Angewandte Chemie

DOI: 10.1002/anie.200900269

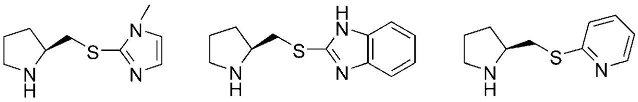
Asymmetric Catalysis

In Situ Enamine Activation in Aqueous Salt Solutions: Highly Efficient Asymmetric Organocatalytic Diels–Alder Reaction of Cyclohexenones with Nitroolefins**

*Dan-Qian Xu, Ai-Bao Xia, Shu-Ping Luo, Jie Tang, Shuai Zhang, Jun-Rong Jiang, and Zhen-Yuan Xu**

The Diels–Alder reaction is one of the most powerful pericyclic reactions for the construction of six-membered functionalized cyclic frameworks. In the wake of the emergence of organocatalysis, great efforts have been devoted to the development of organocatalytic enantioselective versions of this reaction, as it allows in principle the formation of four contiguous asymmetric centers.[1,2] MacMillan and co-workers developed the first highly enantioselective amine-catalyzed Diels–Alder reaction of α,β-unsaturated carbonyl compounds as dienophiles via LUMO-lowering iminium formation.[3] Since then, iminum ion catalysis has been established as an effective platform for enantioselective Diels–Alder reactions.[4] Alternatively, Barbas and co-workers discovered the first amine-catalyzed Diels–Alder reaction of α,β-unsaturated carbonyl compounds as dienes involving in situ enamine activation.[5] This strategy has been successfully applied in several hetero-Diels–Alder reactions.[6] Other organocatalytic Diels–Alder reactions have also been reported that use chiral Brønsted acids,[7] N-heterocyclic carbenes,[8] and cinchona alkaloids.[9]

Water occupies a special place amongst alternative reaction media owing to its unique properties.[10] Apart from the obvious economic and environmental benefits, the aqueous medium can have favorable effects on reaction activity and selectivity. Most notably, intensive investigations have revealed the dramatic acceleration of the Diels–Alder reaction in aqueous solutions.[11] Recently, the positive benefits of aqueous solutions were also discovered in organocatalysis. Ogilvie and Lemay developed a novel cyclic hydrazide catalyst that functioned best in water for the asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes with cyclopentadiene via rapid iminium formation.[12a] Hayashi and co-workers reported that water increased the enantioselectivity and accelerated the Diels–Alder reaction of α,β-unsaturated aldehydes with dienes, catalyzed by a diarylprolinol silyl ether salt, to provide predominantly the exo isomer of the Diels–Alder adducts.[12b] Several highly diastereoselective and enantioselective aldol[13] and Michael[14] reactions were successfully developed to proceed in aqueous media. Herein, we describe the development of a highly efficient organocatalytic system in aqueous salt solutions for the enantioselective Diels–Alder reaction of cyclohexenones with nitroolefins, a reaction which remained elusive to date.[15] The organocatalysts used (Scheme 1) were developed in our group and are highly efficient in enantioselective Michael and oxa-Michael–Henry reactions.[16]



1a **1b** **1c**

Scheme 1. The organocatalysts used in this study.

Initially, using amine catalyst **1a**, good enantioselectivity was obtained in the Diels–Alder reaction between cyclohex-2-enone and β-nitrostyrene in THF, although the reaction rate and conversion both remained low (Table 1, entry 1). Encouragingly, the reaction was not only dramatically accelerated using water as a solvent, but also a higher enantioselectivity was obtained than that in THF, providing the Diels–Alder adduct with 90% conversion and 82% *ee* after 24 h (Table 1, entry 2). The Diels–Alder reaction was further improved in water and saturated brine in the presence of the catalyst **1c** (Table 1, entries 4 and 5). Furthermore, the best results were obtained when seawater, taken directly from the East China Sea, was used as a solvent (Table 1, entry 6). Reaction in boiled seawater gave similar results to those in untreated seawater, suggesting an important role of salts on the reaction rather than microorganisms (Table 1, entry 13 vs. entry 16). Further tests showed that the concentration of aqueous NaCl evidently affected the performance of the reaction.[17] Therefore, owing to the good dispersion of reactants in aqueous salt solutions and the salting-out effect, nearly 100% conversions and high diastero- and enantioselectivities were obtained from seawater and 7.5% NaCl aqueous solution (Table 1, entries 13, 16, and 17).

Among catalysts **1a–c**, catalyst **1c** was the most suitable for the Diels–Alder reaction in terms of conversion and enantioselectivity (Table 1, entries 2–4). The additive acid

---

[*] D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu
State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology
Hangzhou (China)
Fax: (+86) 571-8832-0066
E-mail: greenchem@zjut.edu.cn

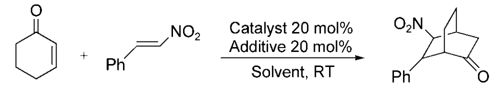
[**] This work was supported by the National Natural Science Foundation of China (No. 20772110) and the Program for Changjiang Scholars and Innovative Research Team in University of China.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900269.

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

WILEY InterScience® DISCOVER SOMETHING GREAT

Table 1: Screening of various reaction conditions for the Diels–Alder reaction of cyclohex-2-enone with β-nitrostyrene.[a]



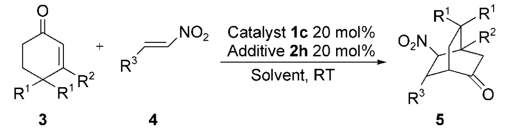
Entry	Cat.	Additive	Solvent	t [h]	Conv. [%][b]	exo/endo[c]	ee [%][d]
1	**1a**	$C_6H_5CO_2H$ **2a**	THF	96	35	>25:1	80
2	**1a**	$C_6H_5CO_2H$ **2a**	H_2O	24	90	>25:1	82
3	**1b**	$C_6H_5CO_2H$ **2a**	H_2O	24	20	>25:1	75
4	**1c**	$C_6H_5CO_2H$ **2a**	H_2O	24	95	>25:1	85
5	**1c**	$C_6H_5CO_2H$ **2a**	brine[e]	20	>99	>25:1	82
6	**1c**	$C_6H_5CO_2H$ **2a**	SW[f]	20	>99	>25:1	85
7	**1c**	CH_3CO_2H **2b**	SW	18	>99	>20:1	82
8	**1c**	CF_3CO_2H **2c**	SW	24	55	>25:1	84
9	**1c**	2-$C_{10}H_7SO_3$[g] **2d**	SW	24	60	>25:1	84
10	**1c**	4-$NO_2C_6H_4CO_2H$ **2e**	SW	20	>99	>20:1	90
11	**1c**	3-$NO_2C_6H_4CO_2H$ **2f**	SW	20	>99	>20:1	85
12	**1c**	2-$NO_2C_6H_4CO_2H$ **2g**	SW	24	98	>20:1	88
13	**1c**	4-$CF_3C_6H_4CO_2H$ **2h**	SW	20	>99	>25:1	95
14	**1c**	2-$CF_3C_6H_4CO_2H$ **2i**	SW	24	97	>20:1	89
15	**1c**	4-$FC_6H_4CO_2H$ **2j**	SW	24	98	>20:1	93
16	**1c**	4-$CF_3C_6H_4CO_2H$ **2h**	SW[h]	20	>99	>25:1	94
17	**1c**	4-$CF_3C_6H_4CO_2H$ **2h**	brine[i]	20	>99	>25:1	96

[a] All the reactions were conducted in solvent (1 mL) using cyclohex-2-enone (1 mmol) and β-nitrostyrene (0.75 mmol) in the presence of 20 mol% catalyst and 20 mol% additive at room temperature with vigorous stirring. [b] Conversion to the product, as determined by GC-MS. [c] Determined by HPLC analysis on a chiralcel OD-H column. [d] Values of *ee* for the exo isomer. [e] Saturated aqueous NaCl solution. [f] SW = seawater taken directly from the East China Sea. [g] 2-Naphthalenesulfonic acid. [h] Boiled seawater. [i] 7.5% aqueous NaCl solution (mass concentration).

was found to play another important role on the reaction (Table 1, entry 6–15). Weak acids, such as acetic acid and benzoic acid and its derivatives, were superior to stronger acids, such as 2-naphthalenesulfonic acid and trifluoroacetic acid. Of the acids investigated, 4-trifluoromethylbenzoic acid was found to be the most effective, and reactions in aqueous salt solutions were complete within 20 h with 94–96% *ee* (Table 1, entries 13, 16, and 17).

Next, the enantioselective organocatalytic Diels–Alder reaction of various cyclohexenones with nitroolefins was investigated in seawater and 7.5% NaCl aqueous solution. As shown in Table 2, the combination of catalyst **1c** and additive acid **2h** exhibited excellent asymmetric catalytic effects, and furthermore, the nitroolefins with different substitution patterns were tolerated in seawater and brine. It appeared that the electronic property and the position of the substituents for the phenyl ring of nitroolefins had a very limited influence on the diastero- and enantioselectivity of the reaction. The nitroolefins bearing groups at the *para*-position of the phenyl ring gave higher yields than those at other positions (Table 2, entry 3 vs. entries 1,2; entry 9 vs. entry 8). The reaction was also applicable to heterocyclic nitroolefins, producing the desired Diel–Alder adduct with 96% yield and 92–94% *ee* (Table 2, entry 12). Surprisingly, both 3- and 4-methyl-substituted cyclohex-2-enones underwent Diels–Alder reaction with excellent yields and high enantioselectivities (Table 2, entries 13, 14). In general, corresponding results from reactions in seawater and 7.5% NaCl aqueous solution were essentially the same, and good to high yields were observed; the enantioselectivities were as high as 96%.

Table 2: Diels–Alder reactions of cyclohexenones with nitroolefins promoted by catalyst **1c** in seawater and brine.[a]



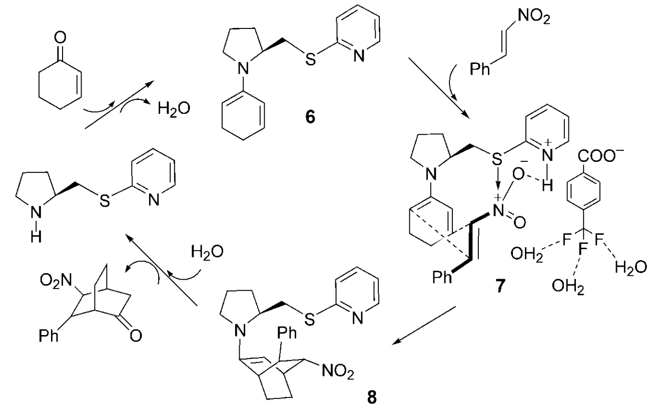
Entry	R^1	R^2	R^3	Prod.	t [h]	Conv.[b] [%][c]	Y[b] [%][d]	ee[b] [%][e]
1	H	H	2-$MeOC_6H_4$	**5a**	20	80 (85)	60 (66)	90 (91)
2	H	H	3-$MeOC_6H_4$	**5b**	12	85 (83)	80 (80)	96 (96)
3	H	H	4-$MeOC_6H_4$	**5c**	20	>99 (97)	98 (95)	93 (93)
4	H	H	4-MeC_6H_4	**5d**	20	>99 (97)	97 (96)	93 (93)
5	H	H	Ph	**5e**	20	>99 (99)	98 (96)	95 (96)
6	H	H	4-FC_6H_4	**5f**	20	>99 (>99)	97 (97)	95 (95)
7	H	H	4-ClC_6H_4	**5g**	20	>99 (95)	99 (93)	94 (94)
8	H	H	3-BrC_6H_4	**5h**	12	60 (63)	55 (56)	88 (90)
9	H	H	4-BrC_6H_4	**5i**	12	95 (93)	92 (90)	92 (94)
10	H	H	3-$NO_2C_6H_4$	**5j**	12	80 (78)	70 (71)	93 (93)
11	H	H	4-$CF_3C_6H_4$	**5k**	12	>99 (>99)	98 (97)	90 (91)
12	H	H	2-furanyl	**5l**	20	>99 (>99)	96 (96)	92 (94)
13	H	Me	Ph	**5m**	36	>99 (98)	95 (95)	83 (85)
14	Me	H	Ph	**5n**	20	98 (>99)	96 (97)	93 (94)

[a] All reactions were conducted in seawater or 7.5% aqueous NaCl solution (1 mL) using cyclohexenones **3** (1 mmol) and nitroolefins **4** (0.75 mmol) in the presence of 20 mol% catalyst **1c** and 20 mol% acid **2h** at room temperature with vigorous stirring. [b] Results from reactions in 7.5% NaCl aqueous solution shown in parentheses. [c] Conversion to the product as determined by GC-MS. [d] Yield of isolated product. [e] Determined by chiral-phase HPLC; values of *ee* for the exo isomer; the ratio (exo/endo) is >25:1 for all the products.

The stereochemical outcome of the Diels–Alder reaction was determined on the basis of the X-ray crystal structure of the adduct **5i**, which revealed that adduct **5i** had the absolute configuration (3*S*, 4*S*, 5*R*, 6*S*).[17]

We propose a mechanism to account for the observed results (Scheme 2). First, the catalyst **1c** forms a chiral enamine **6** with the cyclohexenones **3**, and the nitroolefin **4** forms a complex with the catalyst **1c** and additive acid **2h**. [4+2] pericyclization of the in situ enamine-activated **6** and

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. The catalytic cycle and transition state for the in situ enamine-catalyzed Diels–Alder reaction.

the activated nitroolefin **4** leads to formation of the corresponding enamine **8** via the transition state **7**. Hydrolysis by water finally affords the desired Diels–Alder adduct **5** and releases the catalyst **1c**, which continues the subsequent catalytic cycle. The existence of the intermediates **6** and **8** in the reaction mixture was further confirmed using the ESI-MS (Figure 1). The fact that seawater or brine significantly enhance the catalytic performance of the Diels–Alder reaction suggests that seawater or brine should play other roles in the process besides the salt effect, which might stabilize the transition state **7** through a hydrogen-bonding interaction with the acid **2h** and favor the hydrolysis step to finish the catalytic cycle. It is noteworthy that in our experiments, corresponding Michael adducts of cyclohexenones **3** to nitroolefins **4** were not found during the transformations, suggesting that in the present catalytic system, cyclization is involved in the one-step concerted addition pathway rather than a sequential of the Michael/Michael mechanism.[6,15]

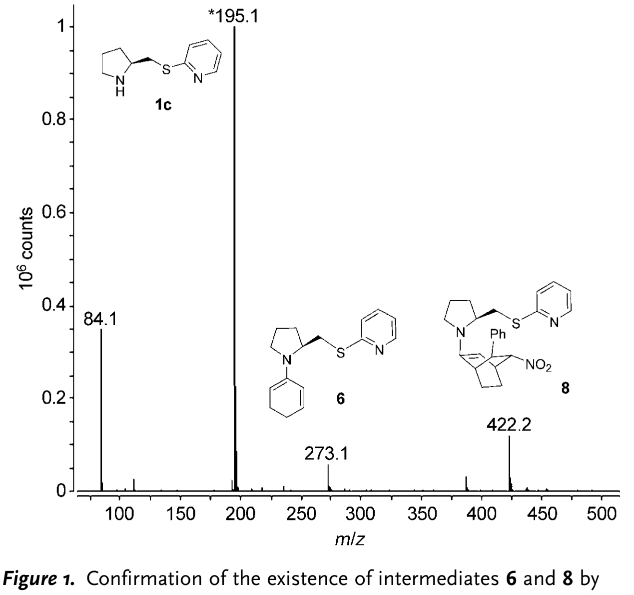


Figure 1. Confirmation of the existence of intermediates **6** and **8** by ESI-MS. The fragment at *m/z* 84.1 corresponds to $[2\text{-}CH_2\text{-}C_4H_8N]^+$.

In summary, we have developed a highly efficient asymmetric organocatalytic Diels–Alder reaction of cyclohexenones with aromatic nitroolefins in seawater and brine with excellent chemo-, regio- and stereoselectivities. Cyclization was involved in the concerted addition process. Most importantly, seawater and brine significantly promoted the reaction performance, and both led to essentially the same results. Further investigations into applying the catalytic system to other synthetically useful asymmetric transformations are underway.

Received: January 16, 2009
Revised: February 25, 2009
Published online: April 24, 2009

Keywords: asymmetric catalysis · bicyclic systems · Diels–Alder reaction · organocatalysis · water chemistry

---

[1] For selected reviews on enantioselective Diels–Alder reactions, see: a) H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007; b) D. A. Evans, J. S. Johnson, *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**; c) K. Maruoka, *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**; d) E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

[2] For selected reviews on organocatalysis, see: a) *Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis* (Eds.: A. Berkessel, H. Groeger), Wiley-VCH, Weinheim, **2005**; b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; e) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; f) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; g) D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[3] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458; c) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616.

[4] For some leading examples, see: a) R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* **2006**, *128*, 3543; b) H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859; c) N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Angew. Chem.* **2007**, *119*, 5836; *Angew. Chem. Int. Ed.* **2007**, *46*, 5734; d) R. Gilmour, T. J. Prior, J. W. Burton, A. B. Holmes, *Chem. Commun.* **2007**, 3954; e) Y. Zou, Q. Wang, A. Goeke, *Chem. Eur. J.* **2008**, *14*, 5335; f) K. Ishihara, K. Nakano, M. Akakura, *Org. Lett.* **2008**, *10*, 2893.

[5] a) R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 3817; b) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 6743.

[6] For some leading examples, see: a) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877; b) F. Aznar, A.-B. García, M.-A. Cabal, *Adv. Synth. Catal.* **2006**, *348*, 2443; c) N. Momiyama, Y. Yamamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 1190.

[7] a) D. C. Braddock, I. D. MacGilp, B. G. Perry, *Adv. Synth. Catal.* **2004**, *346*, 1117; b) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; c) H. Liu, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2006**, *8*, 6023; d) D. Nakashima, H. Yamamoto, *J. Am.*

Chem. Soc. **2006**, *128*, 9626; e) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070.

[8] M. He, B. J. Beahm, J. W. Bode, *Org. Lett.* **2008**, *10*, 3817.

[9] a) Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364; b) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422.

[10] For selected reviews, see: a) *Organic Reaction in Aqueous Media* (Ed.: C. J. Li), Willey, New York, **1997**; b) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie Academic and Professional, London, **1998**; c) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751; d) D. Sinou, *Adv. Synth. Catal.* **2002**, *344*, 221; e) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095; f) M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312; g) C. I. Herrerías, X. Yao, Z. Li, C. J. Li, *Chem. Rev.* **2007**, *107*, 2546.

[11] a) D. C. Rideout , R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816; b) A. Kumar, *Chem. Rev.* **2001**, *101*, 1.

[12] a) M. Lemay, W. W. Ogilvie, *Org. Lett.* **2005**, *7*, 4141; b) Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 6736; *Angew. Chem. Int. Ed.* **2008**, *47*, 6634.

[13] a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972; *Angew. Chem. Int. Ed.* **2006**, *45*, 958; b) S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246; c) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* **2008**, *37*, 1502.

[14] a) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966; b) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431; c) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555; *Angew. Chem. Int. Ed.* **2008**, *47*, 545.

[15] H. Sundén, R. Rios, Y. Xu, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 2549.

[16] a) D. Q. Xu, S. P. Luo, Y. F. Wang, A. B. Xia, H. D. Yue, L. P. Wang, Z. Y. Xu, *Chem. Commun.* **2007**, 4393; b) D.-Q. Xu, Y.-F. Wang, S.-P. Luo, S. Zhang, A.-G. Zhong, H. Chen, Z.-Y. Xu, *Adv. Synth. Catal.* **2008**, *350*, 2610.

[17] See the Supporting Information for more details.

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim