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Enantioselective Michael Addition of Dicyanoolefins to α,β-Unsaturated Aldehydes in Aqueous Medium

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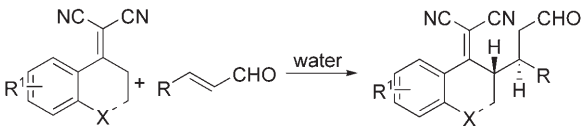
Abstract: A pool of water-compatible catalysts, namely dialkyl-(*S*)-prolinols, has been developed for the enantioselective direct vinylogous Michael addition reaction of vinylmalononitriles to α,β-unsaturated aldehydes in aqueous medium. In many cases, the products can be obtained in almost optically pure form (>96% *ee*) after a single recrystallization.

Keywords: dicyanoolefins; enantioselective Michael addition; organocatalysts; unsaturated aldehydes; water

Organic reactions in water have attracted tremendous attention because of the many advantages that they offer.[1] For example, organic reactions in/on water allow multistep syntheses to be carried out more efficiently without the need for protection-deprotection of the functional groups containing acidic protons. Furthermore compounds containing water molecules or biomolecules can also be used directly.

In the field of asymmetric synthesis, the development of water-compatible catalytic methods still remains a challenge, because most metal catalysts are unstable toward hydrolysis.[2] Water can also interfere with organocatalysis[3] given its capacity for disrupting hydrogen bonds and other polar interactions. To achieve highly catalytic activity and excellent enantioselectivity of organic reactions in water, much effort has been devoted to understanding the nature of the interrupting ionic interactions, hydrogen bonds, and hydrophobic interactions in aqueous media. Just recently, breakthrough contributions were made by the groups of Barbas,[4] Takabe,[4] and Hayashi.[5] They used proline-derived catalysts in the presence of water to demonstrate the direct asymmetric aldol reaction and the Michael reaction with high yields and with excellent diastereoselectivities and enantioselectivities. Thereafter, many organocatalysts have been designed for different enantioselective reactions under aqueous conditions, for example, chiral dialkylprolinol derivatives have been applied in asymmetric conjugate additions to provide high enantioselectivities using water as the only solvent.[6]

Very recently, it has been reported that α,α-dicyanoolefin compounds can selectively behave as acceptors or vinylogous donors in Michael reactions under easily controllable conditions, which simultaneously give multifunctional products with two vicinal chiral tertiary carbon centers.[7] Although a similar reaction has been reported to work in organic solvent,[7a] extending this method to aqueous medium requires the use of new organic catalysts. In conjunction with our interest in the development of new organic reactions in aqueous media for the functionalization of biomolecules,[8] our group has extensively studied the enantioselective direct vinylogous Michael addition reaction of vinylmalononitriles to α,β-unsaturated aldehydes in water. Herein, we report that the water-compatible catalysts derived from L-proline catalyze highly diastereo- and enantioselective direct vinylogous Michael addition reactions in water, resulting in the corresponding *anti*-Michael addition products in high enantioselectivities [Eq. (1)].



(1)

We envisaged that dialkyl-(*S*)-prolinols with alkyl chains as hydrophobic groups should assemble with hydrophobic reactants in water and sequester the transition state from water and, therefore, high asymmetric induction may be achieved in water. Thus, we

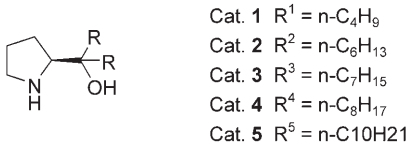


Figure 1. Structures of chiral dialkyl-(*S*)-prolinols.

synthesized a series of chiral dialkyl-(*S*)-prolinols (Figure 1) derived from L-proline and investigated their catalytic activities in asymmetric direct vinylogous Michael addition reactions in water.

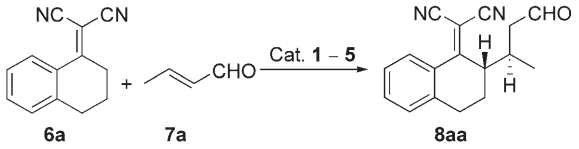
The catalytic activity of catalysts **1–5** for the asymmetric direct vinylogous Michael addition reaction was investigated by performing a model reaction of the vinylmalononitrile **6a** and crotonaldehyde **7a** in aqueous medium. The results are summarized in Table 1.

It is interesting to find that the vinylogous Michael addition reaction proceeds efficiently in water/brine in the presence of catalyst **2**/PNBA (20 mol%) at room temperature, the desired products were obtained with comparable yield and enantioselectivity (Table 1, entries 1 and 2). In order to increase the enantioselectivity, we hypothesized the reaction should be carried out at lower temperature. Therefore, brine was chosen as the solvent for further studies. By lowering the temperature to 0 °C, a significant increase in enantioselectivity was observed, but with a decrease in yield (Table 1, entry 3). However, when the reaction was carried out for 36 h under the same conditions, the product could be obtained in good yield and high enantioselectivity (Table 1, entry 11). Inferior results were obtained when the reactions were catalyzed by other catalysts (Table 1, entries 4–7). In all the reactions tested, only the *anti*-Michael addition products were obtained. Notably, catalyst **2** bearing a hexyl group provided the best results in both isolated yield and enantioselectivity.

Thus, catalyst **2** was selected for the subsequent studies. First, the influence of catalyst loading on the reaction was examined (Table 1, entry 8 *vs.* 3). It was found that there was no significant increase in the yield and enantioselectivity by increasing the catalyst amount to 30 mol%. However, the reaction proceeded sluggishly with a significant drop in enantioselectivity when the catalyst loading was reduced to 10 mol%. By decreasing the reaction temperature further to −10 °C, a comparable enantioselectivity was found, but there was a significant drop in yield (Table 1, entry 10). Therefore, the optimum reaction conditions were achieved by performing the reaction of 1 equiv. of dicyanoolefin with 4 equiv. of α,β-unsaturated aldehyde and 20 mol% catalyst loading at 0 °C in brine.

To examine the scope of the direct vinylogous Michael addition reactions by using the catalyst **2** in brine, a series of α,α-vinylmalononitriles (Figure 2) and α,β-unsaturated aldehydes were evaluated under the optimized reaction conditions, and the results are summarized in Table 2. In general, regardless of the alkyl- and aryl-, or heteroaryl-substituted α,β-unsaturated aldehydes, the reaction proceeded smoothly to afford the Michael adducts in 36 h with good diastereoselectivities and enantioselectivities. When cyclic substrates were used, only the *anti*-products were formed. When the acyclic substrate **6f** was tested, a major product was obtained in 75% *ee*. While the other diastereomer was found in 8% yield and 30% *ee*. Many of these products can be obtained in almost

Table 1. Screening of chiral dialkyl-(*S*)-prolinols for the vinylogous Michael addition reaction.[a]



Entry	Catalyst	Solvent	Temperatue [°C]	Time [h]	Yield [%]	*ee* [%][d]
1	**2**	water	r.t.	16	88	72
2	**2**	brine	r.t.	16	92	73
3	**2**	brine	0	16	72	88
4	**1**	brine	0	16	51	64
5	**3**	brine	0	16	61	86
6	**4**	brine	0	16	32	85
7	**5**	brine	0	16	65	85
8[b]	**2**	brine	0	16	76	89
9[c]	**2**	brine	0	16	38	56
10	**2**	brine	−10	16	45	88
11	**2**	brine	0	36	82	90

[a] The reaction was performed with **6a** (0.1 mmol), **7a** (0.4 mmol), brine (0.5 mL), and catalyst/PNBA (0.02 mmol).
[b] 30 mol% of catalyst was used in this reaction.
[c] 10 mol% of catalyst was used in this reaction.
[d] Determined by chiral-phase HPLC analysis.

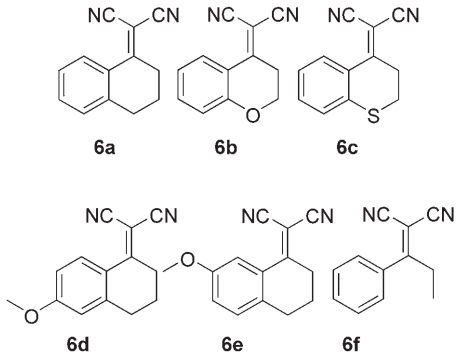
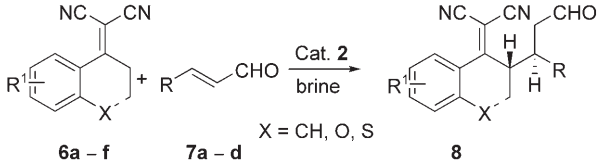


Figure 2. Structures of vinylmalononitriles **6**.

Table 2. Asymmetric vinylogous Michael addition of dicyanoolefins **6** to α,β-unsaturated aldehydes **7**.[a]



6a – f **7a – d** **8**

Entry	**6**	R	Product	Yield [%][b]	*ee* [%][c]
1	**6a**	Me (**7a**)	**8aa**	82	90 (96)[d]
2	**6b**	Me (**7a**)	**8ba**	79	92 (98)[d]
3	**6c**	Me (**7a**)	**8ca**	90	91 (98)[d]
4	**6d**	Me (**7a**)	**8da**	54	88
5	**6e**	Me (**7a**)	**8ea**	46	87
6	**6f**	Me (**7a**)	**8fa**	43/8	75
7	**6a**	Et (**7b**)	**8ab**	81	84
8	**6b**	Et (**7b**)	**8bb**	85	88
9	**6c**	Et (**7b**)	**8cb**	58	90 (>99)[d,e]
10	**6d**	Et (**7b**)	**8db**	64	84
11	**6a**	*n*-Pr (**7c**)	**8ac**	80	85
12	**6b**	*n*-Pr (**7c**)	**8bc**	84	87
13	**6c**	*n*-Pr (**7c**)	**8cc**	86	84
14	**6a**	C_6H_5 (**7d**)	**8ad**	83	85
15	**6b**	C_6H_5 (**7d**)	**8bd**	81	87
16	**6b**	4-ClC_6H_4 (**7e**)	**8be**	76	88 (98)[d]
17	**6b**	4-BrC_6H_4 (**7f**)	**8bf**	74	85 (96)[d]

[a] Reactions performed with 0.1 mmol of **6**, 0.4 mmol of **7**, 20 mol% of catalyst and 20 mol% PNBA in 0.5 mL of brine at 0 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral phase.
[d] After recrystallization with *i*-PrOH.
[e] The absolute configuration was determined to be C-11: *S*, C-13: *R* by X-ray crystallographic analysis.

optically pure form after a single crystallization from isopropyl alcohol (Table 2, entries 1, 2, 3, 9, 16, 17).

Enantiopure **8cb** (>99% *ee*), which contains a sulfur atom, was obtained by crystallizing slowly from isopropyl alcohol and the crystals were suitable for X-ray structural analysis. The relative and absolute configurations of the two contiguous stereogenic carbons in **8cb** could easily be determined by X-ray crystallographic analysis. As shown in Figure 3, the two newly created stereocenters of **8cb** were revealed to possess the (11*S*,13*R*)-configuration with an *anti*-relative stereochemistry.

In conclusion, we have developed new chiral water-compatible dialkylprolinol organocatalysts for the highly enantioselective direct vinylogous Michael addition reaction of vinylmalononitriles to α,β-unsaturated aldehydes in aqueous medium. Further work on applying this kind of chiral water-compatible organocatalyst for other organic transformations is in progress.

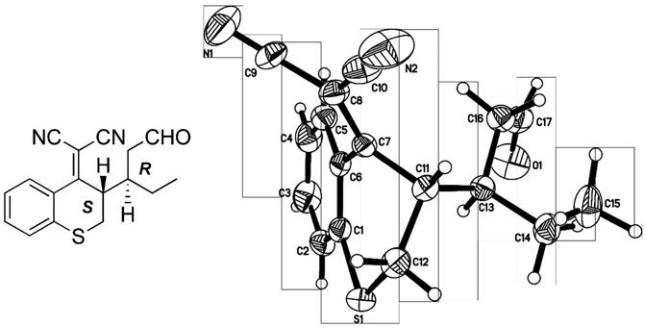


Figure 3. X-ray crystallographic structure of **8cb**.

Experimental Section

Typical Procedure for Direct Vinylogous Michael Addition Reaction: (Table 2, entry 1)

A mixture of **6a** (19.4 mg, 0.1 mmol), **7a** (32 μL, 0.4 mmol), catalyst **2** (5.4 mg, 0.02 mmol) and PNBA (3.4 mg, 0.02 mmol) in brine (0.5 mL) was stirred for 36 h at 0 °C. Then the reaction was quenched by adding 0.5 mL 1 M HCl. The mixture was extracted with EtOAc, dried with anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel to give the desired product **8aa** in 82% yield with 90% *ee*, as determined by HPLC (Chiralpak AS, 0% 2-propanol/hexane, 1 mL min^{-1}): t_{minor} = 18.756 min, t_{major} = 26.674 min.

Crystallographic Data

Crystal data for **8cb**: $C_{17}H_{16}N_2OS$, M = 296.38, orthorhombic, space group *P*212121, *a* = 7.2773(3), *b* = 8.1433(4), *c* = 25.9326(12) Å, V = 1536.80(12) $Å^3$, *Z* = 4, crystal size 0.28 × 0.24 × 0.04 mm, *T* = 223(2) K, Siemens P4 diffractometer, absorption coefficient 0.211 mm^{-1}, reflections collected 3002, independent reflections 2640 (R_{int} = 0.00572), refinement by full-matrix least-squares on F2, data/restraints/parameters 2640/0/191, goodness-of-fit on F2 = 1.080, final *R* indices [I > 2s(I)]: *R*1 = 0.0604, *wR*2 = 0.1621, *R* indices (all data): R_1 = 0.0511, wR_2 = 0.1411. Crystallographic data for the structure **8cb** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 668757. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information

Additional experiment procedures, ^1H and ^{13}C NMR, and HPLC spectra for reaction products are available as Supporting Information.

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