moderate yield with excellent diastereo- and enantioselectivity. In this reaction, a small amount of the other diol from the homoaldol adduct of 3-methylbutanal (7%) was also formed. Use of 2-bromo-3-phenylpropanal resulted in a decrease in yield (entry 2). Improvement of yield was achieved by use of an excess amount of a donor aldehyde, 3-methylbutanal (entries 5 and 6). In all cases examined, both enantiomers of α-haloaldehydes were found to be equally incorporated into the aldol adducts. In addition, almost racemic α-haloaldehydes remained after the reaction, and hence, the kinetic resolution of α-haloaldehydes was not observed.

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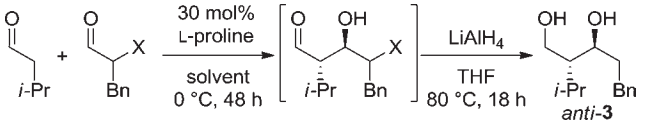
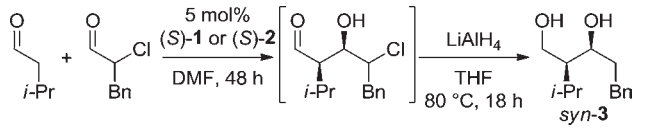
Table 1. *anti*-Selective Cross-Aldol Reaction of 3-Methylbutanal with 2-Halo-3-phenylpropanal Catalyzed by L-Proline[a]



entry	X	solvent	yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	Cl	DMF	48	19/1	97
2	Br	DMF	34	>20/1	97
3	Cl	THF	46	13/1	97
4	Cl	MeCN	47	16/1	98
5[e]	Cl	DMF	59	19/1	96
6[f]	Cl	DMF	65	19/1	96

[a] The reaction of 3-methylbutanal (0.2 mmol) with 2-halo-3-phenylpropanal (0.2 mmol) in a solvent (100 μL) was carried out in the presence of L-proline (0.06 mmol) at 0 °C. [b] Isolated yield after reduction of the aldol product with $LiAlH_4$. [c] Determined by ^1H NMR. [d] The ee of *anti*-**3** was determined by HPLC using chiral column. [e] Use of 6 equiv of 3-methylbutanal (1.2 mmol). [f] Use of 8 equiv of 3-methylbutanal (1.6 mmol).

Table 2. *syn*-Selective Cross-Aldol Reaction of 3-Methylbutanal with 2-Chloro-3-phenylpropanal Catalyzed by (*S*)-1 or (*S*)-2[a]



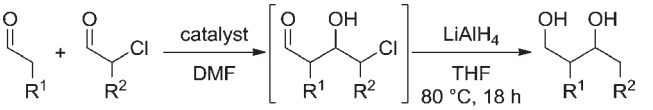
entry	catalyst	temp (°C)	yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	(*S*)-**1**	0	0	-	-
2	(*S*)-**2**	0	13	1/>20	97
3	(*S*)-**2**	rt	68	1/>20	97
4[e]	(*S*)-**2**	rt	61	1/>20	97
5[e,f]	(*S*)-**2**	rt	90	1/>20	96

[a] The reaction of 3-methylbutanal (0.1 mmol) with 2-chloro-3-phenylpropanal (0.1 mmol) in DMF (100 μL) was carried out in the presence of a catalyst (0.005 mmol). [b] Isolated yield after reduction of the aldol product with $LiAlH_4$. [c] Determined by ^1H NMR. [d] The ee of *syn*-**3** was determined by HPLC using chiral column. [e] The reaction was performed for 6 h. [f] Use of 2 equiv of 2-chloro-3-phenylpropanal (0.2 mmol).

Most organocatalytic direct cross-aldol reactions of aldehydes are known to provide *anti*-aldol adducts predominantly,[13] albeit with a few exceptions giving *syn*-adducts.[14] We previously developed the *syn*-selective and enantioselective direct cross-aldol reaction between aldehydes catalyzed by an axially chiral amino sulfonamide (*S*)-**1**.[14a,17] However, this method was applicable only to the combination of aliphatic aldehydes as nucleophile and reactive nonenolizable aldehydes, which cannot form enamine intermediate, as electrophile. In this context, we have been interested in use of less reactive aliphatic aldehydes as electrophile in the *syn*-selective direct cross-aldol reaction.

Unfortunately, no reaction was observed between 3-methylbutanal and racemic 2-chloro-3-phenylpropanal in the presence

Table 3. Cross-Aldol Reaction of Aliphatic Aldehydes with α-Chloroaldehydes Catalyzed by L-Proline or (*S*)-2[a]



entry	conditions	R^1	R^2	yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	A	Me	Bn	91	3.5/1	98
2	A	Et	Bn	84	4.3/1	94
3	A	Bu	Bn	72	3.3/1	94
4	A	Bn	Me	68	5.7/1	94
5	A	*i*-Pr	Bn	65	19/1	96
6[e]	A	*i*-Pr	Me	55	>20/1	94[f]
7	A	Cy	Bn	61	13/1	94
8	B	Me	Bn	88	1/4.6	97
9	B	Et	Bn	82	1/>20	99
10	B	Bu	Bn	88	1/>20	98
11	B	Bn	Me	73	1/3.0	98
12	B	*i*-Pr	Bn	90	1/>20	96
13	B	Cy	Bn	73	1/>20	98

[a] Conditions A: the reaction of a donor aldehyde (1.6 mmol) with an acceptor aldehyde (0.2 mmol) in DMF (100 μL) was carried out in the presence of L-proline (0.06 mmol) at 0 °C for 48 h; Conditions B: the reaction of a donor aldehyde (0.1 mmol) with an acceptor aldehyde (0.2 mmol) in DMF (100 μL) was carried out in the presence of (*S*)-**2** (0.005 mmol) at room temperature for 6 h. [b] Isolated yield after reduction of the aldol product with $LiAlH_4$. [c] Determined by ^1H NMR. [d] The ee of the major diastereomer was determined by HPLC using chiral column. [e] The reaction was performed at room temperature and the aldol adduct was isolated as the dimethylacetal. See Supporting Information for details. [f] The ee was determined by GC using chiral column.

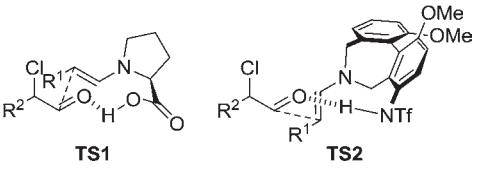


Figure 1. Transition state models for the enantioselective cross-aldol reaction catalyzed by L-proline (left) and (*S*)-**2** (right).

of 5 mol % of (*S*)-**1** in DMF at 0 °C (Table 2, entry 1). We assumed that the catalyst (*S*)-**1** and the resulting enamine intermediate did not have sufficient nucleophilicity for the desired cross-aldol reaction. Accordingly, we have now developed a novel catalyst (*S*)-**2** with the expectation that it would be more nucleophilic. To our delight, the reaction with (*S*)-**2** proceeded to give *syn*-**3** exclusively albeit in low yield (entry 2). This promising result prompted us to undertake optimization studies (entries 3−5). Use of 2 equiv of α-chloroaldehyde at room temperature was found to improve the yield without loss of stereoselectivities (entry 5). It should be noted that *the homoaldol adduct was not obtained even when a large excess of 3-methylbutanal was used.* This result suggested that the enamine intermediate generated from (*S*)-**2** could distinguish between a simple aliphatic aldehyde and an α-chloroaldehyde due to the moderate nucleophilicity, and consequently, the desired *syn*-selective cross-aldol

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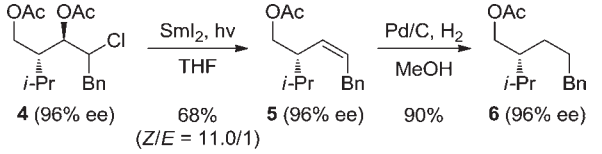
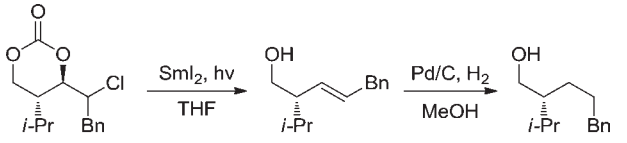
Scheme 2. Synthesis of (*Z*)-Alkene 5



Scheme 3. Synthesis of (*E*)-Alkene 8



reaction was realized with excellent chemoselectivity as well as stereoselectivities.

With the optimal reaction conditions, the diastereo- and enantioselective direct cross-aldol reaction of several other donor aldehydes with acceptor aldehydes was examined, and the results are summarized in Table 3. All reactions proceeded to give either *anti*- or *syn*-cross-aldol products with excellent enantioselectivity, respectively.

The absolute configuration of the product obtained by L-proline was determined to be (2*R*,3*S*) by comparison of the optical rotation with the literature data.[18] On the other hand, the reaction catalyzed by (*S*)-**2** gave the *syn*-diol having (2*S*,3*S*) configuration. On the basis of the observed stereochemistry, transition state models can be proposed as shown in Figure 1. In the case of the proline-catalyzed reaction, the *Re* face of the α-chloroaldehyde approaches the *Re*-face of the dominant *s-trans*-enamine (Figure 1, **TS1**). While both *s-trans*-enamine and *s-cis*-enamine might be formed in the reaction catalyzed by (*S*)-**2**, only *s-cis*-enamine can react with the activated α-chloroaldehyde, giving the (2*S*,3*S*)-isomer predominantly (Figure 1, **TS2**).[14a,b]

The obtained aldol adduct **3** was a versatile intermediate in organic synthesis and readily converted to important chiral building blocks (Scheme 2). Thus, diacetate **4**, which was prepared from the cross-aldol adduct *anti*-**3**, could be converted to the corresponding (*Z*)-alkene **5** by the photoinduced metalation with samarium diiodide and the subsequent β-elimination of *O*-acetyl chlorohydrin.[19] The resulting (*Z*)-alkene **5** was hydrogenated to **6** without loss of optical purity. Interestingly, the β-elimination of cyclic carbonate **7** under identical conditions was found to provide (*E*)-alkene **8** as a major stereoisomer (Scheme 3). These transformations represent the formal asymmetric alkenylation and alkylation of aldehydes.

In summary, we have developed a highly chemo- and stereoselective asymmetric direct cross-aldol reaction between aliphatic aldehydes and α-chloroaldehydes catalyzed by proline and the novel axially chiral amino sulfonamide (*S*)-**2**. This organocatalytic process represents a rare example of cross-aldol reaction between two different aliphatic aldehydes. Further application of the present cross-aldol reaction as well as chiral amino sulfonamide catalyst (*S*)-**2**, particularly for the development of new enantioselective reactions, is under investigation.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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