DOI: 10.1002/adsc.200800771

Pyrrolidine-Camphor Derivative as an Organocatalyst for Asymmetic Michael Additions of α,α-Disubstituted Aldehydes to β-Nitroalkenes: Construction of Quaternary Carbon-Bearing Aldehydes under Solvent-Free Conditions

Chihliang Chang,[a] Ssu-Hsien Li,[a] Raju Jannapu Reddy,[a] and Kwunmin Chen[a,*]

[a] Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan 116, ROC
Fax: (+886)-2-2932-4249; e-mail: kchen@ntnu.edu.tw

Received: December 11, 2008; Revised: March 30, 2009; Published online: May 27, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800771.

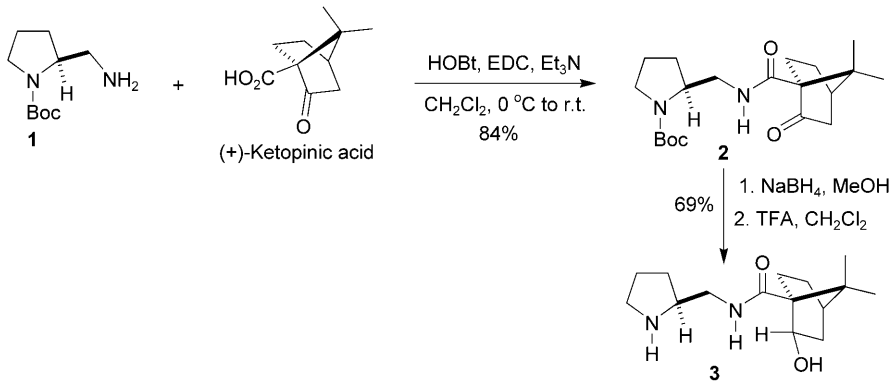
Abstract: A novel pyrrolidine-camphor organocatalyst **3** was designed, synthesized and proven to be an efficient catalyst for the asymmetric Michael reaction. Treatment of α,α-disubstituted aldehydes with β-nitroalkenes in the presence of 20 mol% organocatalyst **3** and 20 mol% benzoic acid under solvent-free conditions provided the desired Michael product possessing an all-carbon quaternary center with high chemical yields (up to 99% yield) and high levels of enantioselectivities (up to 95% *ee*).

Keywords: asymmetric catalysis; Michael reaction; β-nitroalkenes; quaternary carbon centers; solvent-free reaction

Remarkable advances have been realized in the use of small privileged organic molecules to catalyze asymmetric reactions. The development of organocatalysts in asymmetric reaction has attracted much attention in recent years as organocatalysts are generally non-toxic, highly efficient and selective, environmentally friendly, and stable under aerobic and aqueous reaction conditions.[1,2] The Michael reaction is one of the most efficient and powerful atom-economic carbon-carbon bond forming reactions in organic chemistry[3] and, therefore, developing enantioselective Michael reactions has been the focus of many organic chemists for decades.[4] Since the pioneering works of organocatalysts, many methods have been developed for the direct asymmetric Michael addition of unmodified aldehydes/ketones with nitroalkenes to produce enantiomerically enriched nitroalkanes.[5] The synthesis of quaternary stereogenic centers is considered a challenging task in organic synthesis[6] and there has been only a few reports on the use of α, α-disubstituted aldehydes.[7] The use of an α,α-disubstituted aldehyde donor should directly produce a Michael product with an all-carbon quaternary center.

Most recently, many research groups have independently demonstrated that brine and water are good reaction media for asymmetric Michael reactions of aldehydes and ketones with nitroolefins.[8] Performing organic reactions in aqueous medium is one of the most fundamental and challenging goals and considerable progress has been made in recent years.[9] On the other hand, solvent-free conditions,[5k,7a,10] have proved to be very effective in many reaction types due to the intimacy of the reactants. Recently, we have designed and synthesized camphor-containing thiourea derivatives, as organocatalysts for the asymmetric aldol reaction on water.[11] In continuation of our research interest, we herein, report an eco-friendly process for the direct asymmetric Michael reaction of α,α-disubstituted aldehydes with β-nitroalkene acceptors. The novel pyrrolidine-based camphor derivative serves as an efficient bifunctional organocatalyst to catalyze the reaction and provide Michael products possessing an all-carbon quaternary center under solvent-free conditions. High levels of chemical yields and enantioselectivities were generally achieved (up to 99% chemical yield and 95% *ee*).

The design and synthesis of highly stereoselective, readily accessible and tunable catalysts are always desirable for asymmetric catalysis. In this direction, we have developed an efficient synthesis of pyrrolidine-camphor organocatalyst **3**. We began with the known Boc protected (*S*)-2-aminomethylpyrrolidine (**1**),[12] which was treated with ketopinic acid under standard coupling conditions (HOBt, EDC and Et_3N in CH_2Cl_2) to give product **2** with an 84% yield (Scheme 1). Reduction of **2** using sodium borohydride

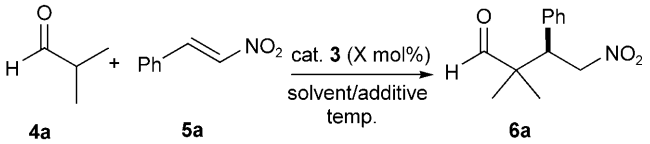


Scheme 1. Synthesis of camphor-containing pyrrolidine organocatalyst **3**.

to provide the corresponding *exo* alcohol as a single diastereomer which was treated with TFA in CH_2Cl_2 provided the desired organocatalyst **3** without incident. The synthetic route of **3** is quite straightforward and can be scaled up to gram quantities (3.0 g). The structure of organocatalyst **3** was fully characterized by IR, ^{1}H-, ^{13}C NMR and HR-MS analyses and the absolute stereochemistry was further confirmed by a single crystal X-ray structure analysis (see Supporting Information).[13]

As a model case, we explored the direct Michael reaction of isobutyraldehyde (**4a**) with *trans*-β-nitrostyrene (**5a**) catalyzed by **3** on water or brine. A low chemical yield was obtained when H_2O was used as the reaction medium with moderate enantioselectivity (Table 1, entry 1). Both the chemical yield and stereo-

Table 1. Optimization of enantioselective Michael addition of isobutyraldehyde (**4a**) to β-nitrostyrene (**5a**) catalyzed by **3**.[a]



Entry	Cat. **3** [mol%]	Solvent	Additive[b]	*T* [°C]	*t* [days]	Yield[c] [%] of **6a**	*ee* [%][d]
1	10	H_2O	–	0	7.0	14	42
2	10	Brine	–	0	7.0	45	68
3	15	Brine	–	0	5.0	56	67
4	20	Brine	–	0	5.0	80	77
5	20	MeOH	–	0	1.0	67	54
6	20	*i*-PrOH	–	0	3.0	46	11
7	20	THF	–	0	3.0	48	53
8	20	CH_2Cl_2	–	0	3.0	34	52
9	20	$CHCl_3$	–	0	3.0	39	52
10	20	Toluene	–	0	3.0	42	70
11	20	Neat	–	0	2.0	62	75
12	20	Neat	TsOH	30	2.0	90	71
13	20	Neat	AcOH	30	2.0	67	77
14	20	Neat	HCl	30	2.0	24	75
15	20	Neat	TFA	30	2.0	26	78
16	20	Neat	Citric acid	30	1.0	77	78
17	20	Neat	$PhCO_2H$	30	0.5	77	79
18	20	Neat	$PhCO_2H$	0	1.0	88	85
19	20	Neat	$PhCO_2H$	−20	1.0	17	87

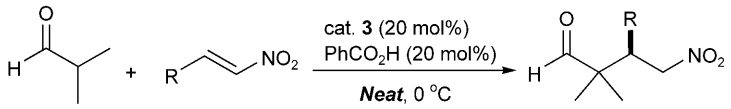
[a] Unless otherwise specified, all reactions were carried out using isobutyraldehyde (**4a**, 0.80 mmol), *trans*-β-nitrostyrene (**5a**, 0.20 mmol) and 10–20 mol% catalyst **3**.
[b] 20 mol% of acid additive was added.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis (see Supporting Information).

selectivity increased when brine was used as the reaction medium at 0 °C (Table 1, entry 2). The reactivity and enantioselectivity increased with increasing amount of catalyst loading (Table 1, entries 3 and 4). At 0 °C the chemical yields and enantioselectivities were not significantly improved in polar solvents like MeOH, *i*-PrOH and THF (Table 1, entries 5–7). The Michael product **6a** was obtained, with poor results, when the reaction was carried out in CH_2Cl_2 and $CHCl_3$ for 3 days (Table 1, entries 8 and 9). Low chemical yield (41%) and good enantioselectivity (70% *ee*) were obtained when the reaction was carried out in toluene at 0 °C (Table 1, entry 10). Only traces amount of the product **6a** was observed when we performed the reaction in DMSO, DMF, CH_3CN and 1,4-dioxane (data not shown). Although good results were achieved in aqueous medium, the reaction still suffered from the longer reaction time (5 days). The reaction was completed in 2 days when it was carried out under neat conditions at 0 °C. A reasonable chemical yield (62%) and good stereoselectivity (75% *ee*) were observed (Table 1, entry 11).

Encouraged by these results, we then proceeded to optimize the catalysis conditions. The presence of a Brønsted acid could promote the formation of the enamine species, and thereby, improve both the reactivity and selectivities. To test this, we then studied the additive effect of the Michael addition in the presence of 20 mol% of various acid additives. High chemical yield (90%) with good enantioselectivity (71%) were obtained when TsOH was used under the solvent-free conditions at 30 °C (Table 1, entry 12). No significant improvement was observed in terms of both reactivity and selectivity when acetic acid was used as an additive (Table 1, entry 13). The use of HCl and TFA provided the desired Michael adduct with low chemical yields (Table 1, entries 14 and 15). This may be due to the protonation of the amine catalyst decreasing the nucleophilicity and subsequently hampering the enamine formation. Significant reactivity and selectivity were observed when the reaction was carried out with 20 mol% citric acid at 30 °C under neat conditions (Table 1, entry 16). The reactivity increased in the presence of benzoic acid to give the desired product **6a** with 77% yield and 79% *ee* (Table 1, entry 17). The enantioselectivity was further improved to 85% *ee* when the reaction was carried out at 0 °C for 1 day (Table 1, entry 18). The reactivity dropped significantly when the reaction was carried out at −20 °C but retained the same level of stereoselectivity (Table 1, entry 19). Among the additives used, benzoic acid turned out to be the most efficient. It is worth mentioning here that only 4 equivalents of isobutyraldehyde were used as a donor to β-nitrostyrene for this catalytic process.[5a–e,g,h,k,n,o]

With these optimal reaction conditions, we further examined a variety of nitroolefins (**5a–l**) with isobutyraldehyde (**4a**) to establish the general utility of this asymmetric transformation (Table 2). All reactions were performed under solvent-free conditions at 0 °C

Table 2. Substrate studies of the Michael addition of **4a** to various β-nitroalkenes (**5a–m**) under solvent-free conditions at 0 °C.[a]



4a **5a – m** **6a – m**

Entry	**5**	R	Product **6**	Time [days]	Yield [%][b]	*ee* [%][c]
1	**5a**	C_6H_5	**6a**	1.0	88	85
2	**5b**	4-Me-C_6H_4	**6b**	0.5	89	84
3	**5c**	2-MeO-C_6H_4	**6c**	3.0	92	71
4	**5d**	3-MeO-C_6H_4	**6d**	0.5	88	85
5	**5e**	4-MeO-C_6H_4	**6e**	0.5	96	83
6	**5f**	2-CF_3-C_6H_4	**6f**	3.0	66	52
7	**5g**	3-CF_3-C_6H_4	**6g**	0.5	88	85
8	**5h**	2-Br-C_6H_4	**6h**	1.0	88	60
9	**5i**	3-Br-C_6H_4	**6i**	0.5	89	85
10	**5j**	4-Br-C_6H_4	**6j**	0.5	98	84
11	**5k**	3-Cl-C_6H_4	**6k**	0.5	92	85
12	**5l**	4-Cl-C_6H_4	**6l**	0.5	88	84
13[d]	**5m**	$PhCH_2CH_2$	**6m**	3.0	56	90

[a] Unless otherwise specified, all reactions were carried out using **4a** (0.80 mmol) with various nitroalkenes **5a–m** (0.20 mmol) in the presence of **3** (20 mol%) and benzoic acid (20 mol%) under neat conditions.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (see Supporting Information).
[d] The reaction was carried out at ambient temperature.

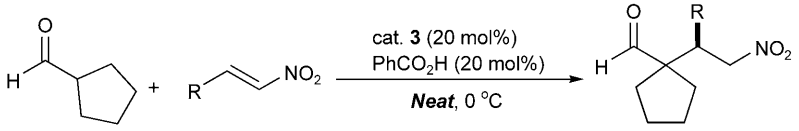
in the presence of 20 mol% of **3** and 20 mol% of benzoic acid. Various 3- or 4-substituted nitroalkenes reacted well with **4a** to provide the Michael products (**6a, b, d, e** and **6i–l**) with 88–98% yields and 83–85% enantioselectivities (Table 2, entries 1, 2, 4, 5, 7 and 9–12). In the case of 2-substituted nitroalkenes (**5c**, **f** and **h**) moderate enantioselectivities were observed (Table 2, entries 3, 6 and 8). This may be due the steric hindrance caused by the 2-substituent of the phenyl ring. In addition to aromatic nitroalkenes, an aliphatic nitroalkene such as (4-nitrobut-3-enyl)benzene (**5m**) was also a good Michael acceptor for this catalytic system. The desired product (**6m**) was obtained with high enantioselectivity under the optimum reaction conditions (Table 2, entry 13).

We then selected cyclopentanecarboxaldehyde (**4b**) as another donor to react with both electron-rich and electron-deficient aromatic nitroalkenes (**5a–l**). These reactions proceeded smoothly and the corresponding Michael products (**7a–l**) were obtained with excellent yields (80–99%) and high levels of enantioselectivity (up to 94%) (Table 3, entries 1–12). Again, the Michael reaction proceeded smoothly with aliphatic nitroalkenes. High chemical yield (85%) and excellent enantioselectivity (95% *ee*) were observed when (4-nitrobut-3-enyl)benzene (**5m**) was used (Table 3, entry 13). In the case of a heteroaromatic nitroalkene the corresponding Michael adduct (**7n**) was obtained with high enantioselectivity (Table 3, entry 14). The use of unsymmetrical α,α-disubsituted aldehydes have not yet been effectively utilized in the asymmetric Michael addition.[7a,e] In this regard, the reaction of unsymmetrical α,α-disubstituted aldehydes (2-methylbutanal and 2-phenylpropionaldehyde) with nitroalkenes catalyzed by **3** was then studied. Unfortunately, no desired product was isolated.[14]

The substituted chiral, non-racemic pyrrolidines are common structural units found in many natural and unnatural products that possess interesting and important biological activities.[15] To demonstrate the utility of this methodology, Michael adduct **7a** was transformed into a spiro-pyrrolidine derivative by means of a one-step procedure (Scheme 2). Hydrogenation of δ-nitroaldehyde **7a** in the presence of Pd/C furnished the products 3-phenyl-spiro-pyrrolidine *N*-oxide (**8**) and 1-hydroxy-3-phenyl-spiro-pyrrolidine (**9**) in high yields. Then, the 3-phenyl-spiro-pyrrolidine *N*-oxide (**8**) was further subject to $NaBH_4$ reduction in EtOH to afford spiro-product **9** in excellent yield (Scheme 2).

In summary, we have developed an efficient synthesis of a novel pyrrolidine-derived organocatalyst **3** which comprises a structurally rigid camphor scaffold. We have also demonstrated a practical application of organocatalyst **3** for Michael additions of α,α-disubstituted aldehydes to β-nitrostyrenes to produce quaternary carbon-containing products with high to excellent chemical yields and high levels of enantioselectivities under solvent-free conditions. This represents an alternative, attractive method for asymmetric

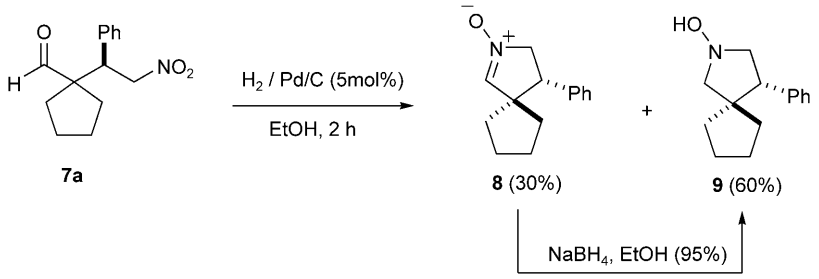
Table 3. Generality of the Michael addition of **4b** to various β-nitroalkenes (**5a–n**) under solvent-free condition at 0 °C.[a]



4b **5a – n** **7a – n**

Entry	**5**	R	Product **7**	Time [days]	Yield [%][b]	*ee* [%][c]
1	**5a**	C_6H_5	**7a**	1.0	95	93
2	**5b**	4-Me-C_6H_4	**7b**	1.0	95	93
3	**5c**	2-MeO-C_6H_4	**7c**	0.5	99	81
4	**5d**	3-MeO-C_6H_4	**7d**	0.5	99	92
5	**5e**	4-MeO-C_6H_4	**7e**	0.5	94	88
6	**5f**	2-CF_3-C_6H_4	**7f**	3.0	80	77
7	**5g**	3-CF_3-C_6H_4	**7g**	1.5	90	94
8	**5h**	2-Br-C_6H_4	**7h**	1.0	85	80
9	**5i**	3-Br-C_6H_4	**7i**	0.5	84	92
10	**5j**	4-Br-C_6H_4	**7j**	1.0	86	92
11	**5k**	3-Cl-C_6H_4	**7k**	0.5	87	92
12	**5l**	4-Cl-C_6H_4	**7l**	1.0	97	92
13	**5m**	$PhCH_2CH_2$	**7m**	1.0	85	95
14	**5n**	2-thienyl	**7n**	1.0	95	89

[a] All reactions were carried out using **4b** (0.80 mmol) with various nitroalkenes **5a–n** (0.20 mmol) in the presence of **3** (20 mol%) and benzoic acid (20 mol%) under neat conditions at 0 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (see Supporting Information).



Scheme 2. Synthesis of spiro-pyrrolidines **8** and **9**.

Michael additions. Further studies of the newly developed catalyst in organocatalysis are currently underway.

Experimental Section

General Procedure for the Asymmetric Michael Reaction

The α,α-disubstituted aldehyde (**4a** or **4b**) (0.80 mmol) was added to a mixture of catalyst **3** (13.6 mg, 0.04 mmol), benzoic acid (4.9 mg, 0.04 mmol) and corresponding nitroalkene (0.20 mmol). The reaction mixture was stirred at 0 °C for the requisite times as indicated in Table 1, Table 2 and Table 3. After the nitroalkene had been consumed as shown by TLC analysis, the reaction mixture was subject to flash column chromatography on silica gel (ethyl acetate/hexanes: 1:10) to afford the pure Michael product.

2,2-Dimethyl-4-nitro-3-phenyl-butanal **(6a):** ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.49$ (s, 1H), 7.34–7.29 (m, 1H), 7.28–7.22 (m, 2H), 7.22–7.15 (m, 2H), 4.85 (dd, $J = 13.1$ and 11.3 Hz, 1H), 4.69 (dd, $J = 13.1$ and 4.2 Hz, 1H), 3.78 (dd, $J = 11.3$ and 4.2 Hz, 1H), 1.12 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 204.1$, 135.3, 128.9, 128.5, 127.9, 76.1, 48.2, 48.0, 21.4, 18.6. The enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column (*i*-PrOH/hexanes: 20/80, flow rate: 0.8 mL min^{-1}, $\lambda = 254$ nm): $t_R = 13.6$ min (major), 18.5 min (minor).

Acknowledgements

We thank the National Science Council of the Republic of China (NSC 96–2113M-003-005-MY3) for financial support for this work. We are grateful to the Academic Paper Editing Clinic at NTNU, and the National Center for High-Performance Computing for providing us with computer time and facilities.

References

[1] For selected reviews on organocatalysis, see: a) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; d) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660.

[2] Special issues on organocatalysis, see: a) *Chem. Rev.* **2007**, *107*, no. 12; b) *Acc. Chem. Res.* **2004**, *37*, no. 8; c) *Adv. Synth. Catal.* **2004**, *346*, 9–10; d) P. I. Dalko, *Enantioselective Organoctalysis*, Wiley-VCH, Weinheim, **2007**; e) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*: *From Biomimetic Concepts to Applications in Asymmetric Synthesis* Wiley-VCH, Weinheim, **2005**.

[3] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.

[4] For reviews of organocatalytic asymmetric conjugate addition reactions, see: a) K. Tomioka, Y. Nagaoka, M. Yamaguchi, in: *Comprehensive Asymmetric Catalysis*, *Vol. III*, chap. 31.1 and 31.2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**; b) S. Sulzer-Mosse, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135; c) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065–2092; d) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; e) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; f) N. Krause, A. Hoffmann-Roder, *Synthesis* **2001**, 171–196; g) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061.

[5] Asymmetric Michael additions of aldehydes and ketones to nitroolefins, see: a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425; b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740; c) A. Alexakis, O. Andrey, *Org. Lett.* **2003**, *5*, 3611–3614; d) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; e) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; f) Y. Xu, W. Zou, H. Sunden, I. Ibrahem, A. Cordova, *Adv. Synth. Catal.* **2006**, *348*, 418–424; g) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165–3169; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097; h) C. Palomo, S. Vera, A. Mielgo, E. Gomez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130–6133; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984–5987; i) S. Mosse, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559–2562; j) S. V. Pansare, K. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625; k) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904; l) E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, *Org. Lett.* **2006**, *8*, 6135–6138; m) Y. Xu, A. Cordova, *Chem. Commun.* **2006**, 460–462; n) T. Mandal, C.-G.

Zhao, *Tetrahedron Lett.* **2007**, *48*, 5803–5806; o) L.-q. Gu, G. Zhao, *Adv. Synth. Catal.* **2007**, *349*, 1629–1632; p) B. Ni, Q. Zhang, A. D. Headley, *Green Chem.* **2007**, *9*, 737–739; q) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609; r) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897–1900; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871–1874; s) P. Garcia-Garcia, A. Ladepeche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797–4799; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721; t) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649–7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542; u) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611.

[6] a) C. L. Rigby, D. J. Dixon, *Chem. Commun.* **2008**, 3798–3800; b) T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097–2099; c) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949; d) M. Bella, K. A. Jörgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672–5673; for reviews of catalytic enantioselective construction of all carbon quaternary chiral centers, see: e) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726–1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690; f) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; g) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; h) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066.

[7] Synthesis of all-carbon quaternary stereogenic center from α,α-disubstituted aldehyde donors to nitroolefins, see: a) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514–6518; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366–6370; b) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599–602; c) J. Wang, H. Li, B. Lou, L. Zu, H. Guo W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321–4332; d) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371; e) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527–2530; see also ref.[5f]

[8] Asymmetric Michael additions of carbonyl compounds to nitroolefins in aqueous media, see: a) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555–558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548; b) Vishnumaya, V. K. Singh, *Org. Lett.* **2007**, *9*, 1117–1119; c) Y.-J. Cao, Y.-Y. Lai, X. Wang, Y.-J. Li, W.-J. Xiao, *Tetrahedron Lett.* **2007**, *48*, 21–24; d) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; e) Z.-Y. Yan, Y.-N. Niu, H.-L. Wei, L.-Y. Wu, Y.-B. Zhao, Y.-M. Liang, *Tetrahedron: Asymmetry* **2006**, *17*, 3288–3293.

[9] For organic reactions in aqueous media, see: a) Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502; b) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102; c) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104; d) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; e) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751–2772; f) C.-J. Li, T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley and Sons, New York, **1997**.

[10] Some of the interesting reports on solvent-free conditions, see: a) E. Rafiee, M. Joshaghani, S. Eavani, S. Rashidzadeh, *Green Chem.* **2008**, *10*, 982–989; b) J. Mack, D. Fulmer, S. Stofel, N. Santos, *Green Chem.* **2007**, *9*, 1041–1043; c) L. Zhang, Y. Luo, R. Fan, J. Wu, *Green Chem.* **2007**, *9*, 1022–1025; d) B. Yan, Y. Liu, *Org. Lett.* **2007**, *9*, 4323–4326; e) M. M. Mojtahedi, E. Akbarzadeh, R. Sharifi, M. S. Abaee, *Org. Lett.* **2007**, *9*, 2791–2793; f) F. Fringuelli, F. Pizzo, C. Vittoriani, L. Vaccaro, *Chem. Commun.* **2004**, 2756–2757.

[11] a) Z.-H. Tzeng, H.-Y. Chen, C.-T. Huang, K. Chen, *Tetrahedron Lett.* **2008**, *49*, 4134–4137; b) Z.-H. Tzeng, H.-Y. Chen, R. J. Reddy, C.-T. Huang, K. Chen, *Tetrahedron* **2009**, *65*, 2879–2888.

[12] N. Dahlin, A. Bogevig, A. Adolfsson, *Adv. Synth. Catal.* **2004**, *346*, 1101–1105.

[13] CCDC 702906 contains the supplementary crystallographic data for the catalyst **3** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Various reaction conditions have been studied that included under the optimum neat conditions, various organic solvents, substrates ratio, acidic additives and only trace amount of the desired product was observed by ^{1}H NMR analysis.

[15] a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446; b) R. Ling, I. V. Ekhato, J. R. Rubin, D. J. Wustrow, *Tetrahedron* **2001**, *57*, 6579–6588; c) S. Karlsson, F. Han, H.-E. Hogberg, P. Caldirola, *Tetrahedron: Asymmetry* **1999**, *10*, 2605–2616; d) S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1995**, *60*, 3221–3235, and references cited therein.

