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

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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.

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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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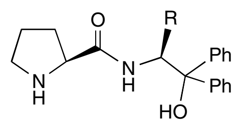
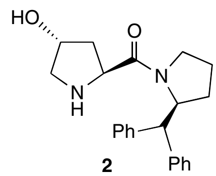


1

a: R=CH_2Ph
b: R=$CH_2CH(CH_3)_2$



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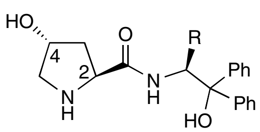
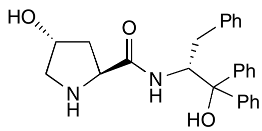
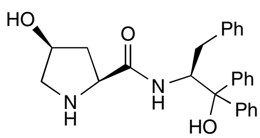


3a-c

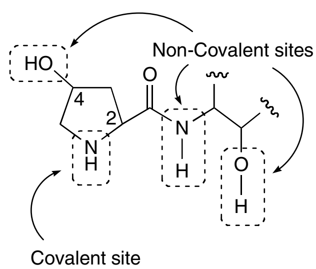
a: R=CH_2Ph, **b**: R=Ph
c: R=$CH_2CH(CH_3)_2$



3d



3e



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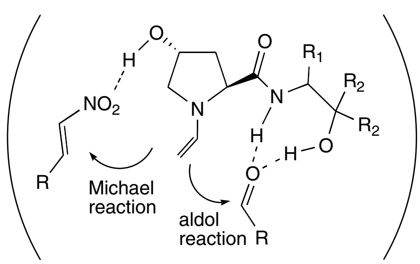
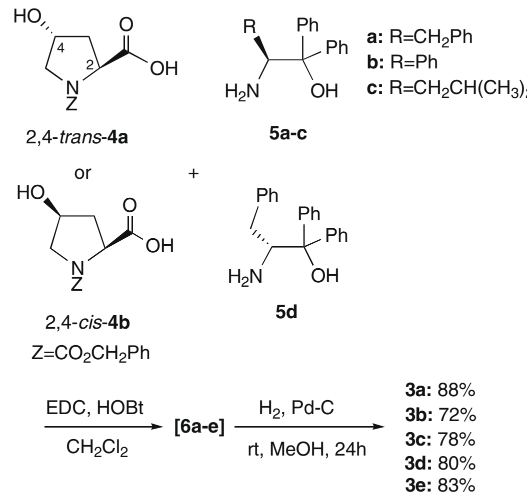


Scheme 1. Concept of catalyst design.

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

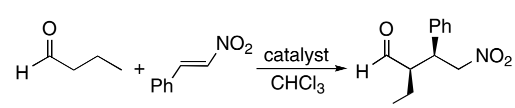


Scheme 2. Preparations of organocatalysts.

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	**la** (20)	rt	20	75	93:7	41
2	**lb** (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 ^1H-NMR and HPLC.
[d] The ee of the *syn* isomer was determined by chiral HPLC using a Daicel OD-H column.

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