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Efficient and Highly Enantioselective Michael Addition of Aldehydes to Nitroalkenes Catalyzed by a Surfactant-type Organocatalyst in the Presence of Water

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It was found that in the presence of 20 mol % HCOOH, (*S*)-prolinol silyl ether organocatalyst bearing a long chain only in 2 mol % loading could catalyze the asymmetric Michael reaction of various aldehydes with *trans*-nitroalkenes at room temperature in the presence of water, giving the desired adducts in excellent yields with high diastereoselectivities and excellent enantioselectivities (up to >99% ee).

Presently organocatalysis is developing very rapidly and is playing increasingly important roles in the synthesis of organic molecules, especially in the construction of complex molecular skeletons.[1] Meanwhile, aqueous reactions have drawn much attention because water is environmentally benign, safe, and cheap as compared to organic solvents. Although there are reports on successful aqueous asymmetric reactions catalyzed by organocatalysts, the reactivities and selectivities of many organocatalysts reduce in the presence of water.[1–3] Recently, the surfactant organocatalysts, which contain both hydrophilic and hydrophobic moieties, proved very effective in aqueous organocatalytic reactions.[2,3] In 2006, Takabe et al. employed **1**/TFA to catalyze the direct Michael addition of ketones with β-nitrostyrene in brine, giving Michael adducts in good yields with high enantioselectivities (up to 97% ee) (Figure 1).[3a] In 2007, Palomo group found that in the presence of benzoic acid, pyrrolidine catalyst **2**, which formed emulsion easily with reaction mixture in the presence of water, could catalyze the Michael reaction of α,β-unsaturated aldehydes with nitromethane or benzyl malonate to furnish desired adducts in satisfactory yields with excellent enantioselectivities (up to 99% ee).[3b] Luo, Cheng et al. revealed that under the catalysis of surfactant imidazolium sulfate **3**, the Michael addition of cyclohexanone to β-nitrostyrenes was performed smoothly with high reactivities and excellent diastereoselectivities and enantioselectivities (up to 98% ee) in the presence of water.[3c] Very recently, Ni et al. developed a novel asymmetric Michael addition of aldehydes to nitroolefins on water, which was catalyzed by recyclable **4**/PhCOOH with hydrophilic groups and hydrophobic groups and provided the Michael adducts with excellent diastereo- and enantioselectivities (up to >99% ee).[3d] Because the Michael addition is one of the most important C–C bond-forming reactions in organic synthesis[4] and there are only a few reports[3a–3d] on the asymmetric Michael addition catalyzed by chiral surfactant organocatalysts in the presence of water, developing new chiral surfactant organocatalysts and their highly stereoselective Michael reaction in the presence of water is still a challenging subject. Herein we wish to present our recent investigation on the synthesis of surfactant-type organocatalysts and the efficient and highly enantioselective Michael addition of aldehydes to nitroalkenes in the presence of water.

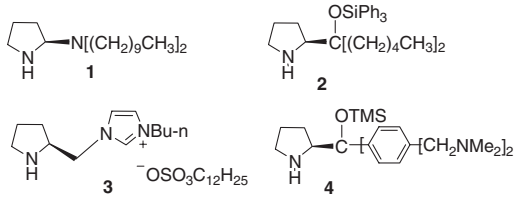
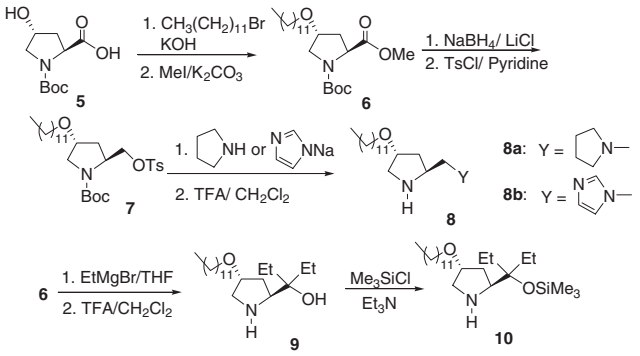


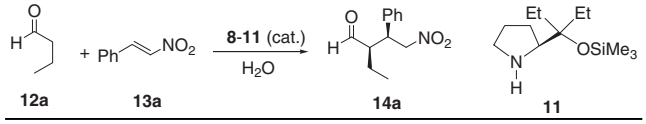
Figure 1.

Because many organocatalysts containing a chiral pyrrolidine backbone show excellent asymmetric induction, *trans*-4-hydroxy-L-proline was chosen as a starting material to introduce a hydrophobic group in the 4-position of the pyrrolidine backbone. Initially, *trans*-4-hydroxy-L-proline was reacted with $(Boc_2)O$ to give *N*-Boc-protected 4-hydroxyproline **5** in an excellent yield according to a literature method (Scheme 1).[5] In the presence of potassium hydroxide, **5** could be etherified smoothly by *n*-dodecyl bromide in DMSO to afford crude *N*-Boc-protected 4-dodecyloxylproline, followed by the reaction with methyl iodide in the presence of potassium carbonate, furnishing pyrrolidine ester bearing a long chain **6** in 86% yield for the two-step reaction.[6] Ester **6** was reduced smoothly with sodium borohydride in the presence of LiCl to give corresponding prolinol, followed by tosylation in pyridine to afford desired tosylate **7** in 88% yield for the two-step reaction.[7] After the reaction of tosylate **7** with pyrrolidine or imidazolyl sodium was performed, the successive deprotection of Boc by TFA in CH_2Cl_2 gave long chain pyrrolidines **8a** in 86% yield and **8b** in 88% yield respectively.[7b,8] Then, ester **6** was reacted with ethyl Grignard reagent, followed by deprotection of Boc with TFA, giving a long chain prolinol **9** in 87% yield for the two-step reaction.[3b] Finally, the reaction of prolinol **9** with TMSCl in CH_2Cl_2 afforded desired prolinol silyl ether bearing a long chain **10** in 93% yield.[3b]



Scheme 1. Synthesis of pyrrolidine organocatalysts bearing long chain **8**–**10**.

Table 1. Optimization of the Michael reaction of *n*-butyraldehyde with *trans*-β-nitrostyrene[a]

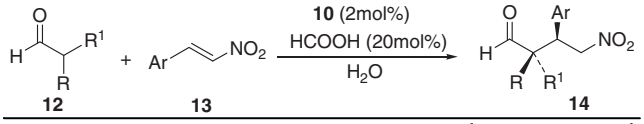


12a 13a 14a 11

Entry	Cat.	Acid	Time/h	Yield/%[b]	d.r.[c]	ee/%[d]
1	**8a**	—	36	24	n.d.	n.d.
2	**8b**	—	36	32	n.d.	n.d.
3	**9**	—	36	23	n.d.	n.d.
4	**10**	—	36	48	75:25	87
5	**8a**	AcOH	36	43	n.d.	n.d.
6	**8b**	AcOH	36	51	n.d.	n.d.
7	**9**	AcOH	36	42	n.d.	n.d.
8	**10**	AcOH	36	87	81:19	90
9	**11**	—	36	<5	n.d.	n.d.
10	**11**	AcOH	36	10	n.d.	n.d.
11	**10**	$PhCO_2H$	36	87	81:19	90
12	**10**	HCOOH	8	95	86:14	93
13[e]	**10**	HCOOH	26	92	91:9	94
14[e,f]	**10**	HCOOH	16	93	92:8	96

[a]The mixture of aldehyde **12a** (0.75 mmol), nitrostyrene (0.5 mmol), organocatalyst (5 mol %), acid (5 mol %), and water (0.5 mL) was stirred at room temperature. [b]Isolated yields. [c]d.r. (*syn*/*anti*) values were determined by ^{1}H NMR or HPLC. [d]Determined by chiral HPLC using a Chiralcel AD-H column. [e]2 mol % **10**. [f]20 mol % acid.

Table 2. Surfactant **10**/HCOOH-catalyzed Michael addition of aldehydes to *trans*-nitroalkenes in the presence of water[a]



12 13 14

14	R	R_1	Ar	Yield/%[b]	d.r.[c]	ee/%[d]
a	CH_3CH_2	H	C_6H_5	93	92/8	96
b	CH_3CH_2	H	4-BrC_6H_4	90	90/10	95
c	$(CH_3)_2CH$	H	C_6H_5	95	96/4	98
d	$(CH_3)_2CH$	H	4-$CH_3OC_6H_4$	94	94/6	96
e	$(CH_3)_2CH$	H	3-$CH_3OC_6H_4$	90	95/5	99
f	$(CH_3)_2CH$	H	1-$C_{10}H_7$	92	96/4	>99
g	$(CH_3)_2CH$	H	4-FC_6H_4	92	94/6	95
h	$CH_3(CH_2)_2$	H	C_6H_5	93	96/4	96
i	$CH_3(CH_2)_3$	H	C_6H_5	95	90/10	97
j	$CH_3(CH_2)_3$	H	4-$CH_3C_6H_4$	90	90/10	95
k	$CH_3(CH_2)_3$	H	1-$C_{10}H_7$	94	92/8	98
l	CH_3	CH_3	C_6H_5	90	—	93
m	$CH_3(CH_2)_5$	H	C_6H_5	91	93/7	94
n	$CH_3(CH_2)_5$	H	4-$CH_3OC_6H_4$	93	95/5	96

[a]The reaction of aldehyde **12** (0.75 mmol) with nitroalkene **13** (0.5 mmol) was performed for 12–18 h at rt in water (0.5 mL). [b]Isolated yields. [c]d.r. (*syn*/*anti*) values were determined by ^{1}H NMR or HPLC. [d]Determined by chiral HPLC using a Chiralcel AD-H column.

With the four chiral organocatalysts bearing a long chain **8a**, **8b**, **9**, and **10** in hand, we chose the Michael addition of *n*-butyraldehyde (**12a**) to *trans*-β-nitrostyrene (**13a**) as a model reaction to probe optimal reaction conditions. It was found that, when 5 mol % of chiral organocatalysts **8a**, **8b**, **9**, and **10** were employed, the Michael reaction occurred in the presence of pure water, but the yields of adduct **10a** were low (Entries 1–4, Table 1). When equimolar of acetic acid was added, which formed surfactant with the long chain amines **8a**, **8b**, **9**, or **10**, it was found that **10** resulted in remarkable increase of the yield up to 87% with good diastereoselectivity and high enantioselectivity (compare Entry 4 with 8, Table 1). The experiment also demonstrated that prolinol silyl ether without a long chain **11** led to a very poor yield under the same conditions as its long chain counterpart **10** (compare Entry 8 with 10, Table 1). Further optimal investigation revealed that using 5 mol % HCOOH instead of acetic acid resulted in the increase of enantioselectivity from 87 to 93% ee (compare Entry 8 with 12). Decreasing the amount of organocatalyst **10** from 5 to 2 mol % led to little increase of diastereoselectivity (*syn*/*anti*) from 86/14 to 91/9 (compare Entry 12 with 13, Table 1). Moreover, when the amount of HCOOH was increased to 20 mol %, our experiment demonstrated that the reaction rate was accelerated and the enantioselectivity was increased to 96% ee (compare Entry 13 with 14, Table 1).

In view of the condition experiments (Table 1), the optimized reaction should be catalyzed by 2 mol % diethylprolinol silyl ether **10** with 20 mol % HCOOH. In 2005, Hayashi et al. successively employed diphenylprolinol silyl ether to catalyze Michael reaction of aldehydes with nitroalkenes, furnishing desired adducts in good yields with excellent enantioselectivities (99% ee in most cases).[9a] In 2008, Ma et al. found that diphenylprolinol silyl ether also catalyzed Michael reaction of aldehydes with nitroalkenes in the presence of water, affording desired adducts in good yields with excellent enantioselectivities (>99% ee).[9b] Our experiment indicated that under the optimal conditions, diethylprolinol silyl ether bearing a long chain **10** could catalyzed the Michael reaction of *trans*-nitroalkenes **13** with various aldehydes **12** smoothly at room temperature, giving the desired adducts **14a**–**14n** in excellent yields (90–95%) (Table 2).[10,11] It was also found that for almost all aldehydes **12**, use of chiral catalyst **10** could result in high diastereoselectivities (*syn*/*anti* = 90/10–96/4) and excellent enantioseletivities (93– >99% ee) in the *nitro*-Michael reaction. For the Michael reaction of aldehyde with alkyl-substituted nitroalkene, the reaction of 3-methylbutanal with (*E*)-1-nitropent-1-ene was tried and it was found that the reaction yield was decreased dramatically. It should be noted that the physical appearances of the reaction mixtures were emulsions under stirring. The absolute configurations of the adducts **14a**–**14n** were assigned by comparison of the results of optical rotation and chiral HPLC with those of known compounds and all adducts **14a**–**14n** are dextrorotatary in $CHCl_3$.[8]

In conclusion, our experiments demonstrated that in the presence of 20 mol % HCOOH, prolinol silyl ether organocatalyst bearing a long chain **10** only in 2 mol % loading could efficiently catalyze the asymmetric Michael reaction of aldehydes **12** with *trans*-nitroalkenes **13** at room temperature in the presence of water, giving the desired adducts **14a**–**14n** in excellent yields (90–95%) with high diastereoselectivities (*syn*/*anti* = 90/10–96/4) and excellent enantioselectivities (93– >99% ee).

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10 General procedure for Michael addition of aldehydes to *trans*-nitroalkene: The mixture of aldehyde **12** (0.75 mmol), organocatalyst **10** (4.2 mg, 0.01 mmol), and HCOOH (9 mg, 0.20 mmol) in water (0.5 mL) was stirred at room temperature for 5 min. Then, powdered *trans*-nitroalkene **13** (0.5 mmol) was added and the reaction mixture was stirred at room temperature. After the reaction was completed (about 12–18 h monitored by TLC), the mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (petroleum ether/AcOEt as eluent) to give the Michael adducts **14a**–**14n**.

11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

