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Direct catalytic asymmetric aldol reactions of aldehydes

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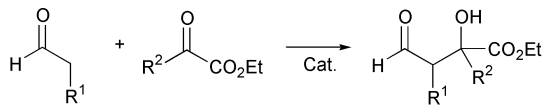
The development of a direct catalytic enantioselective aldol reaction of aldehydes with activated carbonyl compounds catalyzed by chiral amines is presented and the potential demonstrated by the synthesis of optically active β-hydroxycarboxylic acid derivatives.

The aldol reaction is considered to be one of the most important C–C bond forming reactions. The catalytic enantioselective version of this reaction has received considerable attention in recent years. These developments include: (i) Lewis acid-catalyzed Mukaiyama-type[1] and chiral Lewis base-catalyzed[2] aldol reactions, (ii) bimetallic and heterobimetallic bifunctional Lewis acid/Brønsted base-catalyzed direct aldol reactions,[3] (iii) aldolase enzyme and antibody-catalyzed aldol reactions.[4] The direct aldol reaction facilitated by chiral amines is a new challenging dimension to this important C–C bond forming reaction.[5,6]

A lot of effort has been devoted to the development of the enantioselective aldol reaction catalyzed by chiral amines.[5,6] These reactions have been restricted to ketones, which by reaction with the chiral amine generate an enamine intermediate, which reacts with another carbonyl compound. However, the use of aldehydes for the direct catalytic enantioselective aldol reaction compared with ketones is a challenge due to lower reactivity of the enamine intermediate generated from aldehydes compared with ketones. A recent communication by Denmark *et al.*[7] showing the first cross aldol reaction of aldehydes using geometrically defined trichlorosilyl enolates prompted us to present the first enantioselective direct aldol reaction of aldehydes **1** with activated carbonyl compounds **2** catalyzed by chiral amines **4** [eqn. (1)].†

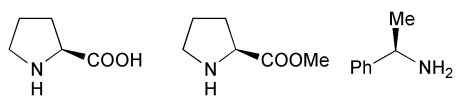


(1)

1
a: R^1 = Me
b: R^1 = Et
c: R^1 = *i*-Pr
d: R^1 = $CH_2CH{=}CH_2$
e: R^1 = $(CH_2)_5CH_3$
f: R^1 = Ph
g: R^1 = H

2
a: R^2 = CO_2Et
b: R^2 = CF_3

3
a: R^1 = Me, R^2 = CO_2Et
b: R^1 = Et, R^2 = CO_2Et
c: R^1 = *i*-Pr, R^2 = CO_2Et
d: R^1 = $CH_2CH{=}CH_2$, R^2 = CO_2Et
e: R^1 = $(CH_2)_5CH_3$, R^2 = CO_2Et
f: R^1 = Ph, R^2 = CO_2Et
g: R^1 = H, R^2 = CF_3
h: R^1 = Me, R^2 = CF_3

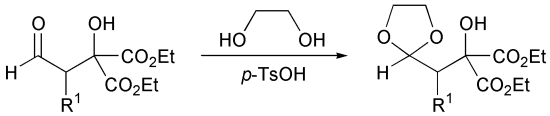


4a **4b** **4c**

In order for the catalytic enantioselective direct aldol reaction of aldehydes to proceed, we have found that activated carbonyl compounds such as diethyl ketomalonate **2a** or ethyl trifluoropyruvate **2b** have to be used. In the screening process for the development of the reaction a variety of different chiral amines were tested as catalysts and it was found that L-proline **4a** showed the most promising enantioselective properties compared to L-proline methyl ester **4b** and (*R*)-(+)-1-phenylethylamine **4c**. The results from the screening process of the catalytic enantioselective direct aldol reaction of propanal **1a** with diethyl ketomalonate **2a** are presented in Table 1.

The chiral amines **4a–c** can catalyze the direct aldol reaction of propanal **1a** with diethyl ketomalonate **2a** and a high yield of the α-hydroxy-γ-oxo ester **3a** is isolated in all solvents studied (Table 1, entries 1–9) except H_2O (entry 10). The highest enantioselectivity of **3a** is obtained at −20 °C in CH_2Cl_2 as the solvent (entry 2), and both high yield and enantioselectivity of **3a** can also be obtained by using 20 mol% of L-proline **4a** as the catalyst (entry 3). If the reaction is performed with 10 mol% of the catalyst a mixture of products is formed. The use of L-proline methyl ester **4b** and (*R*)-(+)-1-phenylethylamine **4c** as the catalyst gave full conversion of the aldehyde, but unfortunately the product is racemic.

The results in Table 1 are all obtained after a reaction time of 3 h. However, prolonged reaction time reduces the ee of **3a** and purification by column chromatography using silica also reduces the enantioselectivity due to epimerization of the chiral carbon atom. However, this problem can easily be circumvented by acetal protection of the carbonyl functionality (**5**) as outlined in eqn. 2, which eliminated the epimerization problem.



(2)

3 **5**

Table 2 presents the reaction of various aldehydes **1a–g** with activated carbonyl compounds **2a**,**b** catalyzed by L-proline **4a** [eqn. (1)].

The aldehydes **1a–e** react with diethyl ketomalonate **2a** to give the aldol products **3a–e** in high yields and high enantioselectivity with up to 90% ee within a short reaction time (entries 1–5). It should be noted that butanal **1b**, 3-methylbutanal **1c** and

Table 1 Some representative results from the screening of reaction conditions for the catalytic enantioselective direct aldol reaction of propanal **1a** with diethyl ketomalonate **2a** in the presence of some chiral amines at rt

Entry	Catalyst (mol%)	Solvent	Yield (%)	Ee[a] (%)
1	**4a** (50)	CH_2Cl_2	90	90
2	**4a** (50)[b]	CH_2Cl_2	94	93
3	**4a** (20)	CH_2Cl_2	93	88
4	**4b** (50)	$CDCl_3$	81	0
5	**4c** (50)	$CDCl_3$	83	0
6	**4a** (50)	Toluene	73	90
7	**4a** (50)	THF	60	90
8	**4a** (50)	DMSO	90	75
9	**4a** (50)	Et_2O	53	90
10	**4a** (50)	H_2O	—	—

[a] Ee measured by GC using a Astec G-TA column for **3a** and HPLC for **5a** using a DAICEL CHIRALPAK AD column. [b] Reaction temperature −20 °C for 4h.

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octanal **1e** give high yield and enantioselectivity (entries 2,3,5) and that the reaction also proceeds well for the unsaturated aldehyde **1d** (entry 4). Although, the reaction of phenylethanal **1f** with **2a** proceeds well, unfortunately, the product obtained (**3f**) was racemic (entry 6). The reactions proceed well also in gram scale; *e.g.* reaction of 3-methylbutanal **1c** with diethyl ketomalonate **2a** catalyzed by L-proline **4a** gives **3c** in quantitative yield and with 92% ee.

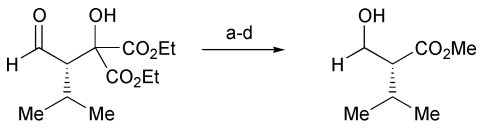
Ethyl trifluoropyruvate **2b** reacts also with aldehydes by the direct catalytic aldol reaction (entries 7,8), and the present reaction gives an easy approach to trifluoromethyl hydroxy aldehydes, which are valuable compounds.[8] Propanal **1a** reacts to give a mixture of two diastereomers with moderate diastereomeric ratio (3 : 2) and with 67% and 81% ee of the two diastereomers, while ethanal **1g** gives a racemic product.

Table 2 Reaction of different aldehydes **1a–g** with the activated carbonyl compounds **2a**,**b** in the presence of L-proline **4a** as the catalyst in CH_2Cl_2 as the solvent at rt

Entry	Aldehyde	Ketone	Reaction time/h	Yield (%)	Ee[a]
1	**1a**	**2a**	3	**3a** (90)	90
2	**1b**	**2a**	1.25	**3b** (91)	85
3	**1c**	**2a**	2	**3c** (88)	85
4	**1d**	**2a**	3	**3d** (94)	88
5	**1e**	**2a**	1.5	**3e** (91)	84
6	**1f**	**2a**	1	**3f** (97)	0
7	**1g**	**2b**	1	**3g** (81)	0
8	**1a**	**2b**	3	**3h** (98)[b]	67/81

[a] Ee measured by GC using Astec G-TA or Chrompack CP-Chiralsil-Dex-cβ columns. [b] A mixture of two diastereomers, dr: 3 : 2.

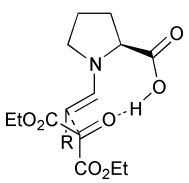
The products obtained from the direct aldol reaction of aldehydes can be converted into optically active β-hydroxy-carboxylic acid derivatives which have been used for the assignment of the absolute configuration of the products. Scheme 1 outlines the reaction sequence for the aldol adduct **3c** to methyl 3-hydroxy-2-isopropylpropanoate **6**. Based on the absolute configuration of **6**,[9] the absolute configuration of **3c**, obtained by applying L-proline **4a** as the catalyst, can be assigned as (*S*).



3c (92% ee) **6** (95% ee)

Scheme 1 a: $NaBH_4$–EtOH, rt/0.5 h; b: KOH–EtOH, rt/18 h — quenched by 1 M HCl; c: CAN–H_2O–MeCN, rt/1 h; d: $TMSCHN_2$–MeOH–toluene, rt/30 min.

Based on the absolute configuration of the aldol product we proposed the transition state model[10] **I**. This L-proline–enamine intermediate is, according to *ab initio* calculations,[11] 2–3 kcal mol^{-1} more stable compared to the enamine oriented *syn* relative to the carboxylic acid. The approach of diethyl ketomalonate is directed by interaction of the incoming carbonyl oxygen atom with the proton of the carboxylic acid (note that using L-proline methyl ester **4b** as the catalyst gave a racemic product).



I

In summary, we have developed the first direct catalytic asymmetric aldol reaction of aldehydes with carbonyl compounds. The reaction proceeds with high enantiomeric excess and gives a simple approach to optically active β-hydroxy-carboxylic acid derivatives.

We are indebted to The Danish National Research Foundation for financial support.

Notes and references

† General reaction conditions: in an oven dried test tube (12 ml) 0.50 mmol aldehydes (36 μl propanal **1a**) and 0.50 mmol ketone (76 μl diethyl ketomalonate **2a**) were dissolved in CH_2Cl_2 (2 ml) and 0.25 mmol L-proline (29 mg) was added as catalyst and the test tube was stopped with a rubber-stopper. The reaction mixture was stirred for 3 h at rt, quenched with H_2O and extracted with CH_2Cl_2. The organic layer was dried (anh. Na_2SO_4), filtered and evaporated to give crude product (105 mg of **3a**, 90% yield). For product **3a** the enantiomers could be separated by GC (Astec G-TA column) to give 90% ee. Data for **3a**: ^{1}H NMR δ 1.11 (d, $3J_{HH}$ = 7.6 Hz, 3H) 1.23 (q, $3J_{HH}$ = 7.2 Hz, 6H), 3.27 (q, $3J_{HH}$ = 7.6 Hz, 1H), 4.01 (br s, 1H), 4.23 (m, $3J_{HH}$ = 7.2 Hz, 4H), 9.60 (s, 1H); ^{13}C NMR δ 8.93, 14.10. 14.18, 50.12, 63.17, 63.31, 79.26, 169.43, 169.56, 200.89.

1 For excellent reviews, see *e.g.*: E. M. Carreira, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin-Heidelberg, 1999, Vol. III, Chapter 29.1; S. G. Nelson, *Tetrahedron: Asymmetry*, 1998, **9**, 357.

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3 See *e.g.*: N. Yoahikawa, Y. M. A. Yamada, J. Das, H. Sasai and M. Sibasaki, *J. Am. Chem. Soc.*, 1999, **121**, 4168 are references therein; B. M. Trost and H. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 12003.

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10 For theoretical investigations on amino acid catalyzed asymmetric aldol reactions see: S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 11273.

11 PC Spartan Plus, Version 2: Based on 3-21G* and 6-31G** basis set optimized structures.