CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000688

Asymmetric Conjugate Addition of Nitromethane to Enones Catalyzed by Chiral *N*,*N'*-Dioxide–Scandium(III) Complexes

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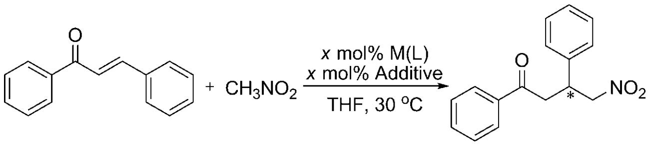
The catalytic conjugate addition of nitroalkanes to α,β-unsaturated ketones is one of the most important processes in organic synthesis,[1,2,3] since the corresponding products are very useful intermediates for the synthesis of a variety of more elaborate structures, such as amino alkanes, amino carbonyls, lactones, and pyrrolidines. In the past decades, tremendous effort has been devoted to this area; however, to the best of our knowledge, most of these syntheses are promoted by organocatalysts[4] or phase-transfer catalysts,[5] although reactions catalyzed by chiral metal complexes, such as heterobimetallic chiral catalysts,[6a] lanthanum trisbinaphthoxide,[6b] and a salen–Al complex,[6c] have also been reported. Furthermore, catalysts in previous studies generally suffer from limitations in substrate scope that mean they are only effective for one particular type of enone and catalysts with high efficiency for both chalcone and "cinnamone" derivatives have rarely been reported. Therefore, finding a simple, efficient synthesis for both of these types of enone, with high enantioselectivity and broad substrate scope, is still challenging and interesting. Herein, we report that a Sc$(OTf)_3$/*N*,*N'*-dioxide complex[7,8] efficiently promotes the Michael addition of nitromethanes to enones, providing the desired adducts in excellent yields (up to 99%) and excellent enantiomeric excesses (up to >99% for chalcone and up to 98% for "cinnamone" derivatives).

Table 1. Asymmetric Michael addition of nitromethane to chalcone.[a]



1a **2a** **3a**

Entry	Metal	Ligand	Additive[b]	*x* [mol%]	Yield [%][c]	*ee* [%][d]
1	La$(OTf)_3$	**L1**	DIPEA	10	32	16
2	Sm$(OTf)_3$	**L1**	DIPEA	10	27	51
3	Y$(OTf)_3$	**L1**	DIPEA	10	39	59
4	Yb$(OTf)_3$	**L1**	DIPEA	10	42	53
5	Sc$(OTf)_3$	**L1**	DIPEA	10	37	97
6	Sc$(OTf)_3$	**L2**	DIPEA	10	trace	n.d.[e]
7	Sc$(OTf)_3$	**L3**	DIPEA	10	trace	n.d.[e]
8	Sc$(OTf)_3$	**L4**	DIPEA	10	40	98
9	Sc$(OTf)_3$	**L5**	DIPEA	10	49	>99
10	Sc$(OTf)_3$	**L5**	DMAP	10	56	99
11[f]	Sc$(OTf)_3$	**L5**	DMAP	10	99	>99
12[g]	Sc$(OTf)_3$	**L5**	DMAP	2	99	99
13[h]	Sc$(OTf)_3$	**L5**	DMAP	1	99	99

[a] Unless otherwise stated, the reaction was carried out with chalcone (0.1 mmol) and nitromethane (1.5 equiv) at 30 °C in THF (0.5 mL) for 48 h. [b] DIPEA = diisopropylethylamine, DMAP = *N*,*N*-dimethylpyridin-4-amine. [c] Yield of the isolated product. [d] Determined by HPLC analysis. [e] n.d. = not determined. [f] Nitromethane (0.1 mL) was used as the solvent and the reaction was performed at 30 °C for 24 h. [g] Reaction was performed with chalcone (0.4 mmol) and nitromethane (0.43 mL) under neat condition at 30 °C for 24 h. [h] Reaction was performed with chalcone (0.8 mmol) and nitromethane (0.86 mL) with no solvent at 30 °C for 72 h.

The reaction between chalcone and nitromethane was selected as the model reaction for optimizing the conditions. A screening of different metals revealed that Sc$(OTf)_3$ was superior to any other at giving the product (Table 1, entry 5 vs. 1–4). Subsequently, the structure of the *N*,*N'*-dioxide ligand was studied (**L1**–**L5**). It was shown that ligands with bulky groups at the *ortho* position of the aniline functionality, such as isopropyl groups, provide good results (Table 1, entry 8 vs. 6 and 7). As for the chiral backbone, if an (*S*)-ramipril-derived *N*,*N'*-dioxide was used instead of those derived from L-proline or (*S*)-pipecolic acid, the result was slightly improved (>99% *ee*; Table 1, entry 9).

To further improve the efficiency of the reaction, several other reaction conditions, such as additives and solvents,

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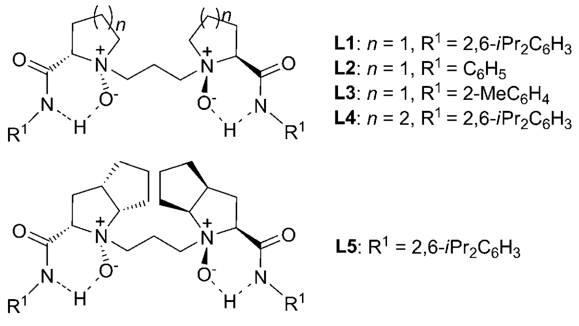
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000688.

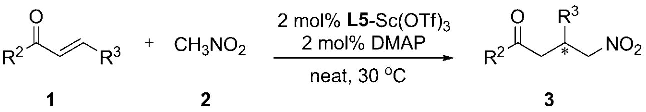


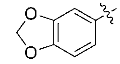
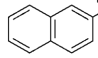
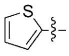
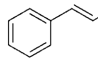
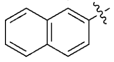
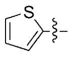
were investigated. These revealed that utilizing DMAP as an additive provides a slight increase in the yield (Table 1, entry 10). If the nitromethane reagent was used as the solvent, both an excellent yield and enantioselectivity were obtained within half the original reaction time (24 h, Table 1, entry 11). Furthermore, even if the catalyst loading was reduced to 2 mol %, the yield and enantioselectivity were maintained after the same reaction time (24 h, Table 1, entry 12). The reaction was also tested under 1 mol % catalyst loading and the corresponding product was obtained without any loss of yield or enantiomeric excess, but a longer reaction time was required (72 h, Table 1, entry 13).

Under the optimized conditions (Table 1, entry 12), a series of functionalized chalcones were examined, giving the corresponding products in excellent yields with 98 to >99 % *ee* (Table 2). It is notable that this catalyst system exhibited a remarkably broad substrate scope, in which neither the electronic properties, nor the steric hindrance of the substituent on benzene had an evident effect on the enantioselectivity (Table 2, entries 1–12, 16–19). Chalcone derivatives containing a naphthalene moiety reacted smoothly with nitromethane to give the expected products in excellent enantioselectivities (Table 2, entries 13 and 20). Furthermore, the excellent enantioselectivities were also achieved for heteroaromatic chalcone derivatives (99 to >99 % *ee*; Table 2, entries 14 and 21). Moreover, the reaction was applicable to (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one, giving an excellent result for the corresponding 1,4-addition product (Table 2, entry 15).

Nitroethane was also investigated as a reagent in this asymmetric conjugate addition reaction. Each diastereomer of the desired product could be obtained separately by using silica gel column chromatography and both were formed in excellent enantioselectivities (Table 2, entry 22).

Table 2. Asymmetric Michael addition of nitromethane to chalcones **1a**–**u**.[a]



Entry	R^2	R^3	Product	Yield [%][b]	*ee* [%][c]
1[d]	Ph	Ph	**3a**	99	99(*S*)[e]
2	Ph	4-FC_6H_4	**3b**	99	99
3	Ph	4-ClC_6H_4	**3c**	99	99(*S*)[e]
4	Ph	3-ClC_6H_4	**3d**	97	99
5	Ph	2-ClC_6H_4	**3e**	98	99
6	Ph	4-BrC_6H_4	**3f**	92	99
7	Ph	4-MeC_6H_4	**3g**	99	99
8	Ph	3-MeC_6H_4	**3h**	99	99
9	Ph	4-$MeOC_6H_4$	**3i**	94	98
10	Ph	3-$MeOC_6H_4$	**3j**	98	99
11	Ph	2-$MeOC_6H_4$	**3k**	95	99
12	Ph		**3l**	99	99
13	Ph		**3m**	81	99
14	Ph		**3n**	86	99
15	Ph		**3o**	95	99
16	4-FC_6H_4	Ph	**3p**	99	>99
17	4-ClC_6H_4	Ph	**3q**	99	>99
18	4-MeC_6H_4	Ph	**3r**	99	99
19	3-MeC_6H_4	Ph	**3s**	99	99
20		Ph	**3t**	99	99
21		Ph	**3u**	87	>99
22[f]	Ph	Ph	**3v**	56/44[g]	98/>99

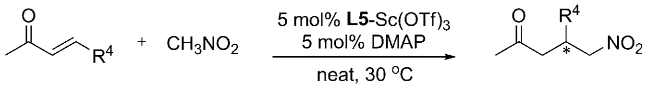
[a] Unless otherwise stated, reactions were performed with chalcones **1** (0.4 mmol) and M/L/A (1:1:1, 2 mol %) in nitromethane (0.43 mL) at 30 °C for 48 h (M = Metal, L = Ligand, A = Additive). [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Reaction was finished after 24 h. [e] The absolute configurations were determined by comparison with the literature.[5c,9] [f] Reaction was carried out with chalcone **1a** (0.25 mmol) and M/L/A (1:1:1, 5 mol %) in nitroethane (0.36 mL) at 30 °C for 4 d. [g] Diastereomers.

Interestingly, this **L5**–Sc(OTf)$_3$ catalyst can also promote the conjugate addition of nitromethane with a wide range of “cinnamone” derivatives. The reactions of “cinnamone” derivatives, compared with those of chalcone derivatives, generally needed a longer reaction time and 5 mol % catalyst loading due to their lower reactivity. As summarized in Table 3, “cinnamones” bearing not only electron-donating, but also electron-withdrawing groups on benzene proceeded in high to excellent yields with excellent enantioselectivities (Table 3, entries 1–8). The reaction of the “cinnamone” derivative containing a naphthyl group was also promoted under the same conditions and provided the desired product in an excellent yield and enantiomeric excess (Table 3, entry 9). An α,β-unsaturated aliphatic ketone was also examined and gave a good yield and enantiomeric excess (Table 3, entry 10).

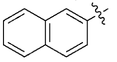
To further investigate the synthetic potential of this strategy, chalcone (10 mmol, 2.08 g) was reacted under the optimal conditions for functionalized “cinnamones” and the corresponding product was obtained without any loss of yield (2.67 g, 99 % yield) or enantiomeric excess (99 % *ee*, Scheme 1).

In summary, we have developed a simple to handle, highly efficient *N*,*N*′-dioxide–scandium(III) catalyst for the asymmetric conjugate addition of nitromethane to chalcone, as well as “cinnamone”, derivatives, under mild conditions.

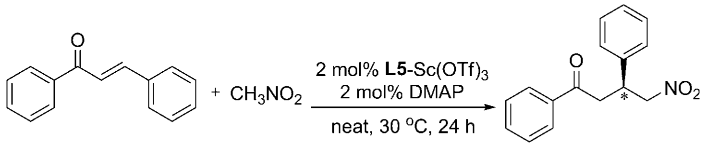
Table 3. Asymmetric Michael addition of nitromethane to cinnamones **4a**–**j**.[a]



4 **2a** **5**

Entry	R^4	Product	Yield [%][b]	*ee* [%][c]
1[d]	Ph	**5a**	97	97(*S*)[e]
2	4-FC_6H_4	**5b**	99	96(*S*)[e]
3	4-BrC_6H_4	**5c**	96	94(*S*)[e]
4	3-MeC_6H_4	**5d**	89	97
5	4-$MeOC_6H_4$	**5e**	99	97(*S*)[e]
6	3-$MeOC_6H_4$	**5f**	95	97
7	2-$MeOC_6H_4$	**5g**	99	98
8	4-$NO_2C_6H_4$	**5h**	82	96(*S*)[e]
9		**5i**	99	97
10	*n*Pr	**5j**	71	87

[a] Unless otherwise stated, reactions were carried out with cinnamones **4** (0.25 mmol) and M/L/A (1:1:1, 5 mol%) in nitromethane (0.28 mL) at 30°C for 72 h. [b] Yield of isolated product. [c] Determined by HPLC or GC analysis. [d] Reaction was finished after 48 h. [e] The absolute configurations were determined by comparison with the literature.[4i]



2.08 g, 10 mmol

2.67 g, 99% yield
99% *ee*

Scheme 1. Reaction carried out on a large scale.

In the presence of only 2–5 mol% catalyst loading, significant results have been obtained with an extremely broad substrate scope, giving the corresponding products in high to excellent yields and excellent enantiomeric excesses. Furthermore, the synthetic potential of this methodology was also demonstrated by the excellent result that could be obtained if the reaction was performed on a gram scale. Further studies into the high diastereoselectivity of the reaction with other nitroalkanes and systematic work on the Michael addition of other enones are in progress.

Experimental Section

General procedure for the conjugate addition of nitromethane to chalcone: The **L5**–Sc(III) triflate complex (2 mol%, 1:1) and nitromethane (0.2 mL) were stirred in a test tube under a N_2 atmosphere at 30°C for 0.5 h. Then, chalcone (0.4 mmol) and DMAP (2 mol%) were added sequentially, followed by more nitromethane (0.23 mL) and the mixture was stirred at 30°C for 24 h. The reaction mixture was then purified by column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1:8–1:10) to afford a white solid (106.7 mg, 99% yield, 99% *ee*). $[\alpha]_D^{28}=-23.2$ ($c=1.0$, in $CHCl_3$) [ref. [9]: $[\alpha]_D^{20}=+21.1$ ($c=0.360$ in $CHCl_3$, 99% *ee*)]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.32$–3.54 (m, 2H), 4.22–4.29 (m, 1H), 4.69–4.74 (dd, $J_1=8.0$ Hz, $J_2=12.4$ Hz, 1H), 4.84–4.89 (dd, $J_1=8.0$ Hz, $J_2=12.4$ Hz, 1H), 7.16–7.38 (m, 5H), 7.44–7.48 (m, 2H), 7.58–7.62 (t, $J=7.2$ Hz, 1H), 7.93–7.95 (d, $J=8.0$ Hz, 2H); HPLC analysis using a chiral AD-H column (*i*PrOH/hexane = 10:90, 1.0 mL min^{-1}, 210 nm), t_r (major) = 14.81 min, t_r (minor) = 20.48 min, 99% *ee*.

General procedure for the scaled up conjugate addition of nitromethane to chalcone: The **L5**–Sc(III) triflate complex (2 mol%, 1:1) and nitromethane (5.0 mL) were stirred in a dry flask under a N_2 atmosphere at 30°C for 0.5 h. Then, chalcone (2.08 g, 10.0 mmol) and DMAP (2 mol%) were added sequentially, followed by more nitromethane (5.75 mL) and the mixture was stirred at 30°C for 24 h. The reaction mixture was then purified by column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1:8–1:10) to afford a white solid (2.67 g, 99% yield, 99% *ee*).

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 20732003 and 20702033), PCSIRT (No. IRT0846) and the National Basic Research Program of China (973 Program; No. 2010CB833300) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR analyses.

Keywords: asymmetric catalysis · enones · Michael addition · N,O ligands

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[1] For reviews of conjugate addition reactions, see: a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**; b) M. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; c) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933.

[2] For recent reviews dealing with enantioselective conjugate addition, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) O. E. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1788; c) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279.

[3] For recent reviews of nitro-Michael reactions, see: O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877.

[4] For methods that use organocatalysts, see: a) A. P. Davis, K. J. Dempsey, *Tetrahedron: Asymmetry* **1995**, *6*, 2829; b) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; c) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; d) M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, P. W. R. Caulkett, *Tetrahedron Lett.* **2003**, *44*, 8677; e) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; f) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897; g) B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.* **2008**, *73*, 3475; h) X. Liang, J. Ye, P. Li, Y. Wang, *Chem. Commun.* **2008**, 3302; i) K. Mei, M. Jin, S. Zhang, P. Li, W. Liu, X. Chen, F. Xue, W. Duan, W. Wang, *Org. Lett.* **2009**, *11*, 2864.

[5] For methods that use phase-transfer catalysts, see: a) S. Colonna, H. Hiemstra, H. Wynberg, *J. Chem. Soc. Chem. Commun.* **1978**, 238; b) P. Bakó, A. Szöllősy, P. Bombicz, L. Tőke, *Synlett* **1997**, 291; c) E. J. Corey, F. Y. Zhang, *Org. Lett.* **2000**, *2*, 4257; d) D. Y. Kim, S. C. Huh, *Tetrahedron* **2001**, *57*, 8933; e) G. Sundararajan, N. Prabagaran, *Org. Lett.* **2001**, *3*, 389; f) M. Hua, H. Cui, L. Wang, J. Nie, J. Ma, *Angew. Chem.* **2010**, *122*, 2832; *Angew. Chem. Int. Ed.* **2010**, *49*, 2772.

[6] For methods that use chiral metal complexes, see: a) E. Keller, N. Veldman, A. L. Spek, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 3403; b) K. Funabashi, Y. Saida, M. Kanai, T. Arai, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7557; c) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313.

[7] For reviews of chiral *N*-oxides, see: a) A. V. Malkov, P. Kočovský, *Eur. J. Org. Chem.* **2007**, 29; b) G. Chelucci, G. Murineddu, G. A. Pinna, *Tetrahedron: Asymmetry* **2004**, *15*, 1373; c) I. A. O'Neil, N. D. Miller, J. V. Barkley, C. M. R. Low, S. B. Kalindjian, *Synlett* **1995**, 617, and references therein.

[8] For recent works that use chiral *N*-oxides, see: a) W. Wang, X. Liu, W. Cao, J. Wang, L. Lin, X. Feng, *Chem. Eur. J.* **2010**, *16*, 1664; b) Y. Liu, D. Shang, X. Zhou, Y. Zhu, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2010**, *12*, 180; c) X. Zhou, D. Shang, Q. Zhang, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2009**, *11*, 1401; d) D. Chen, Z. Chen, X. Xiao, Z. Yang, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 6807; e) Y. Hui, Q. Zhang, J. Jiang, L. Lin, X. Liu, X. Feng, *J. Org. Chem.* **2009**, *74*, 6878; f) K. Zheng, J. Shi, X. Liu, X. Feng, *J. Am. Chem. Soc.* **2008**, *130*, 15770; g) Z. Yu, X. Liu, Z. Dong, M. Xie, X. Feng, *Angew. Chem.* **2008**, *120*, 1328; *Angew. Chem. Int. Ed.* **2008**, *47*, 1308; h) L. Wang, X. Liu, Z. Dong, X. Fu, X. Feng, *Angew. Chem.* **2008**, *120*, 8798; *Angew. Chem. Int. Ed.* **2008**, *47*, 8670; i) D. Shang, J. Xin, Y. Liu, X. Zhou, X. Liu, X. Feng, *J. Org. Chem.* **2008**, *73*, 630.

[9] J. Liu, Z. Yang, X. Liu, Z. Wang, Y. Lin, S. Bai, L. Lin, X. Feng, *Org. Biomol. Chem.* **2009**, *7*, 4120.

Received: March 18, 2010