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4,4′-Disubstituted-L-proline Catalyzes the Direct Asymmetric Michael Addition of Aldehydes to Nitrostyrenes

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Abstract: In a search for small organic molecules as catalysts for the direct asymmetric Michael addition reaction of aldehydes to nitrostyrenes, 4,4′-di(naphthalene-1-ylmethyl)-L-proline **1c** and a catalytic amount of 4-dimethylaminopyridine (DMAP) were found to be an efficient system for the Michael addition of aldehydes to nitrostyrenes with high diastereo- and enantioselectivity and broad substrate range.

Keywords: diastereoselectivity; 4-dimethylaminopyridine (DMAP); disubstituted-L-prolines; enantioselectivity; Michael addition; organocatalysis

Nitroalkanes are versatile synthetic intermediates in organic synthesis owing to the various possible transformations of the nitro group into other useful functional groups. As one useful synthetic method for the preparation of nitroalkanes, the Michael addition of ketones or aldehydes to nitroalkenes has attracted much attention.[1] Since L-proline and L-proline-based catalysts for the direct asymmetric Michael reaction to give the nitroalkanes with poor to good enantioselectivity were reported,[2–4] much effort has been paid to the development of an organocatalytic asymmetric Michael reaction of ketones or aldehydes with nitroolefins.[5–13] Kotsuki et al. reported a chiral pyrrolidine-pyridine conjugate base catalyst and tetrazole derivative in the Michael reactions of ketones with nitroolefins with excellent results, however, with an aldehyde as the donor, poor enantioselectivity resulted.[8] Pyrrolidine-sulfonamide[14] and diphenylprolinol silyl ethers[15] were employed in the Michael additions of aldehydes to nitroolefins as excellent catalysts. Very recently, 3,3′-bimorpholine derivatives,[16] *trans*-4-hydroxyprolylamide,[17] a chiral primary amine-thiourea catalyst[18a] and L-prolinol[18b] were also developed as efficient organocatalysts for the Michael addition of aldehydes to nitroolefins with excellent enantioselectivities.

Despite the excellent results achieved by these systems, the development of a catalytic direct asymmetric Michael addition of aldehydes to nitroolefins, to construct the two chiral centers at the same time, is still a worthwhile endeavor. We have designed a new organocatalyst consisting of 4,4′-disubstituted-L-prolines **1** which efficiently catalyzed the asymmetric aldol reaction of acetone and various aldehydes with excellent enantioselectivies.[19] Herein, we describe the asymmetric Michael addition of aldehydes to nitroolefins catalyzed by 4,4′-disubstituted-L-prolines **1a–c** (Figure 1) resulting in the the desired adducts with good yields and high enantioselectivities of up to 95% *ee*.

To optimize the reaction conditions, the reaction of isovaleraldehyde with nitrostyrene as a probe in the presence of 4,4′-disubstituted-L-proline **1** under various conditions was investigated thoroughly (Table 1). To our delight, the intruduction of the bulky group on the pyrrolidine ring at the 4-position (catalysts **1b** and **1c**) increased the enantioselectivity (Table 1, entries 1, 2 and 5). The higher loading of the catalyst **1c** led to a higher yield of the product with a lower disastereoselectivity (Table 1, entries 3–5). A recent report has shown that the use of DMAP or imidazole as an additive could facilitate the catalytic asymmetric Baylis–

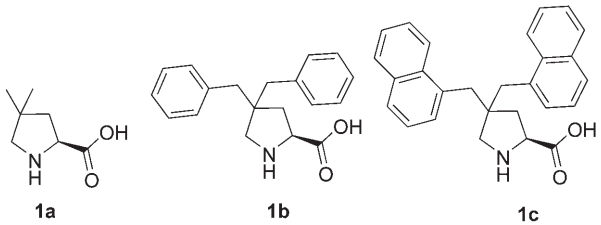
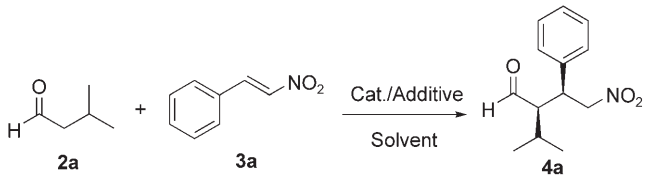


Figure 1. 4,4′-Disubstituted prolines.

Table 1. Catalytic asymmetric Michael addition of aldehyde (**2a**) to nitrostyrene (**3a**) under various conditions.



2a **3a** **4a**

Entry	Catalyst	Loading [mol%]	Temperature [°C]/Time [h]	Additive [mol%]	Solvent	Yield [%][a]	*dr* (*syn*/*anti*)[b]	*ee* [%][c]
1	**1a**	20%	r.t./72	-	*i*-PrOH	71	>98/2	43
2	**1b**	20%	r.t./72	-	*i*-PrOH	73	86/14	64
3	**1c**	5%	r.t./48	-	*i*-PrOH	10	98/2	76
4	**1c**	10%	r.t./48	-	*i*-PrOH	21	98/2	76
5	**1c**	20%	r.t./72	-	*i*-PrOH	76	89/11	76
6	**1c**	20%	r.t./72	DMAP (20)	*i*-PrOH	87	75/25	87
7	**1c**	20%	0°C/72	DMAP (20)	*i*-PrOH	87	89/11	90
8	**1c**	20%	0°C/72	DMAP (20)	MeOH	71	93/7	87

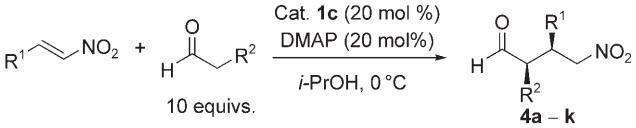
[a] Yield of isolated product.
[b] Determined by ^{1}H NMR.
[c] Reported values refer to the *syn* isomer and were determined by HPLC on a chiral stationary phase.

Hillman reaction.[20] Upon the addition of 4-dimethylaminopyridine (DMAP; 20 mol%), the reaction proceeded more effectively with higher enantioselectivity, albeit with a slight decrease in diastereoselectivity (Table 1, entries 6 and 7). The lower temperature seemed beneficial for the diastereoselectivity and the enantioselectivity of the adduct (Table 1, entry 7). The use of methanol led to a decrease in enantioselectivity and yield of adduct (Table 1, entry 8).

Under the optimal reaction conditions, we next examined the scope of the reaction with various aldehydes and nitroolefins (Table 2). All reactions were performed in *i*-PrOH at 0°C in the presence of 20 mol% of catalyst **1c** and 20 mol% DMAP. In each case, Michael adducts were obtained with good yields (up to 89%), high enantioselectivities (up to 95% *ee*), and disastereoselectivities (up to *syn/anti* 98/2). Various nitroolefins were reacted smoothly with isovaleraldehyde at almost the same high levels of diastereoselectivity and enantioselectivity (Table 2, entries 1–3). Both propanal and *n*-butanal were employed successfully as the Michael donors to afford the adducts with high *ee* values, albeit with moderate diastereoselectivies, probably due to the small bulk of the methyl and ethyl groups in the enamine transition states (Table 2, entries 4 and 5). High enantioselectivity and disastereoselectivity were achieved with increasing bulkiness of the substituents on the aldehyde donor, which proved the past assumption to be reasonable (Table 2, entries 6, 7 and 8). However, isobutyraldehyde was found to be a poor donor, in its reaction with nitrostyrene and 1-bromo-4-[(*E*)-2-nitrovinyl]-benzene, products were obtained with only moderate enantioselectivies with 67% *ee* and 70% *ee*, respectively (Table 2, entries 9 and 10). Low diastereoselectivity (*syn*/*anti* 71/29) and moderate enantioselectivity (73% *ee*) were observed in the reaction of propanal to (*E*)-2-(benzyloxy)-1-methoxy-4-(2-nitrovinyl)benzene (Table 2, entry 11), which may be ascribed to the electon-donating group and bulkiness of the substituents on the nitroolefin. No product was obtained under the conditions when using isovaleraldehyde as a donor and (*E*)-3-methyl-1-nitrobut-1-ene as an acceptor (Table 2, entry 12) due to the bulky substituents of the donor and the acceptor.

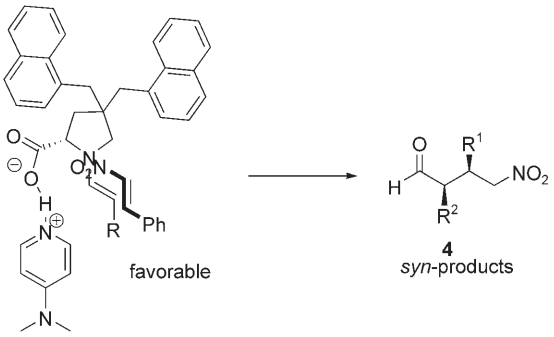
The relative and absolute configurations of the Michael adducts were determined by comparison of ^{1}H NMR spectroscopic data and optical rotation with those of known compounds.[21] The *syn* selectivity we observed is in accordance with Seebach's model.[22] Herein, a model has been proposed to explain the decrease of the diastereoselectivity and the increase of the enantioselectivity of the adducts, in which there are favorable electrostatic interactions between the nitrogen of the enamine and the nitro group in the transition state. The bulkness of the α-methylnaphthyl group is a key factor for the high level of stereocontrol. And the stronger interaction between phenyl and R group together with the DMAP group hindered the *re*-face approach of nitrostyrene, and the reaction afforded the products with higher *ee* values (Scheme 1). Very recently, Clarke's group reported the self-assembly of organocataysts, the result of which showed that the addition of achiral bases could increase the enantioselectivity dramtically.[23] The proposed approach of self-assembly of organocataysts indicated that hydro-

Table 2. Michael additions of aldehydes to nitrostyrenes.



Entry	R^1	R^2	Time [h]	Yield [%][a]	dr (*syn*/*anti*)[b]	*ee* (%)[c]	Product
1	Ph	*i*-Bu	72	87	89/11	90	**4a**
2	4-BrC_6H_4	*i*-Bu	72	75	88/12	91	**4b**
3	α-naphthyl	*i*-Bu	72	89	90/10	87	**4c**
4	Ph	Et	2	77	80/20	94	**4d**
5	Ph	*n*-C_3H_7	24	76	77/23	95	**4e**
6	Ph	*n*-C_4H_9	24	66	98/2	90	**4f**
7	Ph	*n*-C_5H_{11}	24	74	98/2	86	**4g**
8	Ph	*n*-C_6H_{13}	24	79	89/11	94	**4h**
9	Ph	*i*-Pr	72	73	-	67	**4i**
10	4-BrC_6H_4	*i*-Pr	72	80	-	70	**4j**
11	3-OBn-4-OMe-C_6H_3	Et	48	78	71/29	73 (58)[d]	**4k**
12	*i*-Pr	*i*-Bu	48	n.d.	-	-	-

[a] Yield of isolated product.
[b] Determined by ^{1}H NMR.
[c] Reported values refer to the *syn* isomer and were determined by HPLC on a chiral stationary phase.
[d] This is the *ee* of the *anti* isomer.



Scheme 1. Possible transition state.

gen bonding between precatalysts and the achiral bases is important for stereocontrol, which is similar to our proposed model.[24]

In summary, we have demonstrated that 4,4′-disubstituted-L-proline **1c** is an efficient organocatalyst for the asymmetric Michael addition of various aldehydes to various nitrostyrenes with good yields, high diastereoselectivities and enantioselectivities in the presence of DMAP.

Experimental Section

Typical Procedure for the Michael Reaction using the Catalyst 1c in *i*-PrOH

The following procedure for the reaction of isovaleraldehyde (**2a**) with nitrostyrene (**3a**) in *i*-PrOH using catalyst **1c** is representative. To a mixture of catalyst **1** (20 mg, 0.05 mmol), DMAP (6 mg, 0.05 mmol) and isovaleraldehyde **2a** (0.28 mL, 2.5 mmol) in *i*-PrOH (1.0 mL) nitrostyrene **3a** (37 mg, 0.25 mmol) was added at 0 °C under 1 atm of argon. The reaction mixture was stirred for 3 d, then quenched with 5 mL saturated NH_4Cl, extracted with ethyl acetate (3×5 mL), and dried with over Na_2SO_4. Purification by flash chromatography (hexane/EtOAc, 18/1) afforded the product. The relative and absolute configurations of the Michael adducts were determined by comparison with ^{1}H NMR spectroscopic analysis and optical rotation. The enantiomeric excess was determined by HPLC with Daicel Chiralpak AS, AD or OD-H columns.

Acknowledgements

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[24] When the reactants, catalyst and DMAP were mixed, the solution became cloudy while the solution is very clear if DMAP was not added. In point of fact, we presumed that the salt of the catalyst and DMAP may form. However, we have no further experimental evidence to confirm it.

