DOI: 10.1002/adsc.200700353

Highly Enantioselective Organocatalytic Conjugate Addition of Nitromethane to α,β-Unsaturated Aldehydes: Three-Step Synthesis of Optically Active Baclofen

Liansuo Zu,[a] Hexin Xie,[a] Hao Li,[a] Jian Wang,[a] and Wei Wang[a,*]

[a] Department of Chemistry and Chemical Biology, University of New Mexico, MSC03 2060, Albuquerque, NM 87131-0001, USA
Fax: (+1)-505-277-2609; e-mail: wwang@unm.edu

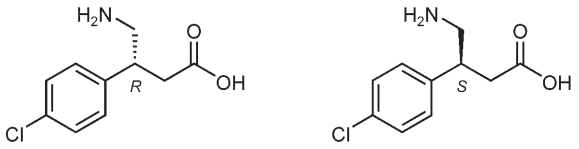
Received: July 17, 2007; Revised: September 22, 2007; Published online: November 21, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: An efficient, organocatalytic, highly enantioselective, conjugate addition reaction of nitromethane with α,β-unsaturated aldehydes has been developed. The process serves as the key step for a practical 3-step synthesis of chiral baclofen, an antispastic drug.

Keywords: asymmetric catalysis; asymmetric synthesis; C–C bond formation; Michael addition; organic catalysis

The synthesis of natural products and therapeutics has served as a principal driving force for discovering new synthetic methods. On the other hand, the synthetic value of useful synthetic methods can be quickly established in the context of the efficient preparation of biologically important pharmaceuticals and natural products. Baclofen (**1**; Figure 1), a potent

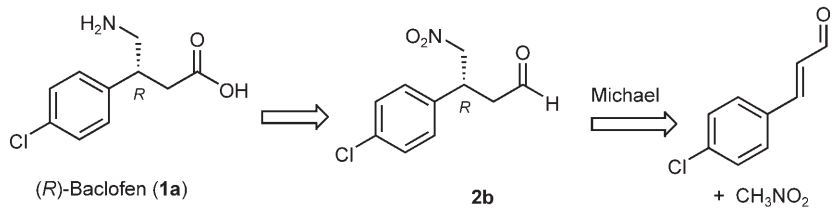


(*R*)-Baclofen (**1a**) (*S*)-Baclofen (**1b**)

Figure 1. The structures of chiral baclofen (**1**).

$GABA_B$ receptor agonist, is used for the treatment of spinal cord injury-induced spasm.[1] Despite the fact that the racemic form of baclofen is used in clinical practice,[1a] the (*R*) enantiomer is the essential active chemical entity and its (*S*) form is inactive. Accordingly, a great deal of effort has been directed to the synthesis of chiral (*R*)-baclofen. These methodologies rely on the use of chiral precursors,[2] chiral auxiliaries,[3] and chemical[4] and enzymatic[5] resolutions. Atom-economic asymmetric catalytic strategies including organometallic[6] and organocatalytic[7] systems also have been developed. However, these approaches suffer from long synthetic sequences and the use of not readily available chemicals, thus limiting their practical application for a large-scale synthesis. The synthetic significance is further underscored by the utilization of baclofen as a lead compound for the design of GABA agonists and antagonists to seek new therapeutic agents targeting on the central nervous system (CNS).[1a,8] The analogues of baclofen can potentially be developed for the treatment of a variety of diseases including epilepsy, Huntington's and Parkinson's diseases, and other psychiatric disorders, such as anxiety and pain.[1a,8] As a consequence, the development of general, efficient synthetic strategies enabling a facile approach to chiral baclofen and its analogues is of considerable significance from the standpoint of the medicinal and organic chemistry. Driven by the lack of such a facile access to this class of compounds, in this communication we disclose a remarkably efficient and practical route for the highly enantioselective synthesis of optically active baclofen in 3 steps from the readily available simple achiral molecules α,β-unsaturated aldehydes and nitroalkanes. The key step relies on a highly efficient organocatalytic enantioselective conjugate addition reaction of nitromethane with α,β-unsaturated aldehydes, which we have successfully developed in the study. This efficient synthetic strategy can be further explored for the rapid preparation of new chiral baclofen analogues in drug discovery.

Our synthetic strategy towards chiral baclofen (**1**) is described in Scheme 1. We hypothesized that compound **1** could be constructed from chiral γ-nitro aldehyde **2** *via* the oxidation of the aldehyde and the sub-



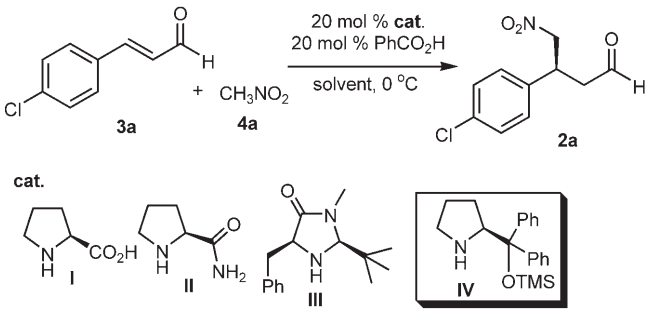
Scheme 1. Retrosynthetic analysis of chiral baclofen (**1**).

sequent reduction of the nitro group in a straightforward manner. This raised a synthetic challenge related to the assembly of the key intermediate **2**. We were intrigued by the possibility offered by a catalytic enantioselective conjugate addition of nitromethane to an α,β-unsaturated aldehyde, which serves as the critical step in the synthesis. If successful, the strategy proposed here would be, to the best of our knowledge, the most efficient approach to chiral baclofen (**1**). Moreover, the merit of the method is highlighted by the use of the readily available simple achiral nitroalkanes and α,β-unsaturated aldehydes.

Conjugate addition reactions have been demonstrated as a powerful tool in organic synthesis.[9] Recently, organocatalytic asymmetric versions of the processes have been hotly pursued.[10] Notably, stabilized carbanions as nucleophiles for the conjugate addition to α,β-unsaturated systems, which involve the formation of new C–C bonds, have been intensively studied. Although significant progress has been made for α,β-unsaturated ketone,[11] ester,[12] amide/imide[13] and nitrostyrene[14] substrates, the development of a catalytic method to promote enantioselective conjugate additions of stabilized carbanions to α,β-unsaturated aldehydes has proven to be more challenging. One of the main reasons for this is the greater susceptibility of α,β-unsaturated aldehydes to 1,2-addition reactions as compared to other unsaturated systems. Thus, it is not surprising that only a few successful examples of these reactions have been presented.[15] Prior to our investigation, no study has been reported using nitroalkanes as a nucleophile for the direct conjugate addition process.[16] During the course of our study, Arvidsson and co-workers described such a process using MacMillan's chiral imidazolidinone as promoter.[17] It is noted that the process affords products with only moderate enantioselectivities (a typical range of *ca.* 70–80% *ee*). Even lower *ee* (47%) was obtained when nitromethane was used. In this context, we reveal an organocatalytic conjugate addition protocol which achieves significantly improved enantioselectivities (87–99% *ee*). Remarkably, excellent levels of enantioselectivities (96–99% *ee*) are achieved for nitromethane as nucleophile. The highly optically active products serve as a useful molecular basis for the synthesis of chiral baclofen and its analogues.

In initial exploratory efforts aimed at the development of chiral amine-catalyzed asymmetric conjugate addition reactions, we screened 4 chiral pyrrolidines and pyrrolidinones **I–IV** (Table 1). A model reaction

Table 1. Optimization of organocatalytic enantioselective conjugate addition reactions.[a]



Entry	Catalyst	Solvent	*t* [h]	Yield[b] [%]	% *ee*[c]
1	**I**	EtOH	36	20	nd[d]
2	**II**	EtOH	36	0	nd[d]
3	**III**	EtOH	36	0	nd[d]
4	**IV**	EtOH	15	75	97
5	**IV**	MeOH	32	75	99
6	**IV**	*i*-PrOH	9	60	97
7	**IV**	CH_2Cl_2	36	0	nd[d]
8	**IV**	toluene	36	0	nd[d]
9	**IV**	THF	36	0	nd[d]
10	**IV**	MeCN	36	0	nd[d]

[a] Reaction conditions: see Experimental Section.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).
[d] Not determined.

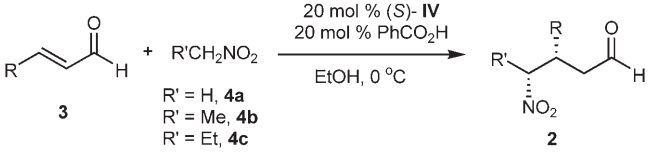
between *trans*-cinnamaldehyde **3a** and nitromethane **4a** in the presence of 20 mol% catalyst and $PhCO_2H$ in EtOH at 0 °C was conducted (entries 1–4). It was found that their activities differed significantly. Among the catalysts probed, (*S*)-diphenylprolinol TMS ether **IV** was the best promoter for the process (entry 4).[18] Notably, an excellent level of enantioselectivity (97% *ee*) and good yield (75%) were achieved. Encouraged by the promising results, we selected the catalyst **IV** for an optimization of the reaction conditions. A survey of solvents revealed that the processes were highly solvent-dependent (entries 4–9).

The reactions carried out in the protic solvents EtOH, MeOH and *i*-PrOH proceeded faster and gave higher yields (75%, 75% and 60%, respectively entries 4–6). More importantly, reactions in these solvents were highly enantioselective (97–99% *ee*). However, no reactions occurred in other media probed (entries 7–10).

Having established the optimal reaction conditions, we next probed the generality of this asymmetric catalytic conjugate addition reaction of nitroalkanes **4** with a variety of α,β-unsaturated aldehydes **3** in EtOH at 0°C (Table 2). The results show that the reactions take place efficiently (65–82%), and excellent levels of enantioselectivity (96–99%) with nitromethane **4a** as nucleophile (entries 1–12) are achieved. Significant structural variation in the α,β-unsaturated aldehydes is tolerated in this reaction, which occurs efficiently, independent of the nature of the substituents on the aromatic ring, where electron-withdrawing groups (entries 1–5), electron-donating groups (entries 6–8), neutral groups (entry 9), or combinations thereof (entry 10) are included. It is also realized that the reaction is inert to steric hindrance (entries 5 and 8). Furthermore, heteroaromatic (entry 11) and conjugated aromatic (entry 12) systems can participate in the processes as well. Finally, we probed the structural effect of the nitroalkanes **4** on the conjugate reactions (entries 13–15). It is found that high *ee*s (87–99%) for both *syn* and *anti* diastereomers are obtained, albeit with an only poor *dr* when nitroethane **4b** and nitropropane **4c** are exploited. These results indicate that the processes described here are superior to those reported by Arvidsson.[17] It is also realized the limitation of the (*S*)-**IV**-catalyzed process is that the reactions proceed sluggishly with aliphatic enals.

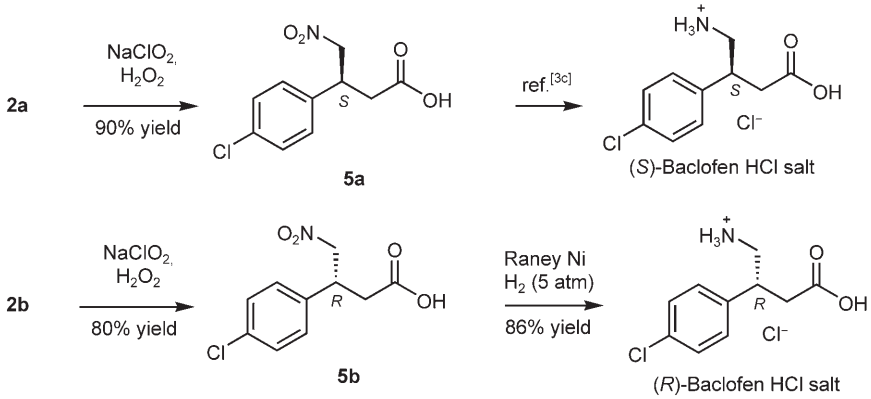
To determine the absolute configuration of the (*S*)-**IV**-catalyzed conjugate addition process, we converted compound **2a** to carboxylic acid **5a**, which had been converted into baclofen (**1**).[3c] This also provides an opportunity to address the synthetic utility of the reaction. As shown in Scheme 2, compound **2a** can be conveniently converted to (*S*)-balcofen (**1b**) HCl salt in two steps (Scheme 2). $NaClO_2$-mediated oxidation

Table 2. (*S*)-**IV**-promoted conjugate addition of nitroalkane to α,β-unsaturated aldehydes.[a]



Entry	R, R′, product	*t* [h]	Yield[b] [%]	% *ee*[c]	*dr*[d]
1	4-ClC_6H_4, H, **2a**	15	75	97	-
2[e]	4-ClC_6H_4, H, **2b**	15	73	−96	-
3[f]	4-$NO_2C_6H_4$, H, **2c**	20	72	99	-
4	3-FC_6H_4, H, **2d**	24	80	96	-
5	2-$NO_2C_6H_4$, H, **2e**	20	65	97	-
6[f]	4-$MeOC_6H_4$, H, **2f**	20	77	99	-
7	3-$MeOC_6H_4$, H, **2g**	20	76	96	-
8	2-$MeOC_6H_4$, H, **2h**	20	70	97	-
9	Ph, H, **2i**	24	82	96	-
10	3-MeO-4-AcC_6H_3, H, **2j**	20	65	99	-
11[f]	2-furanyl, H, **2k**	34	68	96	-
12[f]	1-naphthyl, H, **2l**	20	70	96	
13[g]	Ph, Me, **2m**	9	92	*syn* 87[f]; *anti* 99	6/5
14[g]	2-$NO_2C_6H_4$, Me, **2n**	12	87	*syn* 92[f]; *anti* 94	3/2
15[f]	2-$NO_2C_6H_4$, Et, **2o**	30	90	*syn* 92[f]; *anti* 99	3/1

[a] Unless specified, see Experimental Section.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H or Chiralcel OD-H).
[d] Determined by ^1H NMR.
[e] (*R*)-**IV** used.
[f] The *ee* was determined after converted to corresponding enone with $Ph_3P=CHCOPh$.
[g] Reaction performed at room temperature.



Scheme 2. Synthesis of (*S*)- and (*R*)-baclofens (**1**).

of aldehyde **2a** gives rise to **5a** in 90% yield,[19] which can be subsequently reduced to baclofen by hydrogenation in the presence of Raney-Ni following the known procedure.[3c] The analytical data of the synthesized **5a** match those previously reported,[3c] thus confirming the absolute (*S*) configuration. We also synthesized the enantiomer **2b** in 73% yield and 96% *ee* under the same reaction conditions using (*R*)-**IV** as a catalyst (Table 2, entry 2). It is noted that the 4-chloro enal **3a** was readily prepared from commercially available 4-chlorobenzaldehdye.[20] Moreover, experimentally, the (*R*)-**2b** was demonstrated to be efficiently transformed to (*R*)-baclofen (**1a**) HCl salt using the same procedures in a gram-scale (Scheme 2).

In conclusion, motivated by the lack of the efficient methods for the preparation of therapeutic agent chiral baclofen and its analogues, we have developed an efficient organocatalytic, highly enantioselective conjugated addition reaction of nitroalkanes with α,β-unsaturated aldehydes. This mild and simple experimental protocol affords conjugate adducts with useful levels of enantiocontrol (≥87–99% *ee*). As demonstrated, the highly optically pure products can be conveniently transformed into the highly enantio-enriched baclofen in two steps. It is our expectation that the 3-step synthetic route will provide a potential for the large-scale of preparation of the drug in the industrial setting and the strategy could be exploited for the preparation of chiral rolipram and its analogues.

Experimental Section

Typical Procedure (Table 2, entry 1)

A mixture of **3a** (0.10 mmol), nitromethane (**4a**) (0.3 mmol), benzoic acid (0.02 mmol), and catalyst (*S*)-**IV** (0.02 mmol) in EtOH (0.2 mL) was stirred for 15 h at 0 °C. The crude product was purified by column chromatography on silica gel to give the desired product **2a** in 75% yield with 97% *ee*, determined by HPLC (Chiralpak AS-H, *i*-PrOH/hexanes = 30/70, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{major} = 31.64 min, t_{minor} = 43.79 min; $[\alpha]_D^{25}$: −11.7 (*c* 1.0, $CHCl_3$).

Acknowledgements

The financial support for this research by the Department of Chemistry and the Research Allocation Committee, University of New Mexico, the National Science Foundation (CHE-0704015) and the American Chemical Society-PRF (G1 type) is gratefully acknowledged.

References

[1] a) H. R. Olpe, H. Demieville, V. Baltzer, W. L. Bencze, W. P. Koella, P. Wolf, H. L. Haas, *Eur. J. Pharmacol.* **1978**, *52*, 133; b) N. G. Bowery, *Trends Pharm. Sci.* **1982**, *31*, 401.

[2] a) M. Hayashi, K. Ogasawara, *Heterocycles* **2003**, *59*, 785; b) S. Yoshifuji, M. Kaname, *Chem. Pharm. Bull.* **1995**, *43*, 1302; c) C. Herdeis, H. P. Hubmann, *Tetrahedron: Asymmetry* **1992**, *3*, 1213.

[3] a) A. Armstrong, N. J. Convine, M. E. Popkin, *Synlett* **2006**, 1589; b) D. Enders, O. Niemeier, *Heterocycles* **2005**, *66*, 385; c) P. Camps, D. Munoz-Torrero, L. Sanchez, *Tetrahedron: Asymmetry* **2004**, *15*, 2039; d) E. Licandro, S. Maiorana, C. Baldoli, L. Capella, D. Perdicchia, *Tetrahedron: Asymmetry* **2000**, *11*, 975; e) P. Resende, W. P. Almeida, F. Coelho, *Tetrahedron: Asymmetry* **1999**, *10*, 2113; f) N. Langlois, N. Dahuron, H.-S. Wang, *Tetrahedron* **1996**, *52*, 15117; g) A. Schoenfelder, A. Mann, S. Le Coz, *Synlett* **1993**, 63.

[4] S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun.* **2000**, 1009.

[5] a) F. Felluga, V. Gombac, G. Pitacco, E. Valentin, *Tetrahedron: Asymmetry* **2005**, *16*, 1341; b) C. Mazzini, J. Lebreton, V. Alphand, R. Furstoss, *Tetrahedron Lett.* **1997**, *38*, 1195; c) E. Brenna, N. Caraccia, C. Fuganti, D. Fuganti, P. Grasselli, *Tetrahedron: Asymmetry* **1997**, *8*, 3801; d) R. Chenevert, M. Desjardins, *Can. J. Chem.* **1994**, *72*, 2312.

[6] a) A. S. Paraskar, A. Sudalai, *Tetrahedron* **2006**, *62*, 4907; b) T. Nemoto, L. Jin, H. Nakamura, Y. Hamada, *Tetrahedron Lett.* **2006**, *47*, 6577; c) J.-M. Becht, O. Meyer, G. Helmchen, *Synthesis* **2003**, 2805; d) O. Belda, S. Lundgren, C. Moberg, *Org. Lett.* **2003**, *5*, 2275; e) V. V. Thakur, M. D. Nikalje, A. Sudalai, *Tetrahedron: Asymmetry* **2003**, *14*, 581; f) M. P. Doyle, W.-H. Hu, *Chirality* **2002**, *14*, 169; g) C. Baldoli, S. Maiorana, E. Licandro, D. Perdicchia, B. Vandoni, *Tetrahedron: Asymmetry* **2000**, *11*, 2007.

[7] a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; b) E. J. Corey, F.-Y. Zhang, *Org. Lett.* **2000**, *2*, 4257.

[8] a) N. G. Bowery, D. R. Hill, A. L. Hudson, *Neuropharmacology* **1985**, *24*, 207; b) N. G. Bowery, A. L. Hudson, G. W. Price, *Neuroscience* **1987**, *20*, 365; c) S. Shuto, N. Shibuty, S. Yamada, T. Ohkura, R. Kimura, A. Matsuda, *Chem. Pharm. Bull.* **1999**, *47*, 1188.

[9] M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033.

[10] Recent reviews of organocatalytic conjugate addition reactions, see: a) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; c) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 7496; d) W. Notz, F. Tanaka, C. F. Barbas, III, *Acc. Chem. Res.* **2004**, *37*, 580; e) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481.

[11] a) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem. Int. Ed.* **2007**, *46*, 389; b) J. Wang, H. Li, L.-S. Zu, W. Jiang, H.-X. Xie, W.-H. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652; c) C. E. T. Mitchell, S. E. Brenner, J. S. Garcia-Fortanet, S. V. Ley, *Org. Biomol.*

Chem. **2006**, *4*, 2039; d) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66; e) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 947; f) C. Palomo, R. Pazos, M. Oiarbide, J. M. Garcia, *Adv. Synth. Catal.* **2006**, *348*, 1161; g) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; h) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346; i) B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967; j) S. B. Tsogoeva, S. B. Jagtap, *Synlett* **2004**, 2624; k) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; l) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975.

[12] a) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948; b) T. Ooi, S. Fujioka, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 11790; c) D. B. Ramachary, K. N. Anebouselvy, S. Chowdari, C. F. Barbas, III., *J. Org. Chem.* **2004**, *69*, 5838; d) D. B. Ramachary, C. F. Barbas, III, *Chem. Eur. J.* **2004**, *10*, 5323; e) D. B. Ramachary, N. S. Chowdari, C. F. Barbas, III, *Angew. Chem. Int. Ed.* **2003**, *42*, 4233.

[13] a) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032; b) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204.

[14] a) J. Wang, H. Li, L.-S. Zu, W. Jiang, W. Wang, *Adv. Synth. Catal.* **2006**, *348*, 2047; b) S. H. McCooey, T. McCabe, S. J. Connon, *J. Org. Chem.* **2006**, *71*, 7494; c) J.-X. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; d) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; e) J. Wang, H. Li, W.-H. Duan, L.-S. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713; f) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *117*, 6734; g) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105; h) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906; i) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[15] For a review of MacMillan's catalyst-catalyzed reactions based on the iminium chemistry, see: a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79; for selected examples, see: b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; c) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; d) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894; e) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192; f) L.-S. Zu, H. Li, H.-X. Xie, J. Wang, W. Jiang, Y. Tang, W. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 3732; g) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928; h) S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 4305; i) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 4301.

[16] Organocatalytic indirect Mukaiyama–Michael reactions, see: a) W. Wang, H. Li, J. Wang, *Org. Lett.* **2005**, *7*, 1637; b) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 9022; and recently Enders and co-workers reported cascade nitroalkane addition processes: c) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem. Int. Ed.* **2007**, *46*, 467; d) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861.

[17] L. Hojabri, A. Hartikka, F. M. Moghaddam, P. I. Arvidsson, *Adv. Synth. Catal.* **2007**, *349*, 740.

[18] Reviews of chiral diarylprolinol silyl ethers catalyzed reactions, see: a) D. Enders, C. Grondal, M. R. M. Huttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; for leading references, see: c) M. Marigo, T. C. Wabnitz, D. Fielenbach, Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794; d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; e) Y.-G. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804.

[19] E. Dalcanale, F. Montanari, *J. Org. Chem.* **1986**, *51*, 567.

[20] P. K. Mahata, O. Barun, H. Ila, H. Junjappa, *Synlett* **2000**, 1345.

