Highly Enantioselective (*S*)-Homoproline-catalyzed Michael Addition Reactions of Ketones to β-Nitrostyrenes

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(Received March 25, 2005; CL-050404)

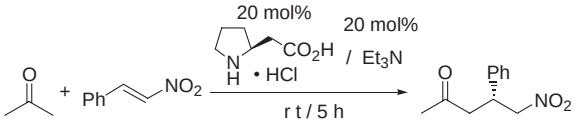
Being catalyzed by (*S*)-homoproline a highly enantioselective organocatalytic Michael addition reaction of ketones to β-nitrostyrenes has been achieved.

The Michael reaction is widely used as one of the most important carbon–carbon bond-forming reactions in synthetic organic chemistry.[1] Particularly, the asymmetric Michael reaction to nitroalkenes[2] is a very attractive method for the construction of useful chiral building blocks of various natural products, because the nitro group is easily transformed into an amino group, nitrile oxide and so on. Recently, L-proline or its derivatives-catalyzed asymmetric carbon–carbon bond-forming reactions such as aldol reaction,[3] the Michael addition,[4] and Mannich-type reaction[5] were studied intensively by many organic chemists. Excellent enantioselectivity was attained in various types of organocatalytic asymmetric reactions, but the Michael addition has some serious limitations. For example, there are scattered examples over 90% ee, and substrate generality is not so high. Therefore, the development of a more efficient organocatalytic and enantioselective Michael reaction was required in asymmetric synthesis.

On the other hand, we have recently developed highly efficient organocatalytic asymmetric acylation of a wide variety of racemic alcohols and *meso*-diols catalyzed by a chiral 1,2-diamine derived from (*S*)-proline.[6] And then, we have accomplished an efficient and practical synthesis of (*S*)-homoproline, which is a one-carbon homologated proline, starting from (*S*)-proline in 7 steps.[7] (*S*)-Homoproline seems to be a potentially interesting organocatalyst, but no examples using (*S*)-homoproline itself in asymmetric synthesis has been reported so far. We envisaged that (*S*)-homoproline might catalyze highly enantioselective carbon–carbon bond formation such as aldol reaction and the Michael addition. Herein, we wish to report the highly enantioselective Michael addition of ketones to β-nitrostyrenes catalyzed by (*S*)-homoproline.

Initially, we tried the Michael addition of acetone to *trans*-β-nitrostyrene under the influence of 20 mol % of (*S*)-homoproline hydrochloride and triethylamine which was added in order to remove HCl in (*S*)-homoproline hydrochloride in various solvents at room temperature for 5 h. The results are summarized in Table 1. The Michael addition in DMSO gave the desired Michael adduct in 27% chemical yield with 25% optical yield,[8] and an undesired dinitro adduct was also obtained as a by-product (Run 1). The use of DMF as a solvent gave comparable enantioselectivity to DMSO (Run 2). THF and CH_2Cl_2 gave higher enantioselectivity than DMSO or DMF, but the reaction proceeded slowly (Runs 3 and 4). Acetonitrile gave a poor result (Run 5). Using alcohols as a solvent improved both the chemical yield and optical yield (Runs 6–9). MeOH gave the corresponding Michael adduct in 19% chemical yield with 32% optical yield (Run 6). EtOH and *i*-PrOH promoted the reaction more efficiently than MeOH and gave the corresponding Michael adduct in moderate chemical yields (Runs 7 and 8). The highest enantioselectivity was observed by using *t*-BuOH in 37% ee (Run 9). Furthermore, when the reaction time in *t*-BuOH became longer (24 h), the corresponding Michael adduct was obtained in 88% chemical yield and 42% optical yield (Run 10). The reaction in no solvent was not effective (Run 11).

Table 1. (*S*)-Homoproline-catalyzed asymmetric Michael addition in various solvents[a]



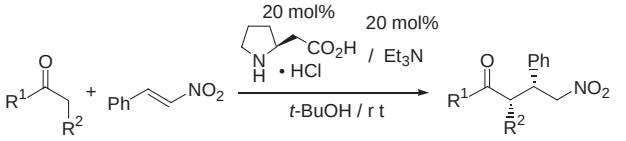
Run	Solvent	Yield[b]/%	ee[c]/%
1	DMSO	27	25
2	DMF	33	25
3	THF	5	32
4	CH_2Cl_2	5	37
5	CH_3CN	7	13
6	MeOH	19	32
7	EtOH	51	28
8	*i*-PrOH	49	28
9	*t*-BuOH	39	37
10[d]	*t*-BuOH	88	42
11	neat	11	35

[a]Molar ratio of acetone:nitrostyrene:homoproline:Et_3N = 45:1:0.2:0.2. [b]Isolated yield. [c]Determined by HPLC analysis with a chiral column. [d]Reaction was performed for 24 h.

Next, we examined a variety of Michael donors in *t*-BuOH (Table 2). The Michael addition of ethyl methyl ketone as a Michael donor catalyzed by 20 mol % of (*S*)-homoproline proceeded with high enantioselectivity compared with acetone (Run 1). The use of *N*-methylmorpholine in place of triethylamine gave similar enantioselectivity (Run 2). The best result in enantioselectivity was obtained using diethyl ketone as a Michael donor. Diethyl ketone needed longer reaction time and yielded the desired Michael adduct in 51% chemical yield with 94% ee which is the best ee among those reported so far for this substrate (Run 4). 2-Hexanone has lower reactivity and comparatively high enantioselectivity (Run 5). When cyclohexanone was used, the reaction smoothly proceeded for 20 h, and yielded the corresponding Michael adduct in 90% chemical yield with 90% ee (Run 6).

Finally, we demonstrated a successful Michael addition with various Michael acceptors using cyclohexanone as a Michael donor. As is evident from the successful results shown in Table 3,[9] (*S*)-homoproline is quite effective in many instances and produc-

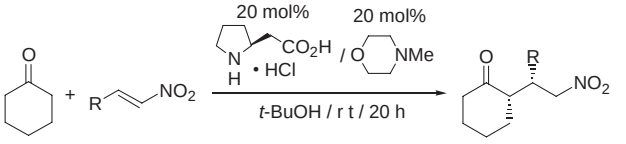
Table 2. (*S*)-Homoproline-catalyzed asymmetric Michael addition with various Michael donors[a]



Run	R^1	R^2	Time	Yield[b] /%	rr[c]	*syn*: *anti*[d]	ee[e] /%
1	Me	Me	24 h	71	61:39 (80)[f]	93:7	72
2[g]	Me	Me	24 h	79	57:43 (84)[f]	92:8	73
3	Et	Me	8 d	68	—	92:8	90
4[g]	Et	Me	8 d	51	—	98:2	94
5[g]	Me	*n*-Pr	5 d	54	59:41 (76)[f]	92:8	81
6[g]	-$(CH_2)_4$-		20 h	90	—	98:2	90

[a]Molar ratio of nitrostyrene:homoproline:Et_3N = 1:0.2:0.2. [b]Isolated yield. [c]Regioisomeric ratio (non-terminal:terminal). [d]Determined by ^{1}H NMR of crude product. [e]Determined by HPLC analysis with a chiral column. [f]Enantiomeric excess of terminal regioisomer in parenthesis. [g]20 mol % of *N*-methylmorpholine was used instead of Et_3N.

Table 3. (*S*)-Homoproline-catalyzed asymmetric Michael addition with various Michael acceptors[a]



Run	R	Yield[b]/%	*syn*:*anti*[c]	ee[d]/%
1	C_6H_5	90	98:2	90
2	4-ClC_6H_4	85	88:12	93
3	4-NCC_6H_4	95	84:16	96
4	4-MeC_6H_4	77	96:4	90
5	4-$MeOC_6H_4$	72	94:6	77
6[e]	2-naphthyl	79	94:6	92

[a]Molar ratio of ketone:nitrostyrene:homoproline:*N*-methylmorpholine = 2:1:0.2:0.2. [b]Isolated yield. [c]Determined by ^{1}H NMR of crude product. [d]Determined by HPLC analysis with a chiral column. [e]Reaction was performed for 24 h.

es the desired products in high stereoselectivity and enantioselectivity. Using 4-chloronitrostyrene and 4-cyanonitrostyrene having an electron-withdrawing group showed higher enantioselectivity (Runs 2 and 3). Nitrostyrene derivatives having an electron-donating group gave higher diastereoselectivity (Runs 4 and 5). When 2-(2-nitrovinyl)naphthalene was used as a Michael acceptor, the corresponding Michael adduct was obtained in 79% chemical yield with 92% enantiomeric excess (Run 6).

In conclusion, we have developed a novel asymmetric Michael addition reaction of ketone to β-nitrostyrene and its derivatives using (*S*)-homoproline as a chiral organocatalyst. The reaction was performed in a highly diastereoselective and enantioselective manner over 90% ee. Further studies to extend the various asymmetric carbon–carbon bond-forming reactions and to exploit the usefulness of (*S*)-homoproline are currently underway in our laboratory.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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8 The absolute configurations of all Michael adducts were determined by comparison of optical rotation with reported value.[4]
9 Typical experimental procedure is as follows (Table 3, Run 1): To a solution of (*S*)-homoproline hydrochloride (9.9 mg, 0.06 mmol) in *t*-BuOH (0.5 mL) were added cyclohexanone (63 μL, 0.6 mmol) and *N*-methylmorpholine (7 μL, 0.06 mmol). After stirred for 30 minutes, nitrostyrene (44.8 mg, 0.3 mmol) in *t*-BuOH (1 mL) was added, and stirred for additional 20 h at room temperature. The reaction was quenched with saturated NH_4Cl, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by TLC gave 2-(1-phenyl-2-nitroethyl)cyclohexanone (66.2 mg, 0.27 mmol).

Published on the web (Advance View) June 4, 2005; DOI 10.1246/cl.2005.962