



## 4-Trifluoromethanesulfonamidyl prolinol *tert*-butyldiphenylsilyl ether as a highly efficient bifunctional organocatalyst for Michael addition of ketones and aldehydes to nitroolefins

Chao Wang, Chun Yu, Changlu Liu, Yungui Peng\*

School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, PR China

### ARTICLE INFO

#### Article history:

Received 24 December 2008

Revised 24 February 2009

Accepted 27 February 2009

Available online 4 March 2009

### ABSTRACT

4-Trifluoromethanesulfonamidyl prolinol *tert*-butyldiphenylsilyl ether bifunctional organocatalyst **3a** is a highly efficient catalyst for the asymmetric Michael addition reactions of ketones and aldehydes to nitrostyrenes, leading to *syn*-selective adducts with excellent yields (>99%), high diastereoselectivities (up to 99:1 dr) and excellent enantioselectivities (up to 99% ee). Control experiments suggested that the *trans*-configuration relationship between the bulky group (–CH<sub>2</sub>OTBDPS) and the sulfonamido group at the 4-position of the pyrrolidine ring was important to achieve high yield and stereoselectivity.

© 2009 Elsevier Ltd. All rights reserved.

As an important approach to synthetically useful  $\gamma$ -nitro carbonyl compounds,<sup>1</sup> the asymmetric Michael addition of carbonyl compounds to nitroalkenes has been of great interest. In recent years, tremendous efforts have been focused on the development of an organocatalytic asymmetric version of the reaction.<sup>2–12</sup> Among the organocatalytic systems, pyrrolidine-based system was found to be the most useful. Thus, it has been intensively studied and improved, leading to many variations, such as chiral pyrrolidinyl triazole,<sup>3</sup> tetrazole,<sup>4</sup> aminomethylpyrrolidine,<sup>5</sup> 2,2-bipyrrolidine,<sup>6</sup> pyrrolidine-pyridine,<sup>7</sup> pyrrolidine sulfonamide,<sup>8</sup> pyrrolidine-thiourea,<sup>9</sup> diphenylprolinol ethers or their derivatives,<sup>10</sup> and others.<sup>11</sup> Most of these systems share a common feature: a hydrogen-bond donor substituent at the  $\alpha$ -position of the pyrrolidine nitrogen atom, which is believed to play a critical role in helping the catalytic reaction to proceed. For example, Wang reported an excellent pyrrolidine-sulfonamide system for the asymmetric Michael addition reactions of aldehydes and ketones. However, the drawback of the system was high catalyst loading (10–20 mol %).<sup>8a–c</sup> Palomo made some improvement, reporting that a hydrogen-bond donor at the 4-position of the pyrrolidine can help the catalytic reaction of aldehyde proceed with 5 mol % catalyst loading.<sup>11b</sup> Most recently, primarily based on the concept of steric control, Ma developed an even more effective catalytic system, in which the catalyst loading was lowered to 0.5–2 mol %. Not only was the catalyst capable of promoting the reaction of aldehydes,<sup>10e</sup> but also worked well even for acetaldehyde, the ‘simplest’ nucleophile, as reported by List<sup>10f</sup> and Hayashi<sup>10g</sup> independently. In the case of less reactive donors such as ketones, development of new catalytic systems and

improvement of the catalyst performance have also attracted more and more attention recently since the pioneering work of List.<sup>2a</sup> Although highly diastereo- and enantioselective conjugate additions involving ketones were reported by the groups of Kotsuki,<sup>7</sup> Tang,<sup>9a</sup> Cheng,<sup>3a,11c,d</sup> and Singh,<sup>5g</sup> a relatively high catalyst loading, typically 10–20 mol %, was required to achieve good results. Therefore, design and synthesis of highly efficient and readily tunable catalysts remain a challenge for the asymmetric Michael addition of ketones to nitroolefins.

Interested in developing an efficient chiral organocatalytic system to achieve high yield and enantioselectivity in Michael addition, we developed pyrrolidine-based silyl ether **1** as an organocatalyst for direct Michael addition reactions,<sup>12a</sup> in which the enantioselectivity, controlled primarily by steric interactions. Although a high level of both enantioselectivity (73–95% ee) and diastereoselectivity ( $\geq 20:1$  dr) was achieved, the catalytic efficiency was low (up to 20 mol % catalyst loading). In Palomo's catalytic system,<sup>11b</sup> the hydrogen-bond donor was a hydroxyl group and the strength of the hydrogen bond between the hydroxyl proton and the nitro group was moderate. Inspired by his work, we believed that introduction of a hydrogen bond into TBDPS protected prolinol system would enhance the catalytic efficiency and enantioselectivity. We also believed that the selectivity could be further enhanced by a stronger hydrogen-bond donor at the 4-position of the catalyst **1**. Thus, we designed and synthesized a series of novel catalysts (**2–6**) that bear diverse proton donors at the 4-position and –CH<sub>2</sub>OTBDPS group at the 2-position of the pyrrolidine nitrogen atom (Fig. 1). As expected, these molecules were excellent catalysts in the asymmetric Michael addition reactions of ketones and aldehydes to nitroolefins. In this Letter, we disclose the preliminary results.

\* Corresponding author. Tel.: +86 23 68254290; fax: +86 23 68254000.  
E-mail addresses: [pengyungui@hotmail.com](mailto:pengyungui@hotmail.com), [pyg@swu.edu.cn](mailto:pyg@swu.edu.cn) (Y. Peng).

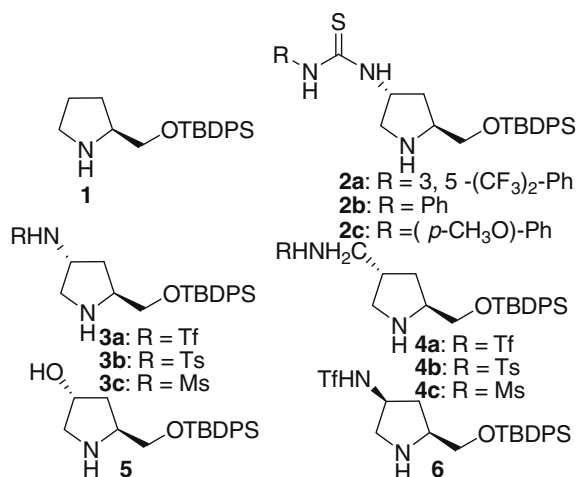


Figure 1. Pyrrolidine-based chiral organocatalysts.

We selected the Michael addition reaction of cyclohexanone **7a** and  $\beta$ -nitrostyrene **8a** as the model reaction to examine the novel catalysts (Table 1). Excellent enantioselectivity (97% ee) and diastereoselectivity (96% dr) with a moderate yield (76%) were achieved when the reaction was catalyzed by **2a** (Table 1, entry 2). When **2b** or **2c** was used as the catalyst, the reactivity decreased dramatically; giving only 25% or 46% in yield after 36 h, respec-

Table 1  
Catalytic asymmetric Michael reaction of cyclohexanone (**7a**) to nitrostyrene (**8a**) under various conditions<sup>a</sup>

Entry	Cat. (%)	Solvent	Time (h)	Yield <sup>b</sup> (%)	dr <sup>c</sup> (syn:anti)	ee <sup>d</sup> (%)
1	<b>1</b> (20)	Hexane	35	34	98:2	93
2	<b>2a</b> (20)	Hexane	36	76	98:2	97
3	<b>2b</b> (20)	Hexane	36	25	98:2	93
4	<b>2c</b> (20)	Hexane	36	41	97:3	92
5	<b>3a</b> (20)	Hexane	36	>99	98:2	97
6	<b>3b</b> (20)	Hexane	36	89	96:4	92
7	<b>3c</b> (20)	Hexane	36	>99	97:3	95
8	<b>4a</b> (20)	Hexane	36	>99	98:2	94
9	<b>4b</b> (20)	Hexane	36	79	98:2	85
10	<b>4c</b> (20)	Hexane	36	92	98:2	85
11	<b>5</b> (20)	Hexane	68	10	94:6	94
12	<b>6</b> (20)	Hexane	78	44	92:8	88
13	<b>3a</b> (5)	Hexane	114	18	n.d	92
14 <sup>e</sup>	<b>3a</b> (5)	Hexane	47	97	98:2	96
15 <sup>e</sup>	<b>3a</b> (5)	Toluene	77	95	96:4	92
16 <sup>e</sup>	<b>3a</b> (5)	Ether	77	95	98:2	95
17 <sup>e</sup>	<b>3a</b> (5)	Benzene	77	98	96:4	93
18 <sup>e</sup>	<b>3a</b> (5)	CH <sub>2</sub> Cl <sub>2</sub>	77	94	95:5	95
19 <sup>e</sup>	<b>3a</b> (5)	THF	77	73	97:3	87
20 <sup>e</sup>	<b>3a</b> (5)	<i>i</i> -PrOH	100	Trace	n.d	n.d
21 <sup>e</sup>	<b>3a</b> (5)	CHCl <sub>3</sub>	77	92	95:5	90
22 <sup>e</sup>	<b>3a</b> (5)	CH <sub>3</sub> CN	72	>99	95:5	98
23 <sup>e</sup>	<b>3a</b> (5)	DMF	77	63	94:6	86
24 <sup>e</sup>	<b>3a</b> (5)	CH <sub>3</sub> OH	77	Trace	n.d	n.d
25 <sup>e,f</sup>	<b>3a</b> (5)	CH <sub>3</sub> CN	40	>99	94:6	96

<sup>a</sup> Unless specified, reactions conducted on a 0.25 mmol scale nitroolefin in solvent (1 mL) with cyclohexanone (2.5 mmol) in the presence of catalyst.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>d</sup> Determined by chiral HPLC analysis.

<sup>e</sup> 5 mol % of benzoic acid was added.

<sup>f</sup> Reaction at 10 °C.

tively. However, the diastereoselectivity in either case remained essentially the same as that of the reaction catalyzed by **2a**, while enantioselectivity decreased slightly from 97% ee (**2a**) to 93% ee (**2b**) and 92% ee (**2c**) (Table 1, entries 3 and 4). The decrease in reactivity and enantioselectivity may be caused by the decrease in the hydrogen bond donating ability of the thiourea hydrogen. Hydrogen bond donating ability is closely linked to acidity, and is governed by the electronic nature of the R group. In catalyst **2a**, with two electron-withdrawing groups (–CF<sub>3</sub>) on the phenyl ring, both the hydrogen bond donating ability and the acidity of the thiourea hydrogen were stronger than those in **2b** or **2c**, and thus the catalytic reactivity of **2a** is superior to that of **2b** or **2c**. We further screened 4-sulfonamido (**3**, **4**, and **6**) and 4-hydroxyl (**5**) prolinol ethers (Table 1, entries 5–12) for catalytic performance. To our delight, the catalytic activity was increased dramatically when **3a** was used as the catalyst in comparison with **2a**, affording over 99% yield without losing enantioselectivity (97% ee) and diastereoselectivity (96% dr) (Table 1, entries 2 and 5). As the acidity and hydrogen bond donating ability of the sulfonamide proton in **3a** are much higher than those in **3b** and **3c**, the catalytic performance of **3a** is superior to that of **3b** and **3c** (Table 1, entries 6 and 7). However, although the acidity of the sulfonamide proton in **3b** is higher than that in **3c**, **3c** is a better catalyst. We believe that the steric hindrance caused by the bulkier toluene group makes the sulfonamide proton less available in **3b** (Table 1, entry 6), thus lowering the hydrogen bond donating ability of the proton.

We also prepared and screened analogues **4**, in which the sulfonamide group is further away from the pyrrolidine ring by a methylene group compared with that of **3**. The results demonstrated that catalysts **4a–c** are inferior to the corresponding **3a–c** in catalytic performance (Table 1, entries 8–10). When the hydrogen-bond donor was a hydroxyl group, similar to the catalytic system reported by Palomo,<sup>11b</sup> catalyst **5** showed very low activity but high selectivity. Only 10% yield was obtained after 68 h (Table 1, entry 11). We further investigated the influence of the 4-position configuration of the catalyst on this reaction. The change of *trans*-4-sulfonamido group (**3a**) to *cis*-4-sulfonamido group (**6**) led to lower yield and decreased diastereoselectivity and enantioselectivity (Table 1, entry 12). This indicated that the *trans*-4-sulfonamido group on the pyrrolidine ring is important not only for good stereoselectivity, but also for high catalytic activity. In summary, these studies reveal that a strong hydrogen-bond donor at the 4-position of pyrrolidine plays an important role toward stereoselectivity, and that sulfonamide group is superior to thiourea in catalytic activity.

We then examined the influence of catalyst loading on the reaction. Although a load of 5 mol % of catalyst **3a** alone resulted in dramatic decrease in catalytic performance (Table 1, entry 13), addition of benzoic acid boosted the catalytic performance by accelerating the formation of the enamine intermediate between the catalyst and the substrate. In fact, 5 mol % of catalyst **3a** along with 5 mol % of benzoic acid worked just as well as 20% of the same catalyst used alone (Table 1, entries 5 and 14). A series of solvents were also screened (Table 1, entries 14–24). Good yields and enantiomeric excesses were obtained in nonpolar or less polar solvents (Table 1, entries 14–18). The best result was achieved in CH<sub>3</sub>CN (Table 1, entry 22). In contrast, the reaction proceeded sluggishly in polar protic solvents such as *i*-PrOH and CH<sub>3</sub>OH, only trace amount of product was observed (Table 1, entries 20 and 24). We also optimized the reaction temperature and found that reaction ran at 0 °C to afford the highest yield and the best enantioselectivity (Table 1, entries 22 and 25).

With the optimal conditions in hand, the scope of the reaction was examined (Table 2).<sup>13</sup> The results showed that the reaction has broad applicabilities. In general,  $\beta$ -nitrostyrenes possessing electron-withdrawing, electron-donating groups on their aromatic

**Table 2**Catalytic asymmetric Michael reaction of cyclohexanone with various *trans*- $\beta$ -nitrostyrenes<sup>a</sup>

Entry	R	Time (h)	Yield <sup>b</sup> (%)	dr <sup>c</sup> ( <i>syn:anti</i> )	ee <sup>d</sup> (%)
1	Ph	72	>99	95:5	98
2	4-NO <sub>2</sub> Ph	47	>99	92:8	98
3	4-FPh	96	>99	96:4	98
4	4-ClPh	66	>99	97:3	99
5	4-BrPh	72	98	96:4	99
6	2-NO <sub>2</sub> Ph	53	97	97:3	95
7	2-FPh	48	>99	99:1	97
8	2-ClPh	47	>99	99:1	99
9	2-BrPh	53	96	94:6	98
10	3-NO <sub>2</sub> Ph	72	>99	93:7	99
11	3-BrPh	72	99	95:5	97
12	2,4-Cl <sub>2</sub> Ph	29	94	97:3	98
13	4-MePh	67	>99	96:4	95
14	2-MePh	137	90	99:1	98
15	2-MeOPh	71	>99	99:1	94
16	3-MePh	95	>99	97:3	96
17	1-Naphthyl	161	87	99:1	98
18	2-Naphthyl	177	95	96:4	99
19	2-Thienyl	107	>99	93:7	99
20	2-Furyl	67	99	91:9	91
21 <sup>e</sup>	<i>n</i> -Bu	43	81	98:2	90

<sup>a</sup> Unless specified, reactions conducted on a 0.25 mmol scale nitroolefin in CH<sub>3</sub>CN (1 mL) with cyclohexanone (2.5 mmol) in the presence of 5 mol % **3a** and benzoic acid.<sup>b</sup> Isolated yield.<sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy.<sup>d</sup> Determined by chiral HPLC analysis.<sup>e</sup> 20 mol % catalyst loading and reaction performed at room temperature.

ring and heteroaromatic substituents reacted efficiently (>99% yield) with high diastereoselectivity (up to 98% de) and enantioselectivity (up to 99% ee) for *syn* adduct (Table 2, entries 1–20). The

substitution patterns of  $\beta$ -nitrostyrenes had certain influences on reactivity, diastereoselectivity, and enantioselectivity in some substrates. For example, when the methyl group position of  $\beta$ -nitrostyrene was changed from *para*- to *ortho*-, the reaction time was prolonged from 67 h to 137 h, the yield decreased from 99% to 90%, and the diastereoselectivity and enantioselectivity increased from 92% de to 98% de and 95% ee to 98% ee, respectively (Table 2, entries 13 and 14). When the aliphatic *trans*-nitroolefin CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>CH=CHNO<sub>2</sub> was employed as substrate for the process, good results (81% yield, 90% ee, and 96% dr) were obtained (Table 2, entry 21).

Aldehyde and other ketone substrates were investigated as well (Table 3). The ring size of cyclic ketones strongly affects the reaction rate (Table 3, entries 2 and 3). Cyclopentanone and cycloheptanone were less reactive; however, good yields and moderate selectivities were achieved with catalyst **3a**. The results were much better than those reported previously.<sup>8c,9a,14</sup> With unsymmetrical ketone substrates, the reaction took place at the more substituted sites, presumably because the enamine intermediates formed under thermodynamic control (Table 3, entries 5–7).

TBDMS protected  $\alpha$ -hydroxyl acetone gave the product in 91% yield, 94% ee, and 85:15 dr (Table 3, entry 6), while 2-butanone gave 88% yield, 86% ee, and 94% dr (Table 3, entry 7). 3-Pentanone afforded *syn* adduct with excellent enantio- (93% ee) and diastereoselectivity (Table 3, entry 8). To the best of our knowledge only two reports detailing *syn*-selective catalytic systems have thus far been found for the analogous transformation of more challenging acyclic ketone such as 3-pentanone with >90% ee.<sup>2k,8c</sup> Finally, good enantioselectivity (75–80% ee) and diastereoselectivity (78–90% dr) were obtained when aldehydes were used as donors (Table 3, entries 9–11).

The achievement of high stereoselectivity may be explained by acyclic synclinal transition state model originally proposed by Seebach and Golinski.<sup>15</sup> As shown in Figure 2, for cyclohexanone, the bulky group (–CH<sub>2</sub>OTBDPS) should effectively shield the *si*-face of an enamine double bond, which would make nitrostyrene acceptors approach from the nonshielded side to give the observed major enantiomer. The hydrogen bond between the sulfonamide

**Table 3**Enantioselective addition of various ketones and aldehydes to nitroolefin<sup>a</sup>

Entry	R <sub>1</sub>	R <sub>2</sub>	Time	Yield <sup>b</sup> (%)	dr <sup>c</sup> ( <i>syn:anti</i> )	ee <sup>d</sup> (%)
1 <sup>e,f</sup>			15 h	98	99:1	71
2 <sup>e,f</sup>	–(C <sub>3</sub> H <sub>6</sub> )–		10 d	88	57:43	80 (87)
3 <sup>e,f</sup>	–(C <sub>5</sub> H <sub>10</sub> )–		8 d	80	90:10	49
4 <sup>e,f</sup>	CH <sub>3</sub>	H	42 h	>99	–	50
5 <sup>e</sup>	CH <sub>3</sub>	OH	5.5 d	56	69:31	69 (0)
6	CH <sub>3</sub>	OTBS	5 d	91	85:15	94
7 <sup>e,f</sup>	CH <sub>3</sub>	CH <sub>3</sub>	4.8 d	88	97:3	86
8 <sup>e,f</sup>	Et	CH <sub>3</sub>	9 d	93	93:7	93
9	H	Et	66 h	98	89:11	75
10	H	Pr	66 h	>99	90:10	80
11	H	C <sub>6</sub> H <sub>13</sub>	60 h	>99	95:5	79

<sup>a</sup> Unless specified, reactions conducted on a 0.25 mmol scale nitroolefin in CH<sub>3</sub>CN (1 mL) with ketone (2.5 mmol) in the presence of 5 mol % **3a** and benzoic acid; absolute configuration was demonstrated in supporting information.<sup>b</sup> Isolated yield.<sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy.<sup>d</sup> Determined by chiral HPLC analysis.<sup>e</sup> 20 mol % catalyst loading.<sup>f</sup> Reaction performed at room temperature.

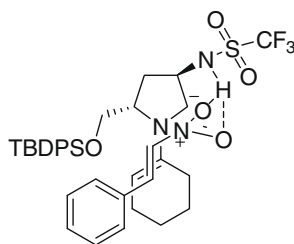


Figure 2. Proposed transition state model.

proton and the nitro group could activate the nitrostyrene effectively.

In conclusion, we have designed and synthesized novel pyrrolidine-sulfonamide and -thiourea silylether based bifunctional organocatalysts, and we have successfully applied these catalysts to the asymmetric Michael addition reactions of ketones and aldehydes to nitroolefins. When **3a** was used as the catalyst, 5 mol % catalyst loading afforded not only quantitative yields (>99%) but also exceptional stereoselectivities (up to 98% dr and 99% ee). We have demonstrated that fine tuning of the strength of the hydrogen bond could result in high performance catalysts, a strategy to design more effective organocatalysts for direct asymmetric Michael reactions. Further investigation on the application of this organocatalyst is in progress.

## Acknowledgments

We thank the Natural Science Foundation of China (NSFC 20572087 and 20872120), the Ministry of Education, PR China (No. 106141) and the Program for New Century Excellent Talents (NCET-06-0772) in University for generous financial support.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.211.

## References and notes

- (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (b) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1995**, *58*, 1592; (c) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 612.
- (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (d) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005; (e) Tsogoeva, S. B.; Wei, S. W. *Chem. Commun.* **2006**, 1451; (f) Huang, H. B.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170; (g) Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366; (h) Xu, Y. M.; Córdova, A. *Chem. Commun.* **2006**, 460; (i) Xu, Y. M.; Zou, W. B.; Sundén, H.; Ibrahim, I.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 418; (j) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *11*, 1701; (k) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599; (l) Liu, K.; Cui, H. F.; Nie, J.; Dong, K. Y.; Li, X. J.; Ma, J. A. *Org. Lett.* **2007**, *9*, 923.
- (a) Luo, S. Z.; Xu, H.; Mi, X. L.; Li, J. Y.; Zheng, X. X.; Cheng, J. P. *J. Org. Chem.* **2006**, *71*, 9244; (b) Yan, Z. Y.; Niu, Y. N.; Wei, H. L.; Wu, L. Y.; Zhao, Y. B.; Liang, Y. M. *Tetrahedron: Asymmetry* **2006**, *17*, 3288.
- (a) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808; (b) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84; (c) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611.
- (a) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737; (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509; (c) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527; (d) Pansare, S. V.; Pandya, K. J. *Am. Chem. Soc.* **2006**, *128*, 9624; (e) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966; (f) Zhu, M. K.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491; (g) Vishnumaya; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117.
- (a) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611; (b) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901; (c) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559; (d) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147; (e) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559; (f) Mossé, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577.
- Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.
- (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369; (b) Zu, L. S.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077; (c) Wang, J.; Li, H.; Lou, B. S.; Zu, L. S.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321; (d) Diez, D.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; García, P.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2007**, *63*, 740.
- (a) Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901; (b) Cao, Y. J.; Lai, Y. Y.; Wang, X.; Li, Y. J.; Xiao, W. J. *Tetrahedron Lett.* **2007**, *48*, 21.
- (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; (b) Zu, L. S.; Li, H.; Wang, J.; Yu, X. H.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 5131; (c) Li, Y. W.; Liu, X. Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2034; (d) Albertshofer, K.; Thayumanavan, R.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2007**, *48*, 693; (e) Zhu, S. L.; Yu, S. Y.; Ma, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 545; (f) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719; (g) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722.
- (a) Martin, H. J.; List, B. *Synlett* **2003**, 1901; (b) Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984; (c) Luo, S. Z.; Mi, X. L.; Song, L. Z.; Xu, H.; Cheng, J. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093; (d) Luo, S. Z.; Mi, X. L.; Liu, S.; Xu, H.; Cheng, J. P. *Chem. Commun.* **2006**, 3687; (e) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2064; (f) Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135; (g) Clarke, M. L.; Fuentes, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 930; (h) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2007**, 178; (i) Li, P. H.; Wang, L.; Wang, M.; Zhang, Y. C. *Eur. J. Org. Chem.* **2008**, 1157; (j) Mandal, T.; Zhao, C. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714; (k) Xue, F.; Zhang, S. I.; Duan, W. H.; Wang, W. *Adv. Synth. Catal.* **2008**, *350*, 2194.
- (a) Liu, F. Y.; Wang, S. W.; Wang, N.; Peng, Y. G. *Synlett* **2007**, *15*, 2415; The catalyst **1** has also been used in catalytic epoxidation reactions: (b) Zhao, G. L.; Ibrahim, I.; Sundén, H.; Cordova, A. *Adv. Synth. Catal.* **2007**, *349*, 1210.
- General procedure for asymmetric Michael addition of ketones or aldehydes to nitroolefins catalyzed by **3a**. A mixture of catalyst **3a** (5 mol %), PhCOOH (5 mol %), and ketone or aldehyde (2.5 mol) in 1 mL of CH<sub>3</sub>CN were stirred at room temperature for 20 min, and then cooled to 0 °C. Nitroolefin (0.25 mmol) was added. The mixture was stirred at 0 °C until the completion of the reaction monitored by TLC. The product was purified by silica gel column chromatography (petroleum ether and ethyl acetate as eluent). (S)-2-((R)-2-nitro-1-phenylethyl)cyclohexanone (Table 2, entry 1): >99% yield. mp 125–126 °C;  $[\alpha]_D^{25}$  –26.1 (c 1.42, CHCl<sub>3</sub>). HPLC condition: chiripak AD-H, 254 nm, 0.5 mL/min, hexane/i-PrOH = 90/10,  $t_r$  (major) = 25.90 min,  $t_r$  (minor) = 21.61 min, ee = 98%, dr = 95:5.
- Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *J. Mol. Catal. A: Chem.* **2007**, *263*, 186.
- Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.