Molecular recognition of ketomalonates by asymmetric aldol reaction of aldehydes with secondary-amine organocatalysts

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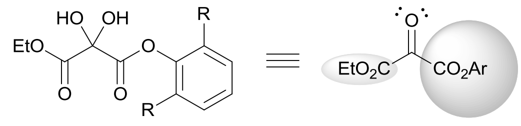
A diastereo- and enantioselective aldol reaction between aldehydes and a synthetically useful ketomalonate 1c as a hydrated form was developed, and either *anti*- or *syn*-aldol adducts having a chiral tetrasubstituted carbon center were obtained in high enantioselectivities by use of a tetrazole analogue of L-proline (*S*)-2 or an axially chiral amino sulfonamide (*S*)-3 as catalyst.

Asymmetric aldol reactions provide expedient access to optically active β-hydroxy carbonyl compounds that are fundamental chiral building blocks for a number of biologically active and pharmaceutically important compounds.[1] Among these reactions, catalytic asymmetric aldol reactions of ketone electrophiles afford tertiary alcohols, and a chiral tetrasubstituted carbon center is efficiently constructed with these methods.[2-4] In the area of organocatalysis, the development of direct asymmetric aldol reaction has been the subject of intensive research over the last decade; however, reactive aldehydes were employed as electrophiles in the most amine-catalyzed aldol reactions.[5-7] Although a number of asymmetric aldol reactions between ketone nucleophiles and ketone electrophiles have been developed,[8] only a few examples of using aldehyde nucleophiles, which tend to be dimerized through the homo-aldol reaction, toward ketone electrophiles have been reported so far.[9] Additionally, an efficient method for the stereoselective synthesis of both diastereomers of such aldol adducts from the same set of reactants by simply replacing the catalyst has been scarcely investigated. Accordingly, we have been interested in the development of organocatalytic asymmetric aldol reaction between aldehyde nucleophiles and ketone electrophiles based on the molecular recognition approach. The difficulty in developing the asymmetric aldol reaction of ketones can be attributed to the lower intrinsic electrophilicity of ketones over aldehydes, combined with the smaller steric difference between the two groups on the carbonyl moiety. To overcome the low reactivity of ketone acceptors, we chose ketomalonate **1**, which is obtained in a hydrate form, as electronically activated ketone equivalent by two different modifiable ester groups (Fig. 1). One ester group of **1** consists of phenols, which are sterically demanding and sufficiently good leaving group, to induce diastereoselectivity as well as to discriminate two ester groups of **1**. Herein, we wish to report both *anti* and *syn*-selective synthesis of chiral tertiary alcohols based on the molecular recognition approach from the stereocontrolled aldol reaction of the hydrated ketomalonate **1** having modifiable substituents with aldehydes catalyzed by either the tetrazole analogue of L-proline (*S*)-**2**[10] or an axially chiral amino sulfonamide of type (*S*)-**3**.[11]



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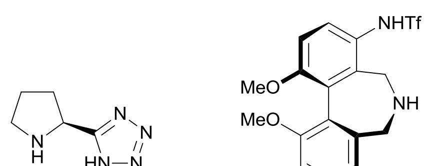
sterically and electronically differentiated carbonyl

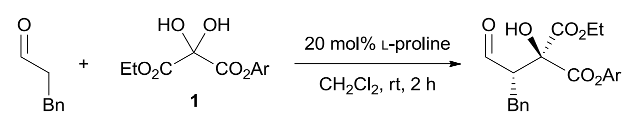
Fig. 1 Unsymmetrical ketomalonate **1** in a hydrate form for asymmetric cross-aldol reaction.

We first examined the effect of 2,6-substituents on phenyl group of hydrated ketomalonate **1** in the aldol reaction, and the results are summarized in Table 1. In the presence of 20 mol% of L-proline, the reaction between 3-phenylpropanal and **1a** (Ar = 2,6-Me_2-C_6H_3) in dichloromethane at room temperature proceeded smoothly to give the desired *anti*-aldol adduct *anti*-**4a** as major diastereomer in good yield with excellent enantioselectivity (entry 1). Unfortunately, however, **4a** was found to be readily isomerized to a 1:1 mixture of the *anti* and *syn*-isomers after isolation. Use of a more hindered acceptors **1b** (Ar = 2,6-^{i}Pr_2-C_6H_3) and **1c** (Ar = 2,6-^{t}Bu_2-C_6H_3) resulted in higher *anti*-selectivity, and no isomerization was observed (entries 2 and 3). When the reaction of **1c** was carried out with 10 mol% of catalyst (*S*)-**2**, the tetrazole derivative of L-proline, further improvement of *anti*-selectivity was achieved (entry 4).



(*S*)-**2** (*S*)-**3**

Table 1 *anti*-Selective aldol reactions between 3-phenylpropanal and **1** catalyzed by L-proline *[a]*



anti-**4**

Entry	Ar	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	2,6-Me_2-C_6H_3	83	1.8/1	96
2	2,6-$^{i}Pr_2$-C_6H_3	94	2.2/1	96
3	2,6-$^{t}Bu_2$-C_6H_3	99	2.6/1	95
4[e]	2,6-$^{t}Bu_2$-C_6H_3	88	3.0/1	99

[a] Unless otherwise noted, the reaction of 3-phenylpropanal (0.125 mmol) with **1** (0.1 mmol) was performed in the presence of L-proline (0.02 mmol) in CH_2Cl_2 (100 μL) at room temperature for 2 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] The ee of *anti*-**4** was determined by HPLC using chiral column after conversion to the corresponding γ-lactone. [e] Use of (*S*)-**2** (0.01 mmol) instead of L-proline.

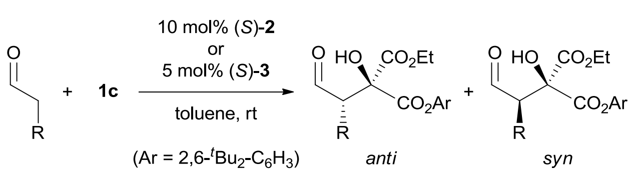
Having identified a suitable ketone acceptor, solvent screening was then carried out. The desired *anti*-aldol product *anti*-**4c** was formed as major diastereomer in moderate to good yield with excellent enantioselectivity in all solvents investigated (see Supplementary Information). Thus, toluene appeared to be the best solvent in terms of diastereoselectivity (Table 2, entry 3).

We then turned our attention to the development of the *syn*-selective aldol reaction of **1c** catalyzed by an axially chiral amino sulfonamide (*S*)-**3**, which can switch the minor diastereomer in the reaction catalyzed by proline and its derivatives to the major diastereomer.[11] In the presence of 5 mol% of (*S*)-**3**, the reaction between 3-phenylpropanal and **1c** in toluene at room temperature afforded the desired *syn*-aldol adduct *syn*-**4c** in good yield with high enantioselectivity (Table 2, entry 8). Among solvents tested, toluene was found to be a suitable solvent in terms of yield and *syn*-selectivity (see Supplementary Information).

With the optimal reaction conditions, the diastereo- and enantioselective aldol reaction of **1c** with several other donor aldehydes was examined, and the results were summarized in Table 2. All reactions catalyzed by (*S*)-**2** proceeded smoothly to give *anti*-aldol adducts as major diastereomer in good yield with excellent enantioselectivity (entries 1–5). Regardless of aldehyde structure, the diastereochemical outcome of the aldol adducts could be switched by using (*S*)-**3** (entries 6-10).

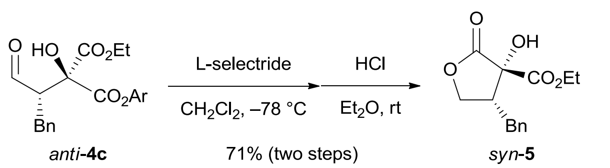
The obtained aldol products *anti*-**4c** and *syn*-**4c** were versatile intermediates in organic synthesis and readily converted to important chiral building blocks such as γ-lactones. Thus, reduction of aldol product *anti*-**4c** with L-selectride at –78 °C and the subsequent lactonization with 1N HCl in one pot provided α-hydroxy-γ-lactone *syn*-**5** in good yield without loss of the diastereoselectivity (Scheme 1). In the case of *syn*-**4c**, the corresponding α-hydroxy-γ-lactone *anti*-**5** was readily obtained by treatment with L-selectride (Scheme 2). In both cases, the carbonyl group of more reactive aryl ester was preferentially incorporated into the lactone ring. A hydroxy group on *anti*-**5** was converted to an amino group through mesylation, S_N2 reaction with NaN_3, and reduction under mild conditions.

Table 2 Stereocontrolled aldol reactions between various aldehydes and **1c** catalyzed by (*S*)-**2** or (*S*)-**3** [a]

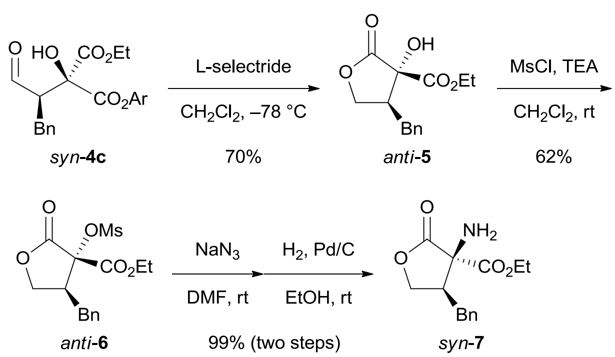


Entry	R	Catalyst	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	Me	(*S*)-**2**	83	3.5/1	95
2[e]	Et	(*S*)-**2**	80	3.9/1	97
3	Bn	(*S*)-**2**	89	4.1/1	98
4	CH_2Cy	(*S*)-**2**	71	3.8 /1	96
5[e]	^{i}Pr	(*S*)-**2**	85	4.3/1	96
6	Me	(*S*)-**3**	74	1/4.0	97
7	Et	(*S*)-**3**	75	1/5.6	95
8	Bn	(*S*)-**3**	90	1/6.2	95
9	CH_2Cy	(*S*)-**3**	94	1/4.9	95
10[f]	^{i}Pr	(*S*)-**3**	65	1/3.5	95

[a] The reaction of an aldehyde (0.125 mmol) with **1c** (0.1 mmol) was performed in the presence of (*S*)-**2** (0.01 mmol) or (*S*)-**3** (0.005 mmol) in toluene (100 μL) at room temperature for 2 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] The ee of the major isomer was determined by HPLC using chiral column after conversion to the corresponding γ-lactone. [e] The reaction was performed for 3 h. [f] The reaction was performed for 5 h.



Scheme 1 Synthesis of α-hydroxy-γ-lactone *syn*-**5**.



Scheme 2 Synthesis of α-hydroxy-γ-lactone *anti*-**5** and α-amino-γ-lactone *syn*-**7**.

Based on the observed stereochemistry, transition state models can be proposed as shown in Figure 1. In the case of the reaction catalyzed by (*S*)-**2**, the activation and direction of the ketomalonate **1c** by the acidic functionality of (*S*)-**2** is expected to occur by coordination to the sterically more accessible lone pair on the carbonyl oxygen atom of **1c**. Consequently, the *Re* face of ketomalonate **1c** approaches the

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Re-face of the dominant s-*trans*-enamine, and the *anti*-aldol adduct was obtained as major diastereomer (Fig. 2, **TS1**). On the other hand, while both s-*trans*-enamine and s-*cis*-enamine might be formed in the reaction catalyzed by (*S*)-**3**, only s-*cis*-enamine can react with the activated ketomalonate **1c**, giving the *syn*-aldol adduct predominantly (Fig. 2, **TS2**).[12]

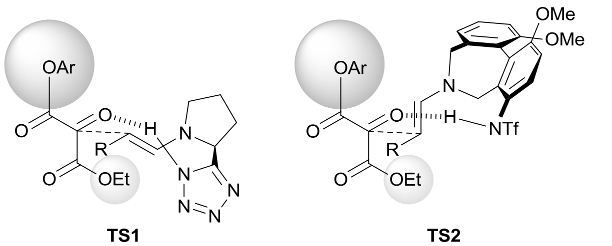

Fig. 2 Transition state models for the asymmetric aldol reaction catalyzed by (*S*)-**2** (left) and (*S*)-**3** (right).

In summary, we have developed a diastereoselective and enantioselective direct aldol reaction of hydrated ketomalonate **1c** with aldehydes catalyzed by proline derivative (*S*)-**2** and the axially chiral amino sulfonamide (*S*)-**3**. This organocatalytic process represents a rare example of stereocontrolled aldol reaction between aldehyde donor and ketone acceptor. Further application of the present aldol reaction and the aldol reactions using other ketone acceptors are under investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/b000000x/

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