Tetrahedron Letters 50 (2009) 193–197

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Organocatalytic activity of 4-hydroxy-prolinamide alcohol with different noncovalent coordination sites in asymmetric Michael and direct aldol reactions

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ARTICLE INFO

Article history:
Received 17 October 2008
Accepted 23 October 2008
Available online 30 October 2008

Keywords:
Organocatalyst
4-Hydroxy-prolinamide alcohol
Michael reaction
Aldol reaction
DFT calculations

ABSTRACT

4-Hydroxy-prolinamide alcohol with different noncoordination sites as a molecule showed excellent asymmetric catalytic activity in both the Michael reaction (up to 98% ee) and the direct aldol reaction (up to >99% ee), and the catalyzing reactions with high enantioselectivity are supported by a DFT theoretical study of their transition state.

Asymmetric organocatalysis has emerged as an important and rapidly growing field in synthetic organic chemistry, and excellent covalent and noncovalent organocatalysts have been developed for use in a wide range of reactions.[1] In these organocatalysts, proline-based covalent organocatalysts have been developed and applied in several reactions.[1] Previously reported proline-based catalysts[2,3] usually have one covalent site or both a covalent and a noncovalent site in a molecule. However, to the best of our knowledge, an example of proline-based catalyst that properly uses the plural noncovalent coordination site in the molecule at each reaction has not been reported. In the present study, we planned to develop an organocatalyst that properly uses the noncoordination sites by the substrate used. For the design of the planned catalyst, we paid close attention to the reports of Palomo et al.[4] and Singh and co-workers[5] They have recently developed the proline-based organocatalysts **1** and **2**, respectively, for use in Michael and direct aldol reactions. These compounds feature both a covalent site and a noncovalent site, the latter of which activates the substrate molecule via hydrogen-bonding interactions. Thus, *trans*-4-hydroxyprolinamide **2** is able to hydrogen bond with a substrate molecule through the hydroxyl group at the 4-position on the pyrrolidine ring, making it effective in Michael reactions, and the amide moiety at the 2-position on the pyrrolidine ring acts to control the equilibrium between enamine conformers and blocks one enamine face to afford a high enantioselectivity. Conversely, the amide alcohol at the 2-position on the pyrrolidine ring in 2-prolinamide alcohol **1** facilitates hydrogen bonding with the substrate and results in effective catalysis in direct aldol reactions. However, as described below, **2** did not work effectively in aldol reactions and **1** did not work in Michael reactions in the present study. Given these advantages and disadvantages of catalysts **1** and **2**, we designed a series of 4-hydroxy-prolinamide alcohols **3a–e** with different noncovalent coordination sites in the molecules (Scheme 1).

Compounds **3a–e** contain one covalent site and three noncovalent binding sites in a single molecule. For example, the hydroxyl group at the 4-position on the pyrrolidine ring might bind a substrate, and other noncovalent sites at 2-position might act to control the equilibrium between enamine conformers and block one enamine face when the catalyst is used in a Michael reaction. On the other hand, the amide-alcohol substituent at the 2-position on the same molecule might bind a substrate and might catalyze a direct aldol reaction.

This report focuses on the characterization of organocatalysts having one covalent site and two noncovalent sites on a molecule that properly uses the two noncovalent coordination sites by the Michael or direct aldol reactions. The Michael[6] and direct aldol[7] reactions have attracted a great deal of attention because of the important role these reactions play in carbon–carbon bond formation in synthetic organic chemistry.

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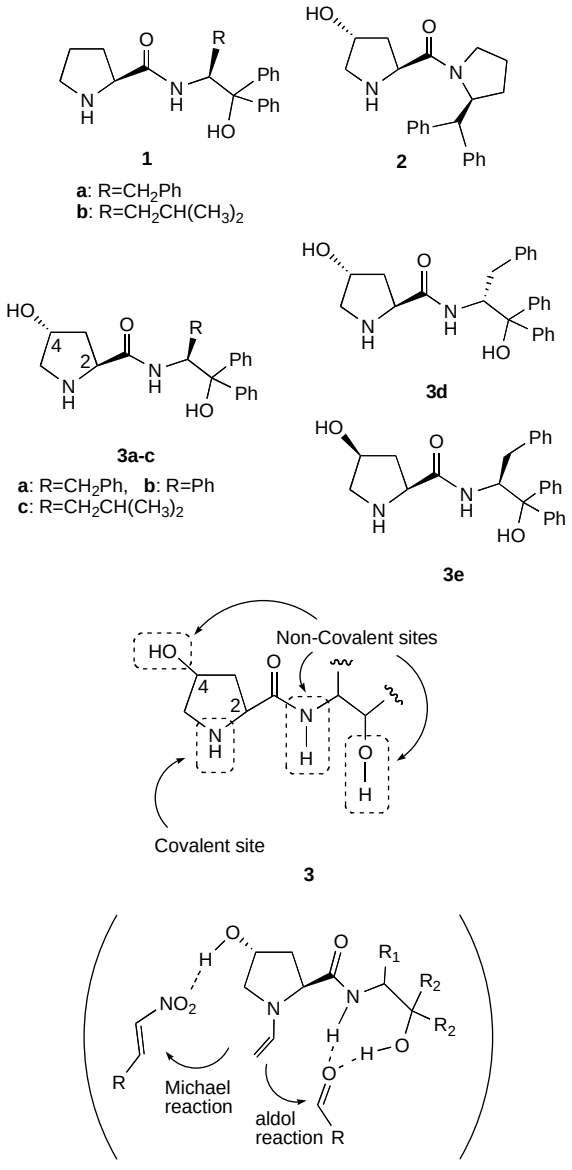
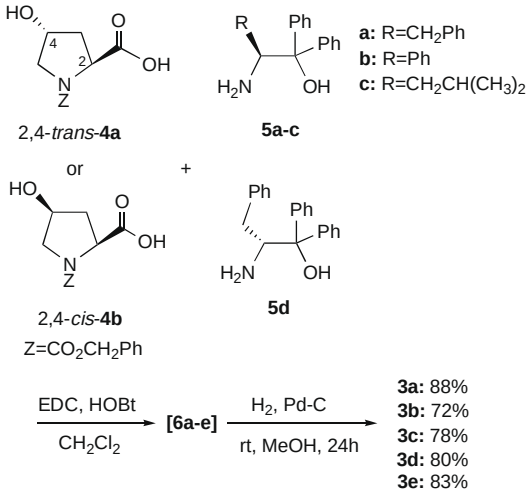
doi:10.1016/j.tetlet.2008.10.122



Scheme 1. Concept of catalyst design.



Scheme 2. Preparations of organocatalysts.

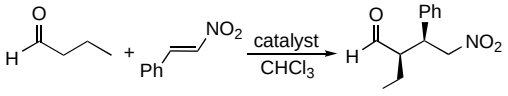
We report herein that 4-hydroxy-2-prolinamide alcohol **3** exhibits a high degree of enantioselectivity in both the Michael (up to 98% ee) and direct aldol (up to >99% ee) reactions using several substrates. This is the first example of a catalyst that makes proper use of coordination site itself during a reaction, and also changes from the coordination site to a substituent for a steric control.

The 2,4-trans- and 2,4-cis-catalysts, **3a–e**, respectively, were prepared by the condensation of 2,4-*trans*- or 2,4-*cis*-1-Cbz-hydroxy-2-prolines, **4a** and **4b**, with the corresponding β-amino alcohols **5a–d** in the presence of stoichiometric amounts of HOBt and EDC. The N-protected compounds **6a–e** were then debenzyloxycarbonylated using H_2 and Pd–C (10%) at yields up to 88% (Scheme 2).

To ascertain the efficacy of organocatalysts **3a–e**, the relative cross-reactivity of known catalysts **1a,b** and **2** was examined in the direct aldol and Michael reactions, respectively. Catalyst **2**, having the hydroxy group at the 4-position on the pyrrolidine ring, which has been shown to be effective in direct aldol reactions, was applied to the Michael reaction, and catalyst **1**, having an amido-alcohol substituent at the 2-position, which is generally used in Michael reactions, was applied to the aldol reaction. A model Michael reaction was run in $CHCl_3$ containing 20 mol % of catalyst **1a,b**. Butyraldehyde **7** and β-nitrostyrene **8** were used as the Michael donor and acceptor, respectively (Table 1). The model aldol reaction consisted of benzaldehyde **10** and neat acetone **11** in the presence of 10 mol % catalyst **2** (Table 3). As a result, catalysts **1a** and **1b** did not produce the Michael adduct **9** in satisfactory chemical yields, and exhibited negligible enantioselectivity (Table 1, entries 1 and 2). Likewise, catalyst **2** exhibited little catalytic activity when applied to the direct aldol reaction (Table 3, entry 1). These results imply that the amino and hydroxyl groups at the 2-position in catalysts **1a** and **1b** do not effectively make a hydrogen bond with substrate **8** in the Michael reaction. The hydroxyl group at the 4-position on catalyst **2** is similarly ineffective in forming hydrogen bonds with substrate **11** in the direct aldol reaction.

The Michael and aldol reactions were repeated with the 4-hydroxy-prolinamide alcohols **3a–e** as catalysts. The Michael reaction was performed at room temperature using aldehydes **7**

Table 1
The effect of the catalyst in the Michael reaction of butyraldehyde with nitrostyrene[a]

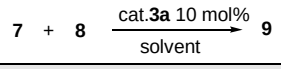


7 8 9

Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield[b] (%)	dr[c] *syn*/*anti*	ee[d] (%)
1	**Ia** (20)	rt	20	75	93:7	41
2	**Ib** (20)	rt	48	65	94:6	57
3	**3a** (20)	rt	20	99	93:7	90
4	**3b** (20)	rt	20	99	95:5	61
5	**3c** (20)	rt	20	61	93:7	74
6	**3a** (20)	−45 to 0	20	98	95:5	98
7	**3a** (10)	−45 to 0	20	89	96:4	96
8	**3a** (5)	−45 to 0	48	72	95:5	98
9	**3a** (2.5)	8	72	54	93:7	98
10	**3d** (5)	−45 to 0	20	95	96:4	80
11	**3e** (5)	−45 to 8	20	52	88:12	37

[a] All reactions were conducted in $CHC1_3$ (1 mL) using nitrostyrene (0.34 mmol), a catalyst (5–20 mol %), and aldehyde (1.7 mmol).
[b] Isolated yields.
[c] The *syn*/*anti* ratio was determined by ^{1}H-NMR and HPLC.
[d] The ee of the *syn* isomer was determined by chiral HPLC using a Daicel OD-H column.

Table 2
Solvent effect to the Michael reaction[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	dr[c] *syn/anti*	ee[d] (%)
1	CH_2C1_2	−45 to 0	20	82	96:4	96
2	Hexane	−45 to 0	48	85	97:3	95
3	MeOH	−45 to 0	20	60	88:12	85
4	Brine	0	20	95	94:6	84

[a] All reactions were conducted in a solvent (1 mL) using nitrostyrene (0.34 mmol), catalyst **3a** (0.034 mmol), and aldehyde (1.7 mmol).
[b] Isolated yields.
[c] The *syn/anti* ratio was determined by 1H-NMR and HPLC.
[d] The ee of the *syn* isomer was determined by chiral HPLC using Daicel OD-H column and AD-H column.

and **8** (Table 1). As shown in Scheme 1, compounds **3a**–**c** differed according to the substituent group at the α-carbon, an (*S*)-configured chiral center, while the *gem*-diphenyl group was present at the β-carbon for all three species. The relative efficacy of these compounds is shown in Table 1. Catalyst **3a**, which bears a benzyl group at the α-carbon, afforded excellent chemical yield (99%) and good enantioselectivity (90% ee). Catalyst **3b**, with a phenyl group at the α-carbon, demonstrated excellent catalytic activity, but the enantioselectivity was greatly reduced (61% ee). Catalyst **3c**, with an *iso*-butyl group at the α-carbon, was not completely soluble, producing a moderate chemical yield (61%) and enantioselectivity (74% ee). Thus, catalyst **3a** was deemed effective in the Michael reaction. Efficacy was further increased by lowering the reaction temperature to between −45 and 0 °C, and decreasing the amount of catalyst to 20 mol %. Under these conditions, a dramatic increase in enantioselectivity was observed (98% ee) together with excellent chemical yields (98%).

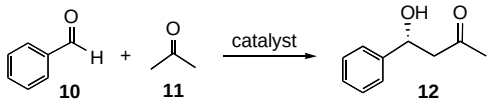
The molar ratio of catalyst in the reaction mixture was an important variable. Reaction mixtures containing 10 mol % **3a** were equally enantioselective as reactions containing 20 mol %, but the chemical yield decreased to 89%. At 5 mol % **3a**, the reaction products exhibited excellent asymmetric induction and were obtained in good yield. At 2.5 mol %, the reaction was sluggish and the chemical yield was moderate even after 72 h. Despite the poor yield, however, the enantioselectivity (98% ee) was comparable to that obtained at higher levels of catalyst loading.

The catalytic activities of both the 2,4-trans-catalyst **3d**, bearing a (*R*)-benzyl group at the α-carbon, and the 2,4-cis-catalyst **3e**, with a (*S*)-benzyl group at the α-carbon, were also evaluated (Table 1). Catalyst **3d** was no more effective than catalyst **3a**, and **3e** was unsatisfactory in both chemical yield and enantioselectivity.

To determine the extent of solvent effects on the catalytic activity of these materials, the same reaction was performed using **7** and **8** in different organic and aqueous solvents between −45 and 0 °C or between −25 and 0 °C in the presence of 10 mol % of catalyst **3a**. As shown in Table 2, the enantioselectivity was highly dependent on the nature of the solvent. High chemical yields and enantioselectivities were obtained in dichloromethane and hexane, while the same reaction performed in MeOH yielded poor results. The reaction in brine resulted in a dramatic increase in the production of **9** with an excellent chemical yield (95%) and good enantioselectivity (84% ee) after 20 h. Generally, the organocatalyzed Michael reaction in water did not proceeds smoothly and generally required the addition of TFA to increase the reaction rate, as stated previously.[2e]

The activity of catalysts **3a**–**e** was then evaluated in a direct aldol reaction consisting of 10 mol % catalyst with benzaldehyde **10** and acetone **11** at 0 °C. The results are shown in Table 3. Catalyst **3a** was fairly effective in the aldol reaction, with a yield and enantioselectivity of 83% and 89% ee, respectively. However, both of these factors were reduced with catalyst **3b**. Catalyst **3c** did not show any catalytic activity.

Table 3
The effect of the catalyst in the aldol reaction of benzaldehyde with acetone[a]



Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2** (10)	0	24	Trace	
2	**3a** (10)	0	24	83	89
3	**3b** (10)	0	24	87	85
4	**3c** (10)	0	24	—	—
5	**3a** (10)	−25	24	72	98
6	**3b** (10)	25	24	90	>99
7	**3a** (5)	−25	24	71	99
8	**3b** (5)	−25	33	99	>99
9	**3a** (2.5)	−25	46	72	98
10	**3b** (2.5)	−25	46	68	97
11	**3d** (5)	0	36	20	52
12	**3e** (5)	0	36	36	34

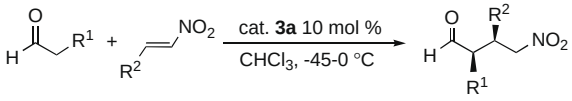
[a] A solution of a catalyst (0.05 mmol) in dry acetone (0.5 mL) was stirred at a suitable temperature for half an hour. An aldehyde (0.5 mmol) was added and the resulting mixture was stirred at 0 °C or −25 °C for 24–46 h.
[b] Isolated yields.
[c] Determined by chiral HPLC using a Daicel AD-H column.

The same reactions were then performed at −25 °C using only catalysts **3a** and **3b**. The results in Table 3 show that the enantioselectivity was significantly enhanced. Further enhancement was realized by reducing the molar ratio of catalyst in the reaction mixture. At 5 mol %, both **3a** and **3b** exhibited almost complete enantioselectivity (**3a**: 99% ee, **3b**: >99% ee). In addition, **3b** afforded the corresponding product **12** in quantitative yield. These catalysts maintained their efficiency even at 2.5 mol %, but the diastereomeric isomers of **3a**, **3d**, and **3e** did not show sufficient asymmetric catalytic activity.

According to the results shown in Tables 1 and 3, organocatalyst **3a** demonstrated superior asymmetric induction in the Michael reaction of butyraldehyde **7** with nitrostyrene **8** and the direct aldol reaction of **10** with **11**.

The nature of the substrate also plays a critical role in the efficacy of the catalyst. Therefore, Michael and direct aldol reactions were examined using several substrates. Michael reactions performed with a variety of aldehydes and nitrostyrenes were carried out from −45 to 0 °C using 10 mol % of catalyst **3a** (Table 4). The

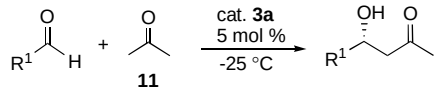
Table 4
The catalytic asymmetric Michael reaction of aldehydes with nitroalkenes[a]



Entry	R^1	R^2	Time (h)	Yield[b] (%)	dr[c] *syn/anti*	ee[d] (%)
1	CH_3	Ph	48	71	99:1	93
2	CH_3	4-ClC_6H_4	48	65	96:4	94
3	*n*-C_3H_7		20	96	—	95
4	*n*-C_3H_7	*c*-CH_2Ph	48	72	95:5	93

[a] All reactions were conducted in $CHCl_3$ (1 mL) using a nitroolefin (0.34 mmol), catalyst **3a** (0.034 mmol) and aldehyde (1.7 mmol).
[b] Isolated yields.
[c] The *syn/anti* ratio was determined by ^{1}H-NMR and HPLC.
[d] The ee of the *syn* isomer was determined by chiral HPLC using a Daicel OD-H column and AD-H column.

Table 5
The catalytic asymmetric aldol reaction of aldehydes with acetone[a]



Entry	R^1	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-$MeOC_6H_4$	36	95	98
2	4-FC_6H_4	36	82	99
3	2-ClC_6H_4	40	95	97
4	4-ClC_6H_4	36	92	97
5	C_6H_{11}	46	48	99

[a] A solution of catalyst **3a** (0.025 mmol) in dry acetone (0.5 mL) was stirred at a suitable temperature for half an hour. An aldehyde (0.5 mmol) was added and the resulting mixture was stirred at −25 °C for 36–46 h.
[b] Isolated yields.
[c] Determined by chiral HPLC using a Daicel AD-H column.

catalytic activity was moderate in reactions between propionaldehyde and 4-chlorobenxaldehyde or **8**, while excellent enantioselectivity and chemical yield was obtained for reactions between valeraldehyde and 2-(2-nitrovinyl)thiophene or aliphatic (3-nitro-2-propenyl)benzene.

The effects of the substrate on the catalytic activity in direct aldol reactions were also evaluated using several different aldehydes with ketones (Tables 5 and 6). In nearly all cases using acetone (Table 5), an excellent enantioselectivity (97–99% ee) and relatively good chemical yields (82–95%) were obtained. Almost complete enantioselectivity was realized with the aliphatic cyclohexanecarboxaldehyde (99% ee), but the reaction was sluggish and the chemical yield was low even after 46 h. Using cyclohexanone as a donor, good chemical yields and fairly good to excellent enantioselectivities were obtained with different aromatic aldehydes, except for the chemical yield of electron-deficient 4-nitrobenzaldehyde (Table 6, entries 1–3). Furthermore, the reactions with biologically important heterocyclic ketones afforded good chemical yields and excellent enantioselectivities (entry 4: 70%, 96% ee, entry 5: 52%, 98% ee). In addition, the reaction of 4-pyridinecarboxaldehyde with cyclohexanone also gave a good chemical yield and a fairly good enantioselectivity (68%, 93% ee, entry 6).

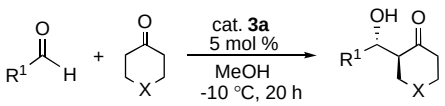
To better understand these experimental results, mechanistic studies of these reactions were performed with density functional theory (DFT) calculations at the B3LYP/6-31G* level (the details are given in Supplementary data). As model reactions, we chose the Michael reaction of butylaldehyde **7** with β-nitrostyrene **8** and the aldol reaction of benzaldehyde **10** with acetone **11** using catalyst **3a**. For the determination of transition state (TS) models, we referred to recent quantum mechanistic calculations performed for the Michael[4] and direct aldol[8] reactions, which assume active hydrogen bonding between the substrate and catalyst.

In the Michael reaction, two acyclic TS models with hydrogen bonding are assumed, as indicated by Palomo et al.[4] One is the *si*-face approach of donor **8** in the *anti*-enamine, which is defined by the relative position between the double bond and the chiral carbon atom (C3) of the pyrrolidine ring, and the other is the *re*-face approach of **8** in the *syn*-enamine (Fig. 1). However, more conformations are possible in the present enamine, due in part to rotations of the amide-alcohol substituent and the benzyl ring. Furthermore, we assumed that β-nitrostyrene **8** forms aldol-type hydrogen bonds. Optimization of the TS energetics yielded two main models, **mic-TS1-*anti*** and **mic-TS2-*anti***, which led to the product **9** by the formation of a C–C bond on the *si*-face. The former model consists of a NH···OH hydrogen bond, which forms a five-membered ring, while the latter involves a C=O···HO hydrogen bond to form a seven-membered ring. The difference in activation energy (ΔE_a) between these two models is only 0.39 kcal/mol. Thus, two mechanistic routes to the formation of product **9** are plausible. The alternative *re*-syn TS models (**mic-TS1-*syn*** and **mic-TS2-*syn***) are unstable by 2.66 and 3.23 kcal/mol, respectively, in the activation energy (E_a). These results agree with the high enantioselectivity observed in the present Michael reaction. The ΔE_a values described here represent the energetic difference between the initial complex (IC) and the TS. Noteworthy is that the IC of the *si-anti* approach is more stabilized than that of the *re-syn* approach (ΔE is ~2 kcal/mol in the complex stabilization). In contrast, the mechanistic route via an aldol-type transition state (**mic-TS-5-*anti***) could be rejected because of the high energy barrier (ΔE_a is 5.30 kcal/mol).

DFT calculations for the aldol reaction predict only one conformation of the TS per product due to the steric hindrance of the two *gem*-diphenyl groups of **3a**. ΔE_a for the two enantiomeric products of the aldol reaction, **al-TS1-(*R*)** and **al-TS1-(*S*)**, is 5.27 kcal/mol. This result agrees with the high enantioselectivity observed in the direct aldol reaction (Fig. 2).

In summary, we have demonstrated the organocatalytic activity of a new class of 4-hydroxy-L-prolinamide alcohols having one covalent site and two different noncovalent coordination sites on a molecule and observed excellent asymmetric catalysis in both Michael and direct aldol reactions. Of the compounds evaluated, catalyst **3a** exhibited the highest chemical yield and enantioselectivity in both reactions and on a variety of substrate molecules. In addition, catalyst **3a** maintained these characteristics at only 2.5 mol % in the Michael reaction and 5 mol % in the aldol reaction. These results suggest that two noncovalent sites on a single catalyst molecule can be specific for two distinct substrates. Thus, the catalyst **3a** might make proper use of the noncovalent coordination site itself by the substrate. Thus, when the hydroxy group at the 4-position on the pyrrolidine ring makes a hydrogen bond with a substrate molecule in Michael reactions, the amide moiety at the 2-position on the pyrrolidine ring acts to control the equilibrium between enamine conformers and blocks one enamine face to afford a high enantioselectivity. Conversely, the amide alcohol moiety at the 2-position on the pyrrolidine ring facilitates hydrogen bonding with the substrate in direct aldol reactions. Moreover, theoretical study of the transition state structure of both the Michael and direct aldol reactions also provides insight into the origins of the concept to afford the observed high enantioselectivity in both reactions. Further studies, including catalyst design modifications and mechanistic investigations, are in progress.

Table 6
The catalytic asymmetric aldol reaction of some ketones and aldehydes[a]



Entry	R^1	X	Yield[c] (%)	*anti*/*syn*[d]	ee[e] (%)
1	Ph	CH_2	70	96:4	94
2	4-$NO_2C_6H_4$	CH_2	43	89:11	96
3[b]	3-$MeOC_6H_4$	CH_2	77	83:17	90
4	Ph	0	70	92: 8	96
5	Ph	S	52	>99:1	98
6	4-Pyridinyl	CH_2	68	83:17	93

[a] The reaction was performed with an aldehyde (0.4 mmol), a ketone (1.2 mmol), catalyst **3a** (0.02 mmol), and dry MeOH (0.2 mL) at −10 °C for 20 h.
[b] The reaction was carried out in water at room temperature.
[c] Isolated yields.
[d] The *syn*/*anti* ratio was determined by ^{1}H NMR and HPLC.
[e] The ee of the *anti* isomer was determined by chiral HPLC using a Daicel AD-H column and Daicel OD-H column.

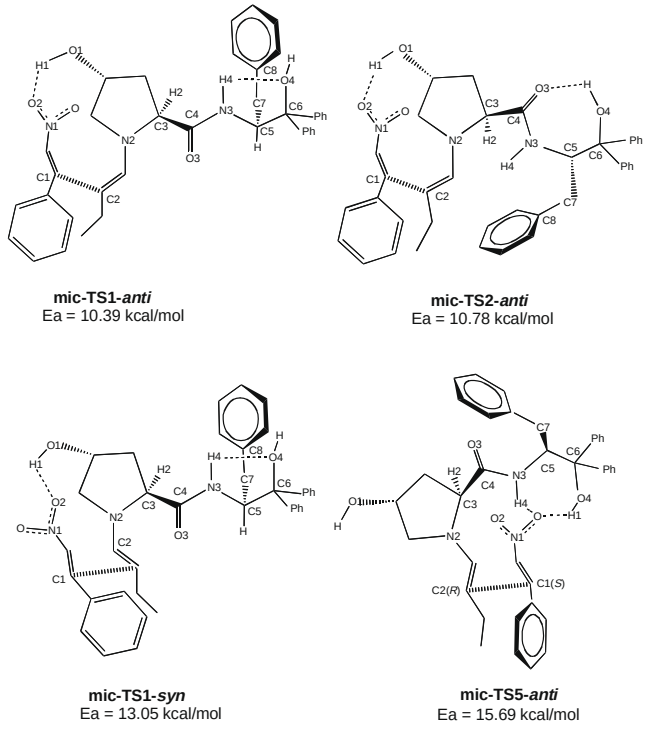


Figure 1. TS models in the Michael reaction.

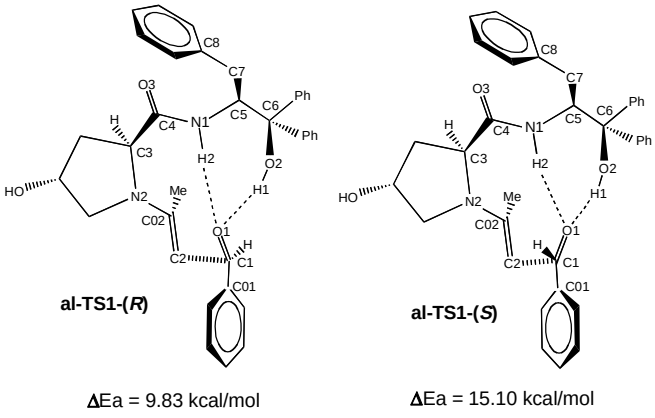


Figure 2. TS models in the direct aldol reaction.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.122.

References and notes

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