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L-Proline derived triamine as a highly stereoselective organocatalyst for asymmetric Michael addition of cyclohexanone to nitroolefins

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Abstract—L-Proline derived triamine **4** has been developed as a highly efficient and stereoselective organocatalyst for the asymmetric Michael addition of cyclohexanone to nitroolefins. In the presence of $(CF_3SO_2)_2NH$, **4** catalyzed the reaction of cyclohexanone to a variety of nitroolefins with high yields (up to 99%) and excellent diastereoselectivities (up to 99:1 dr) and enantioselectivities (up to 98% ee).

1. Introduction

The Michael addition is one of the most important carbon–carbon bond-forming reactions in organic synthesis. Asymmetric organocatalytic Michael addition has attracted intense interests in the recent few years due to its environmental friendliness and the generation of multiple stereogenic centers in a single step.[1–4] So far quite a number of chiral small organic molecules have been developed as stereoselective catalysts for this transformation.[1–4] L-Proline **1** was first reported to catalyze the intermolecular Michael addition of carbon nucleophiles to nitroolefins, which, however, afforded the adducts with poor enantioselectivity, albeit with good diastereoselectivity.[2] Later, various catalysts were designed and synthesized based on proline and applied to this reaction, and significantly improved efficiencies, diastereoselectivities, and enantioselectivities were obtained.[3,4] Most of these catalysts take advantage of the carboxylic acid function of proline to install steric shielding and/or substrate-orienting functional groups.[3] Recently, Palomo presented the first example of highly stereoselective catalysts that make use of a *trans*-4-hydroxyl group on the pyrrolidine ring of proline for the steric orientation of the acceptor.[4a] Herein, we report a new catalyst **4** (Fig. 1) that resorts to the assistance of a *cis*-4-pyrrolidin-1-yl group on the pyrrolidine ring for achieving high stereoselectivity in the asymmetric Michael addition of cyclohexanone to nitroolefins.

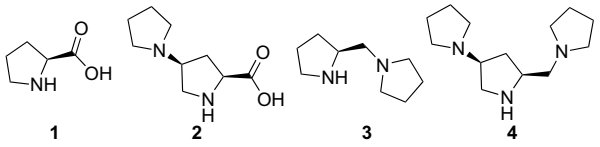

Figure 1. Structures of the catalysts.

In our previous studies, the *cis*-4-pyrrolidin-1-yl group on the pyrrolidine ring was found to have a significantly beneficial effect on the stereoselectivity of catalyst **2** for the asymmetric aldol reaction.[5] We were interested in examining if such an effect still remains for the Michael addition. Thus, catalysts **2** and **4** were tested in the Michael addition of cyclohexanone with nitroolefins. The parent catalysts **1** and **3** were also tested under identical conditions for comparisons.

2. Results and discussion

Compound **4** was easily prepared starting from the commercially available *trans*-4-hydroxy-L-proline according to Scheme 1. The preparation commenced with the protections of the pyrrolidine and the carboxylic acid functions of *trans*-4-hydroxy-L-proline following known procedures.[6] The reduction of the protected intermediate **5** with lithium aluminum hydride followed by mesylation provided

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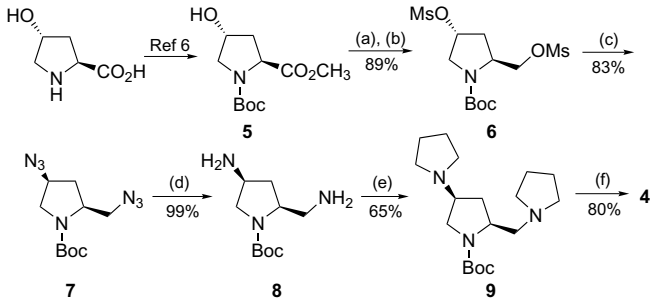


Scheme 1. Preparation of organocatalyst **4**. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) NaN_3, DMF, 60 °C, 12 h; (d) Pd/C (5%), H_2, MeOH, 35 °C, 5 h; (e) $Br(CH_2)_4Br$, Et_3N, DMF, 60 °C, 10 h; (f) TFA, CH_2Cl_2, rt, 12 h.

dimesylate **6** in high yield. Reaction of **6** with sodium azide afforded the diazido compound **7** in 83% yield. Hydrogenolysis of **7** in the presence of 5% Pd/C gave **8** in a nearly quantitative yield. Treatment of **8** with 1,4-dibromobutane resulted in the production of **9** in 65% yield. After the removal of the *N*-Boc protecting group using trifluoroacetic acid (TFA), the desired catalyst **4** was obtained with an overall yield of 35%.

Catalysts **1**–**4** were first checked in the model reaction of cyclohexanone **10** with nitrostyrene **11a** in DMSO at room temperature with a catalyst loading of 20 mol %. As illustrated in Table 1, Compounds **2** and **4** exhibited significantly higher enantioselectivities, albeit similar diastereoselectivities compared to the parent catalysts **1** and **3**, respectively, in the absence of additive (entries 3 and 7 vs 1 and 5, respectively). This clearly indicates that the *cis*-4-pyrrolidin-1-yl group has beneficial effects on the stereoselectivities of catalysts **2** and **4**, which became even more significant when 20 mol % TFA was added to the reaction (entries 4 and 8 vs 2 and 6, respectively).[7] Furthermore, in the presence of TFA, the diastereoselectivity and reactivity of catalyst **4** were also significantly improved upon.[8] Thus, catalyst **4** displayed a well-balanced high reactivity, diastereoselectivity, and enantioselectivity in the presence of TFA, affording 94% yield, 92/8 dr and 89% ee (entry 8).

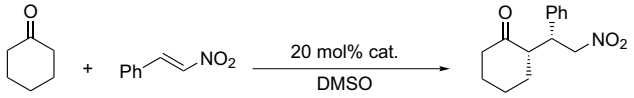
To further optimize the reaction conditions, we next examined the influences of different reaction parameters on the performance of catalyst **4** in the presence of TFA in the Michael addition of **10** to **11a**. The solvent effects were first assessed. DMSO, DMF, THF, acetonitrile, diethyl ether, chloroform, toluene, and ^{i}PrOH, all afforded similarly good yields, drs and ee values at room temperature (Table 2, entries 1–8).[9] ^{i}PrOH gave an overall best result with 92% yield, 93:7 dr and 90% ee (entry 8). Similarly high drs and ee values were also observed in MeOH, H_2O, and brine (entries 9–11). However, the reaction is much slower in these solvents. When the temperature was lowered to 0 °C, the diastereoselectivity and enantioselectivity were both slightly improved with ^{i}PrOH as the solvent (entry 12). Although the reaction rate did decrease to a large extent at this temperature, it recovered after the concentration of **11a** was increased from 0.1 to 0.5 M without the

Table 2. Optimization of the reaction conditions[a]

Entry	Solvent	Time (h)	Yield (%)	dr (*syn*/*anti*)	ee (*syn*) (%)
1	DMSO	5	95	92/8	89
2	DMF	10	83	92/8	87
3	THF	10	95	96/4	85
4	CH_3CN	10	99	91/9	91
5	Et_2O	10	99	96/4	86
6	$CHCl_3$	10	99	93/7	89
7	Toluene	10	99	96/4	87
8	^{i}PrOH	10	92	93/7	90
9	CH_3OH	10	65	95/5	90
10	H_2O	10	30	89/11	89
11	Brine	10	49	94/6	89
12[b]	^{i}PrOH	72	80	96/4	94
13[c]	^{i}PrOH	24	91	94/6	93

[a] Unless stated otherwise, conditions: [**11a**] = 0.1 mol/L, 20 mol % **4**/TFA, room temperature, solvent/cyclohexanone = 2:1.
[b] The reaction temperature is 0 °C.
[c] The reaction temperature is 0 °C and the concentration of **11a** is 0.5 mol/L.

Table 1. The organocatalytic Michael addition of cyclohexanone to nitrostyrene[a]



10 **11a** **12a**

Entry	Catalyst	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*) (%)
1	**1**	94	94/6	33
2	**1**/TFA	92	96/4	22
3	**2**	65	95/5	52
4	**2**/TFA	49	94/6	55
5	**3**	45	87/13	73
6	**3**/TFA	99	93/7	81
7	**4**	61	86/14	80
8	**4**/TFA	94	92/8	89

[a] Unless stated otherwise, conditions: [**11a**] = 0.1 mol/L, solvent/cyclohexanone = 2:1, room temperature, 5 h.
[b] Isolated yield of mixture of *syn*/*anti* based on nitrostyrene.
[c] Diastereomeric ratio, determined by chiral-phase HPLC analysis.
[d] Enantiomeric excess, determined by chiral-phase HPLC analysis.

sacrifice of either diastereoselectivity or enantioselectivity (entry 13).

The effects of other Brønsted acids were also examined with catalyst **4** in the Michael addition reaction of **10** to **11a**. As illustrated in Table 3, the reaction rate varies dramatically with different acids. The reaction is faster with the relatively weak acids such as acetic acid, $(CF_3SO_2)_2NH$, benzoic acid, and 4-$CF_3C_6H_4OH$, than with the strong acids such as TFA, *p*-TsOH, and D-(+)-camphor sulfonic acid (entries 1–8). However, the reaction dramatically slows down if the acidity of the acid is too weak (entries 9 and 10). On the other hand, only small deviations of the diastereoselectivity and enantioselectivity were observed with different acids. The highest dr and ee value were observed with $(CF_3SO_2)_2NH$ (entry 5). Although the reaction is not the most active with this acid, it is reasonably efficient and could be completed within 20 h, affording 95% yield, 99/1 dr and 94% ee (entry 11).

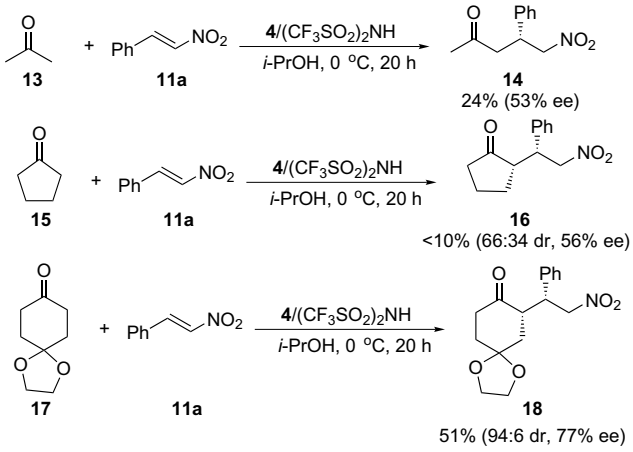
Having established the optimal reaction conditions, we next examined other nitroolefins to expand the substrate scope of catalyst **4**. As shown in Table 4, high isolated yields were obtained for all the selected nitroolefins regardless of the electronic nature of the aromatic substituent R. Most of the nitroolefins afforded excellent drs and ee values. The exception is with the relatively electron-deficient nitroolefins **11g** and **11h**. The former gave a moderate ee value, albeit a high dr (entry 7), whereas both the dr and the ee value obtained with the latter, tend to be moderate (entry 8).

Several other ketones were also examined in the **4**-catalyzed Michael addition with **11a**. Unfortunately, as depicted in Scheme 2, only low to moderate yields and moderate ee values were obtained.

Table 3. Screening of acids in the Michael addition of cyclohexanone to nitrostyrene[a]

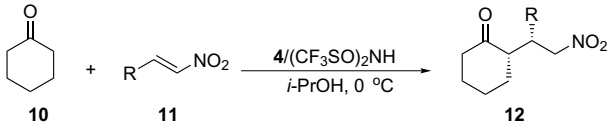
Entry	Acid	Yield (%)	dr (*syn*/*anti*)	ee (*syn*) (%)
1	TFA	47	95/5	93
2	CH_3COOH	90	93/7	92
3	*p*-TsOH	65	95/5	92
4	D-(+)-Camphor sulfonic acid	54	95/5	93
5	$(CF_3SO_2)_2NH$	79	99/1	93
6	C_6H_5COOH	81	93/7	90
7	4-$NO_2C_6H_4COOH$	62	94/6	91
8	4-$CF_3C_6H_4OH$	99	92/8	90
9	C_6H_5OH	29	95/5	90
10	4-$^tBuC_6H_4OH$	22	90/10	86
11[b]	$(CF_3SO_2)_2NH$	95	99/1	94

[a] Unless stated otherwise, conditions: [**11a**] = 0.5 mol/L, 20 mol % **4**, 20 mol % acid, solvent/cyclohexanone = 1:1, 0 °C, 10 h.
[b] The reaction time is 20 h.



Scheme 2. Michael addition of ketones to **11a**.

Table 4. Michael addition of cyclohexanone to various nitroolefins catalyzed by **4**[a]



Entry	R (**11**)	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	Ph (**11a**)	20	95	99/1	94
2	4-FC_6H_4 (**11b**)	24	96	98/2	94
3	4-BrC_6H_4 (**11c**)	24	95	97/3	93
4	4-ClC_6H_4 (**11d**)	20	96	99/1	94
5	2-ClC_6H_4 (**11e**)	8	99	99/1	95
6	3,4-$Cl_2C_6H_3$ (**11f**)	24	95	99/1	98
7	4-CNC_6H_4 (**11g**)	20	97	99/1	84
8	4-$NO_2C_6H_4$ (**11h**)	40	89	85/15	81
9	4-$CH_3OC_6H_4$ (**11i**)	8	94	99/1	94
10	3-$CH_3OC_6H_4$ (**11j**)	12	92	99/1	94
11	4-$CH_3C_6H_4$ (**11k**)	12	96	99/1	94
12	C_4H_3O (**11l**)	12	97	95/5	91

[a] Conditions: [**11**] = 0.5 mol/L, 20 mol % **4**, 20 mol % $(CF_3SO_2)_2NH$, solvent/cyclohexanone = 1:1, 20 h.
[b] Isolated yield of mixture of *syn*/*anti* based on the nitroolefin.
[c] Diastereomeric ratio, determined by chiral-phase HPLC analysis.
[d] Enantiomeric excess, determined by chiral-phase HPLC analysis.

The absolute stereochemical results obtained with the present catalyst system can be explained by a transition state model (Fig. 2) similar to those proposed previously.[3b,g,h,m] The *Si*-face attack of the enamine double bond by the nitroolefin becomes more unfavorable due to conceivable steric and/or electronic repulsions between the *cis*-4-pyrrolidin-1-yl group and the nitro group, which might be a possible reason for the high stereoselectivity of **4**.

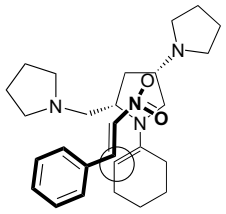


Figure 2. Proposed transition state.

3. Conclusion

In conclusion, we have developed L-proline derived triamine **4** as a highly efficient and stereoselective organocatalyst for the asymmetric Michael addition of cyclohexanone to nitroolefins. High isolated yields and excellent diastereoselectivities and enantioselectivities have been obtained for the addition of cyclohexanone to a variety of nitroolefins under the catalysis of **4**. The presence of a Brønsted acid with proper acidity, such as $(CF_3SO_2)_2NH$, proved to be critical for the excellent performance of this catalyst system.

4. Experimental

4.1. Procedure for the synthesis of catalyst 4

To an anhydrous THF (1 L) solution of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxyproline methyl ester **5** (33.55 g, 137 mmol) was added $LiAlH_4$ (5.26 g, 137 mmol) in small portions at 0 °C. The resulting mixture was stirred at 0 °C until the starting material disappeared (monitored by TLC). The reaction was then quenched with a 15% aqueous sodium hydroxide solution at 0 °C. After filtration, the volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give pure (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-2-hydroxymethyl-4-hydroxypyrrolidine (27.35 g, 92%) as a yellow oil.

To a stirred solution of Et_3N (154 mL, 1.096 mol) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-2-hydroxymethyl-4-hydroxypyrrolidine (27.35 g, 126 mmol) in chloroform (500 mL) was added CH_3SO_2Cl (43.5 mL, 548 mmol) dropwise at 0 °C. The resulting mixture was continued to stir at 0 °C until the starting material disappeared (monitored by TLC). 1 M aqueous hydrochloric acid (400 mL) was used to quench the reaction. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$, Removal of the solvents under reduced pressure gave crude product **6**, which was used for the next step without further purification.

To a solution of the crude product **6** obtained above was added NaN_3 (72 g, 1.096 mol). The mixture was stirred at 60 °C for 12 h. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified by flash chromatography on silica gel to give pure product **7** (23.42 g, 70% over two steps) as a colorless oil.

A methanol solution of compound **7** (8.10 g, 30.3 mmol) and 5% Pd/C were charged in a two-necked flask. The mixture was stirred under hydrogen (1 atm) at 35 °C for 5 h, and was then filtered through Celite. The filtrate was concentrated to dryness to give crude product **8** as a brown oil, which was used for the next step without further purification.

To a solution of Et_3N (34 mL, 242 mmol) and the crude product **8** obtained above was added 1,4-dibromobutane (14.7 mL, 121 mmol), the mixture was stirred at 60 °C for 10 h. Upon completion, the reaction was quenched with water. The solvent was removed under reduced pressure, and the residue dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified through column chromatography on silica gel to give pure product **9** (14.05 g, 64% over two steps) as a brown oil.

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylmethyl)-4-(pyrrolidin-1-yl)pyrrolidine **9**: ^1H NMR (600 MHz, MeOD) δ (ppm): 1.48 (s, 9H), 1.83 (m, 9H), 2.45–2.48 (m, 1H), 2.59–2.63 (m, 10H), 2.82–2.97 (m, 1H), 3.02–3.06 (m, 1H), 3.78–3.82 (m, 1H), 3.94 (m, 1H).

Compound **9** (4.44 g, 13.7 mmol) was treated with a mixture of TFA–CH_2Cl_2 (v/v = 1/2, 120 mL). After stirring for 12 h, the reaction mixture was concentrated under reduced pressure. The residue was purified through column chromatography on silica gel to give pure product **4** (2.44 g, 80%) as a yellow oil.

(2*S*,4*S*)-2-(Pyrrolidin-1-ylmethyl)-4-(pyrrolidin-1-yl)pyrrolidine **4**: $[\alpha]_D^{25} = 6.4$ (*c* 0.5, CH_2Cl_2), ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 1.34–1.39 (m, 1H), 1.74–1.81 (m, 8H), 2.16–2.21 (m, 1H), 2.41–2.43 (dd, $J = 5.4$, 11.9 Hz, 1H), 2.50–2.55 (m, 6H), 2.57–2.60 (m, 2H), 2.63–2.66 (m, 1H), 2.68–2.73 (m, 1H), 2.88–2.91 (dd, $J = 7.6$, 10.9 Hz, 1H), 3.07–3.09 (dd, $J = 6.8$, 10.5 Hz, 1H), 3.34 (br, 1H), 3.35–3.39 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 23.3, 23.4, 37.4, 51.0, 53.5, 54.5, 56.9, 61.8, 66.0. ESI HRMS exact mass calcd for $(C_{13}H_{26}N_3+H)^+$ requires *m*/*z* 224.2121. Found: 224.2114.

4.2. General procedure for the Michael addition of cyclohexanone to nitroolefins

To a mixture of cyclohexanone **10** (0.21 mL) and ^{i}PrOH (0.19 mL) were added catalyst **4** (0.04 mmol) and $(CF_3SO_2)_2NH$ (0.04 mmol). After stirring at 0 °C for 20 min, nitroolefin **11** (0.2 mmol) was introduced. The

reaction mixture was stirred at the same temperature for 8–40 h and was then quenched with saturated aqueous NH_4Cl. EtOAc was added to dilute the mixture. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel to give the corresponding Michael adduct for further analysis.

Acknowledgment

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7. It has previously been reported that the addition of an acid can enhance the catalytic effects of chiral organocatalyst for the Michael addition, see: Ref. 3b–d, 3g,m,n,p.
8. It should be noted that the addition of one more equivalent of TFA had little effect on the diastereoselectivity and enantioselectivity, but dramatically decreased the reaction rate (36% yield, 93:7 dr and 88% ee).
9. Such solvent compatibility of this catalyst is quite unusual compared with the other catalytic systems for the same reaction, see Refs. 3 and 4.