Prolinol *tert*-Butyldiphenylsilyl Ether as Organocatalyst for the Asymmetric Michael Addition of Cyclohexanone to Nitroolefins

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Abstract: The direct Michael additions of cyclohexanone to nitroolefins catalyzed by prolinol *tert*-butyldiphenylsilyl ether were conducted successfully in good yields (up to 99%) and high stereoselectivities (up to 98:2 diastereomeric ratio and 95% enantiomeric excess).

Key words: asymmetric, organocatalyst, Michael addition, cyclohexanone, nitroolefin

The Michael addition reaction is widely recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] In particular, the asymmetric Michael addition of carbonyl compounds to nitroalkenes is a very useful synthetic method for the preparation of nitroalkanes, which are valuable building blocks in organic synthesis and can be readily transformed into amines, ketones, carboxylic acids, nitrile oxides, etc.[2] As a result, considerable efforts have been devoted to the development of organocatalytic asymmetric Michael addition of ketones and aldehydes to nitroolefins over recent years,[3] and various effective catalytic systems have been developed,[4] including chiral acyclic primary amines,[4a] thiourea–amine bifunctional catalysts,[4b–4e] and small dipeptides,[4f,g] as well as pyrrolidine-based catalytic systems such as chiral pyrrolidinyl triazole,[5] tetrazole,[6] aminomethylpyrrolidine,[7] 2,2-bipyrrolidine,[8] pyrrolidine–pyridine,[9] pyrrolidine sulfonamide,[10] pyrrolidine–thiourea,[11] diphenylprolinol ethers or their derivatives,[12] and others.[13] In general, the pyrrolidine-catalyzed Michael addition occurs via an enamine intermediate, and stereocontrol has been achieved by effectively shielding one side of the enamine double bond and/or via hydrogen bonding between the catalyst and the nitro group of β-nitrostyrene as suggested in the literature.[9,14] (*S*)-Diphenylprolinol trimethylsilyl ether has been employed as a catalyst for this process and high levels of enantio- and diastereoselectivity were obtained for aldehydes.[12a] The bulky diphenyltrimethylsiloxymethyl group on the pyrrolidine ring efficiently blocks one side of the enamine double bond, thus giving high levels of enantio- and diastereoselectivity. However, poor reactivities were observed with this catalyst when ketones were used as substrates.[10c] It appears that the steric bulkiness of the diphenyltrimethylsiloxymethyl group circumvents the efficient formation of the enamine intermediate with ketones, resulting in poor reactivities.

In our work directed toward devising highly enantioselective catalysts for the addition of ketones to nitroolefins, we envisioned that by properly adjusting the size of the shielding group or its distance from the second amine part of the pyrrolidine-based catalyst, high reactivity and enantioselectivity could be obtained. Therefore, we have designed and synthesized several chiral pyrrolidine catalysts by simply etherifying the prolinol or its analogue (Figure 1), and found that **1b** was an excellent catalyst for the asymmetric Michael addition of cyclohexanone to nitroolefins. Herein, we wish to report the preliminary results on this subject.

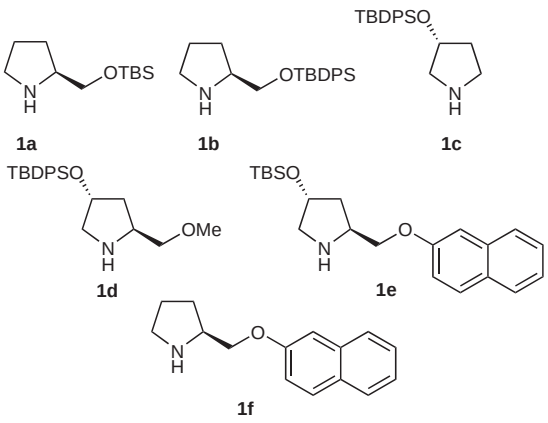

Figure 1 Chiral catalysts tested

The experiments were conducted by taking cyclohexanone as a donor and β-nitrostyrene as an acceptor using 20 mol% of the catalyst **1** (Table 1). Catalyst **1b** (Table 1, entry 2) showed better catalytic activity (86% yield) and higher enantioselectivity (87% ee) than the other screened catalysts **1a**, **1d**–**1f** (Table 1, entries 1 and 4–6), probably because **1b** matches with our supposition and bears a proper distance between the second amine part of the pyrrolidine and the bulky group *tert*-butyldiphenylsilyl by the C–O and O–Si bonds. The reduced steric repulsion between the enamine and *tert*-butyldiphenylsilyl moieties thus allowed the catalyst to exhibit higher reactivity. Nonetheless, the bulky group could also effectively shield one face of the enamine double bond for high enantioselectivity. However, **1c** gave no product enantioselectivity in spite of showing good reactivity (Table 1, entry 3). This indicated that the chiral center adjacent to the second

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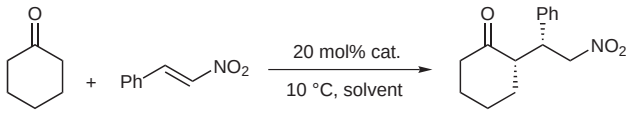
Table 1 Catalytic Asymmetric Michael Addition Reaction of Cyclohexanone **2** to Nitroolefin **3** under Various Conditions[a]



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

Entry	Cat.	Solvent	Time (h)	Yield (%)[b]	Temp.	*syn*/*anti*[c]	ee[d] (%)
1	**1a**[15]	hexane	30	79	r.t	89:11	71
2	**1b**[15]	hexane	35	86	r.t	98:2	87
3	**1c**	hexane	14	87	–10 °C	n.d.	0
4	**1d**	hexane	35	23	r.t.	n.d.	43
5	**1e**	hexane	35	24	r.t.	n.d.	65
6	**1f**	hexane	35	10	r.t.	n.d.	84
7	**1b**	cyclohexane	35	80	r.t	99:1	85
8	**1b**	$CHCl_3$	35	42	r.t	96:4	87
9	**1b**	PE	35	78	r.t	98:2	86
10	**1b**	Et_2O	35	46	r.t	96:4	88
11	**1b**	DMF	35	15	r.t	n.d.	n.d.
12	**1b**	CH_2Cl_2	35	10	r.t	97:3	85
13	**1b**	THF	32	43	r.t	97:3	83
14	**1b**	MeOH	40	0	r.t	–	–
15	**1b**	hexane	35	65	10 °C	97:3	89
16	**1b**	hexane	35	34	0 °C	99:1	93

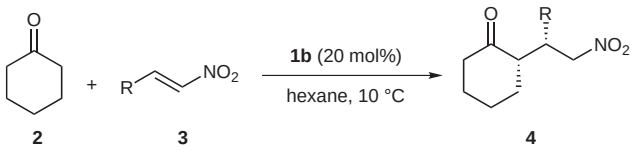
[a] All reactions were carried out using **2** (0.5 mL, 10 equiv) and **3** (0.5 mmol, 1 equiv) in the presence of catalyst (20 mol%) in solvent (2 mL).
[b] Isolated yields.
[c] Determined by ^1H NMR of the crude products.
[d] Determined by chiral HPLC analysis.

amine of the pyrrolidine was very crucial for high enantioselectivity. A naphthyl group could provide good enantioselectivity, but the catalytic activity was low (Table 1, entry 6). The existence of *trans*-3-(*tert*-butyldimethylsilyloxy) group also proved to be detrimental to enantioselectivity (Table 1, entries 5 and 6).

Various conditions were examined using **1b** as the catalyst (Table 1, entries 2 and 7–16). Polar aprotic solvents, such as $CHCl_3$, Et_2O, DMF, CH_2Cl_2, THF, gave low yields (10–46%) but good enantioselectivities (83–88% ee) (Table 1, entries 8 and 10–13). No conversion was observed with protic solvent such as anhydrous methanol (Table 1, entry 14), whereas in nonpolar solvents, such as hexane, cyclohexane, petroleum ether, the Michael reaction proceeded smoothly with good enantioselectivities (Table 1, entries 2, 7 and 9). The best solvent was hexane. We also optimized the reaction temperature (Table 1, entries 2, 15 and 16) and found that reactions ran at 10 °C afforded the product in high yield and with better enantioselectivity.

With the optimal conditions in hand, we investigated a variety of nitroolefins and the results are summarized in Table 2. All reactions were conducted in hexane (2 mL) at 10 °C in the presence of catalyst **1b**. In general, β-nitrostyrenes with both electron-withdrawing and electron-donating aryl group reacted efficiently (50–99% yield) with high diastereoselectivity (>92%) and enantioselectivity (73–95% ee) for *syn* adduct. Finally, the substitution position of β-nitrostyrenes also had an influence not only on reactivity but also on the enantioselectivities. For example, when the nitro group position of β-nitrostyrene was changed from *para* to *meta*, the yield decreased from 95% to 50% and the enantioselectivity increased from 84% ee to 92% ee (Table 2, entries 4 and 7).

Table 2 Catalytic Asymmetric Michael Addition Reactions of Cyclohexanone with *trans*-Nitroolefins[16]



2 **3** **4**

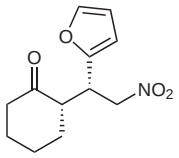
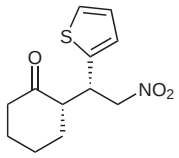
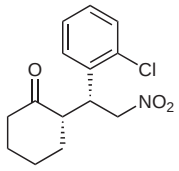
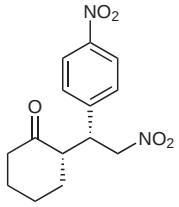
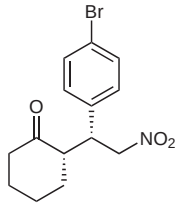
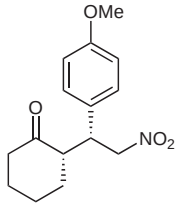
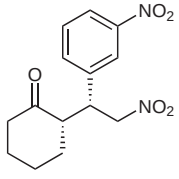
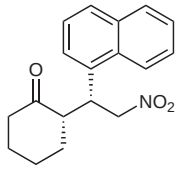
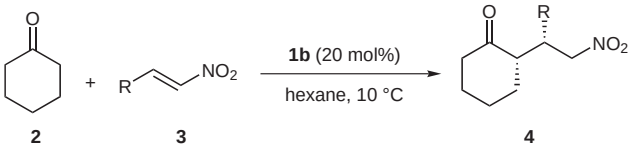
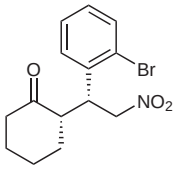
Entry[a]	Product	Time (h)	*syn*/*anti*[b]	Yield[c] (%)	ee[d] (%)
1		69	94:6	92	87
2		71	96:4	63	89
3		72.5	97:3	99	94
4		72.5	96:4	95	84
5[e]		71	98:2	89	95
6		131	95:5	96	73
7		74.5	92:8	50	92
8		71	98:2	96	89

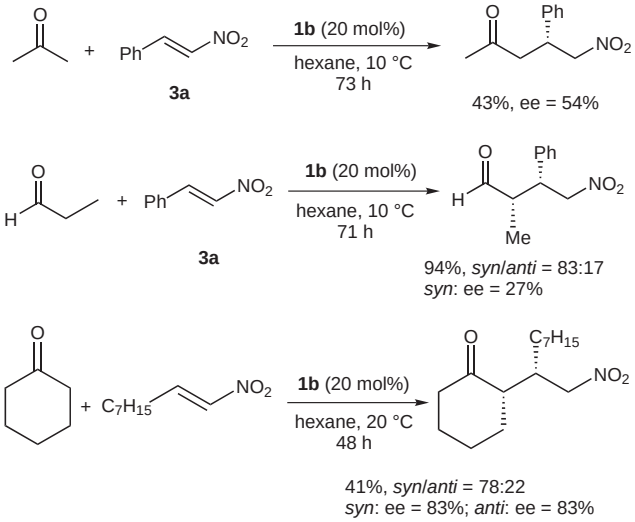
Table 2 Catalytic Asymmetric Michael Addition Reactions of Cyclohexanone with *trans*-Nitroolefins[16] (continued)



2 **3** **4**

Entry[a]	Product	Time (h)	*syn*/*anti*[b]	Yield[c] (%)	ee[d] (%)
9		48	96:4	99	90

[a] All reactions were carried out using **2** (0.5 mL, 10 equiv) and nitroolefins (0.5 mmol, l 1 equiv) in the presence of cat. **1b** (20 mol%) in hexane (2 mL) at 10 °C.
[b] Determined by comparison with the known ^{1}H NMR spectral data and optical rotation values.
[c] Isolated yields.
[d] Determined by chiral HPLC analysis.



Scheme 1 Michael addition reactions of other substrates catalyzed by **1b**

The asymmetric additions of acetone and propanal to nitrostyrene **3a** using **1b** as a catalyst were also investigated. As shown in Scheme 1, acetone gave the desired product in 43% yield with 54% ee. Propanal also worked well to give the desired products in excellent yield with moderate regioselectivity (83:17) but poor enantioselectivity (27%). (*E*)-1-Nitronon-1-ene gave the corresponding product with moderate diastereoselectivity (78:22) and enantioselectivity (83% ee) in 41% yield. Cyclopentanone was inactive and failed to afford the desired adduct.

In summary, we have successfully developed a new pyrrolidine-based organocatalyst for the asymmetric direct Michael addition of cyclohexanone to various

nitroolefins by simply etherifying the prolinol with *tert*-butyldiphenylsilyl chloride in one step. Good yields (up to 99%) and high stereoselectivities (up to 98:2 dr and 95% ee) were obtained when this catalyst was used in the Michael reaction. Further studies to apply this catalyst to other reactions are currently in progress in our laboratory.

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(15) **Procedure for the Preparation of Catalyst 1a**: To a DMF (10 mL) solution of prolinol (3.36 mmol) and imidazole (10.1 mmol) was added TBSCl (6.73 mmol) at 0 °C. The reaction mixture was stirred for 17 h at r.t. and quenched with aq NH_4Cl and the organic materials were extracted with EtOAc and the combined organic phase was washed with brine. Then the organic extracts were dried over anhyd Na_2SO_4 and concentrated in vacuo after filtration. Purification by silica gel column chromatography gave (*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]pyrrolidine (**1a**) in 77% yield; $[\alpha]_D^{r.t.}$ –6.63 (*c* = 0.8, $CHCl_3$). IR (neat): 3406, 2929, 2857, 2738, 1680, 1460, 1394, 1255, 1100, 840, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.10–0.12 (d, *J* = 4.6 Hz, 6 H), 0.90 (s, 9 H), 1.84–1.89 (m, 1 H), 1.93–2.11 (m, 3 H), 3.29–3.38 (m, 2 H), 3.76–3.81 (m, 2 H), 3.94–3.98 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5, –5.3, 24.0, 25.8, 26.8, 45.7, 60.0, 62.1. Preparation of catalyst (*S*)-2-[(*tert*-butyldiphenylsilyloxy)methyl]pyrrolidine (**1b**) was similar to that of catalyst **1a**. **1b**: 85% yield; $[\alpha]_D^{r.t.}$ –5.8 (*c* = 0.94, $CHCl_3$). IR (neat): 3419, 2935, 2866, 2734, 1112, 708, 504 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 1.80–1.99 (m, 1 H), 2.02–2.04 (m, 3 H), 3.30–3.35 (t, *J* = 6.5 Hz, 2 H), 3.71–3.79 (m, 1 H), 3.83–3.84 (m, 1 H), 3.91–3.96 (m, 1 H), 7.39–7.73 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 23.8, 26.8, 45.6, 59.9, 63.0, 127.8, 129.9, 132.5, 135.6, 135.7.

(16) **General Procedure for the Asymmetric Michael Addition of Cyclohexanone 2 to Nitroolefin 3 Catalyzed by 1b**: The catalyst **1b** (0.1 mmol) and cyclohexanone **2** (0.5 mL) were mixed in hexane (2 mL) at r.t. After stirring for 20 min and then cooling to 10 °C, the nitroolefin **3** was added. The mixture was stirred at 10 °C for the specified time (Table 2) and then directly purified by silica gel column chromatography (PE and EtOAc as the eluent) to obtain the product **4**,[17] which was confirmed by the comparison of IR, ^1H NMR and ^{13}C NMR data with that reported in the literature. The enantiomeric ratios were identified by HPLC analysis.

(17) (*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone (**4**): mp 125–126 °C; $[\alpha]_D^{r.t.}$ –26.1 (*c* = 1.42, $CHCl_3$). IR (neat): 2958, 2929, 1699, 1551, 1495, 1448, 1384, 1129, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.58 (m, 1 H), 1.62–1.75 (m, 4 H), 2.04–2.10 (m, 1 H), 2.38–2.47 (m, 2 H), 2.68 (m, 1 H), 3.72–3.80 (dt, *J* = 4.5, 9.9 Hz, 1 H), 4.53–4.66 (dd, *J* = 10.0, 12.3 Hz, 1 H), 4.91–4.97 (dd, *J* = 4.5, 12.4 Hz, 1 H), 7.15–7.17 (d, *J* = 6.9 Hz, 2 H), 7.23–7.34 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 28.5, 33.1, 42.7, 43.9, 52.5, 78.8, 127.7, 128.1, 128.9, 137.7, 211.9. HPLC condition: Chiralpak AD-H, λ = 254 nm, flow rate: 0.5 mL/min, eluent: hexane–*i*-PrOH (90:10), *t* and the paragraph.