DOI: 10.1002/adsc.200900879

Asymmetric Synthesis of 2,3,4-Trisubstituted Functionalised Tetrahydrofurans *via* an Organocatalytic Michael Addition as Key Step

Dieter Enders,[a,*] Chuan Wang,[a] and Andreas Greb[a]

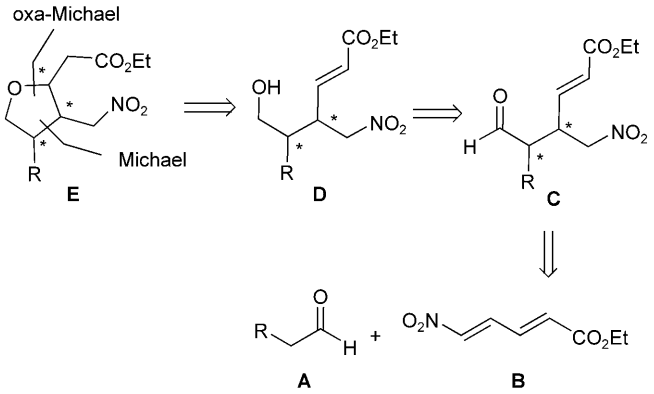
[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax: (+49)-241-809-2127; e-mail: enders@rwth-aachen.de

Received: December 18, 2009; Published online: March 23, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900879.

Abstract: The organocatalytic Michael addition of various aldehydes to (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate has been achieved under the catalysis of diphenylprolinol trimethylsilyl ether furnishing the products in good to excellent yields (61–94%) and high stereoselectivities (*dr* up to >98:2, *ee* = 97 to >99%). Starting from these Michael adducts, 2,3,4-trisubstituted functionalized tetrahydrofurans are available in two steps by reduction of the aldehyde followed by an intramolecular oxa-Michael addition in good yields (54–76%) and stereoselectivities (*dr* up to >95:5, *ee* = 97 to >99%).

Keywords: asymmetric synthesis; Michael addition; nitroalkenes; organocatalysis; tetrahydrofurans

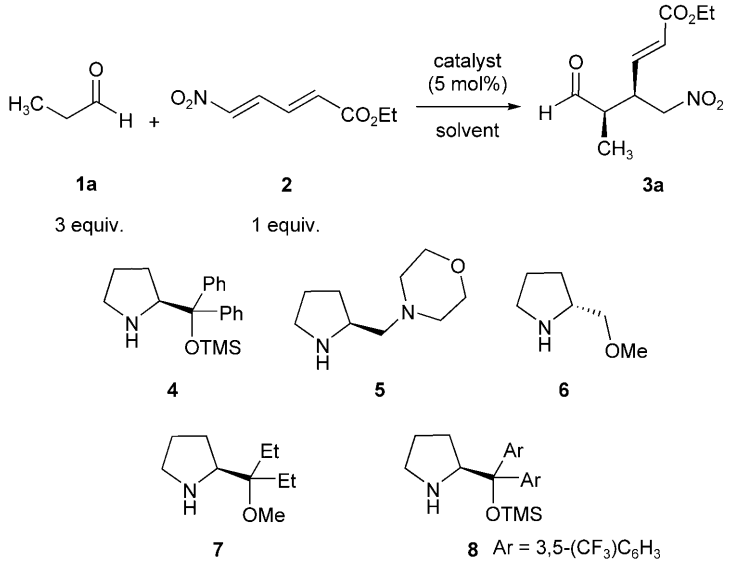


Scheme 1. Asymmetric synthesis of 2,3,4-trisubstituted tetrahydrofurans – retrosynthetic analysis.

After intensive investigations and tremendous progress in the last decade, organocatalysis has been developed to one of the main branches of asymmetric synthesis.[1] Within the field of organocatalysis, the amine-catalysed Michael addition of aldehydes and ketones to nitroalkenes *via* an enamine intermediate, which was independently discovered by List et al., Barbas et al. and our group,[2] has attracted great interest in recent years, since the resulting γ-nitroaldehydes or ketones are precursors of many important compounds such as γ-amino acids. Many efforts have been made to develop new efficient organocatalysts to expand the substrate spectrum of this Michael reaction or to involve it as a key step in domino reactions.[3–5] Our attention was drawn to (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate (**B**) as a Michael acceptor, because the 1,4-adducts (**C**) may be converted into 2,3,4-trisubstituted tetrahydrofurans (**E**) in two steps by reduction of the aldehyde followed by an intramolecular oxa-Michael addition (Scheme 1). Polysubstituted tetrahydrofurans are frequently found as subunits in many natural products such as Annonaceous acetogenins,[6] lignans,[7] polyether ionophores[8] and macrodiolides,[9] which possess various biological activities including antitumour, antihelmic, antimalarial, antimicrobial and antiprotozoal activity. Due to these important biological activities, many efforts have been made for the stereoselective synthesis of polysubstituted tetrahydrofurans.[10,11]

Initially we performed the reaction with (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate (**2**) and 3 equivalents of propanal (**1a**) in dichloromethane at room temperature. The catalyst diphenylprolinol silyl ether **4**[12,13] (5 mol%) was used, which shows good catalytic activity and excellent asymmetric induction in enamine-mediated Michael additions. Encouragingly, the reaction was complete within an hour affording the nitroaldehyde **3a** in excellent yield (89%) and enantioselectivities (98% *ee syn*, 94% *ee anti*). However, only a moderate diastereoselectivity (*syn*:*anti* = 77:23) was achieved (Table 1, entry 1). A brief solvent screen was undertaken and it was found that excellent enantiomeric excesses were obtained in every solvent used

Table 1. Catalyst and solvent screening for the organocatalytic Michael addition.[a]



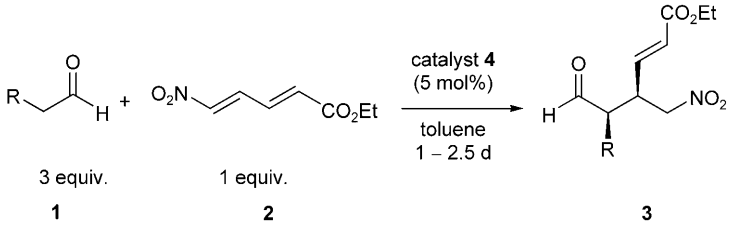
Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*dr*[c] *syn*:*anti*	*ee* [%][d] *syn*:*anti*
1	**4**	CH_2Cl_2	1	89	77:23	98, 94
2	**4**	DMF	2	60	83:17	95, 70
3	**4**	MeOH	2	90	83:17	>99, 86
4	**4**	toluene	2	87	84:16	>99, 77
5	**5**	toluene	2	71	56:44	54, 54
6	**6**	toluene	2	70	60:40	−70, −71
7	**7**	toluene	2	75	84:16	89, 77
8	**8**	toluene	2	20	84:16	n.d.[e]
9[f]	**4**	toluene	9	95	86:14	>99, 94
10[g]	**4**	toluene	24	94	95:5	>99, >99

[a] Unless otherwise specified, reactions were performed on a 1 mmol scale of (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate (**2**) using 3.0 equiv. of propanal (**1a**), 5 mol% catalyst **4**, **5**, **6**, **7** or **8** at room temperature in 2.0 mL solvent.
[b] Yield of the isolated product after flash chromatography.
[c] Determined by ^{1}H NMR spectroscopy on the isolated product.
[d] Determined by HPLC analysis on a chiral stationary phase of the corresponding α,ß-unsaturated ester.
[e] Not determined.
[f] Carried out at 0 °C.
[g] Carried out at −10 °C.

(Table 1, entries 2–4). The best outcome with respect to the diastereoselectivity (84:16) was acquired when the reaction was carried out in toluene (Table 1, entry 4). Next, four additional secondary amines were evaluated for this Michael addition with toluene as solvent. In the cases of the diamine **5** and (*R*)-2-methoxymethylpyrrolidine (RMP, **6**),[14] the reaction occurred with good yields but poor stereoselectivities (Table 1, entries 5 and 6). Under the catalysis of (*S*)-2-(1-methoxy-1-ethylpropyl)-pyrrolidine (**7**),[15] no improved results with regard to both yield and stereoselectivity were obtained in comparison to catalyst **4** (Table 1, entry 7). Employing diarylprolinol silyl ether **8** [Ar = 3,5-$(CF_3)_2C_6H_3$] as catalyst, very low conversion of the starting material was observed after two hours (Table 1, entry 8). In order to improve the diastereoselectivity, the reaction was performed at lower temperatures (Table 1, entries 9 and 10). To our delight, the diastereomeric ratio increased to an excellent level (95:5) when the reaction was carried out at −10 °C. Importantly, the yield of this process remained high (94%) with a perfect enantioselectivity (>99% *ee syn*, >99% *ee anti*, Table 1, entry 10).

Based on these results, we investigated the scope of the reaction by variation of the structure of the aldehydes (Table 2). In the cases of butanal (**1b**), pentanal (**1c**), 3-phenylpropanal (**1f**) and 4-methoxyphenylpropanal (**1h**), the reactions were carried out at 0 °C and warmed up to room temperature yielding the products in good to high yields (61–87%) and stereoselectivities (*dr*: 87:13 to 95:5, *ee*: >97%). Hexanal (**1e**) reacted well at room temperature, providing the Michael adduct **3e** in a good yield (76%) and excellent stereoselectivity (*dr*: 94:6, *ee*: 99%). When 3-methyl-

Table 2. Organocatalytic Michael additions of aldehydes **1** to (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate (**2**).[a]



3	R	*T* [°C][b]	Yield [%][c]	*dr*[d] *syn*:*anti*	*ee* [%][e]
a	Me	−10	94	95:5	>99
b	Et	0 to r.t.	87	93:7	>99
c	*n*-Pr	0 to r.t.	81	95:5	98
d	*i*-Pr	r.t. to 45	78	92:8	98
e	*n*-Bu	r.t.	76	94:6	−99[f]
f	Bn	0	74	90:10	−>99[f]
g	*c*-Hex	r.t.	74	>98:2	99
h	4-MeOC$_6$H$_4$CH$_2$	0 to r.t.	61[g]	87:13	97

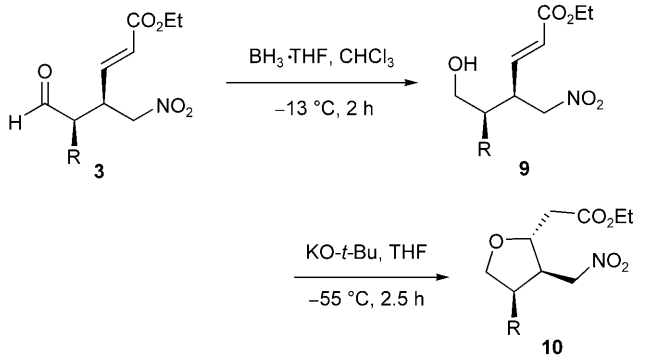
[a] Unless otherwise specified, reactions were performed on a 1 mmol scale of (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate (**2**) using 3.0 equiv. of aldehyde (**1**), 5 mol% catalyst **4** in 2.0 mL solvent.
[b] For the reaction time, see Supporting Information.
[c] Yield of the isolated product after flash chromatography.
[d] Determined by ^{1}H NMR spectroscopy on the isolated product.
[e] Determined by HPLC analysis on a chiral stationary phase of the corresponding α,ß-unsaturated ester.
[f] (*R*)-**4** was used as the catalyst.
[g] Yield after reduction of the aldehyde to the corresponding alcohol (BH_3·THF, $CHCl_3$, −13 °C).

butanal (**1d**) was utilised as the donor, the reaction mixture was heated to 45 °C to achieve a good yield (78%), whereas the stereoselctivity (*dr*: 92:8, *ee*: 98%) remained high. Notably, the reaction employing the sterically hindered cyclohexylacetaldehyde (**1g**) also proceeded well at room temperature, furnishing the corresponding γ-nitroaldehyde **3g** in a virtually enantiopure from (*dr*: >98:2, *ee*: 99%) and in a good yield (74%).

In order to reach the title functionalised 2,3,4-trisubstituted tetrahydrofurans and starting from the Michael adducts **3** only two further steps are necessary. Firstly, we performed the chemoselective reduction of the aldehyde group in the presence of the α,ß-unsaturated ester moiety, which was accomplished by utilising borane as the reducing reagent. Subsequently, the resulting alcohols **9** were treated with KO-*t*-Bu in THF at −55 °C furnishing the 2,3,4-trisubstituted tetrahydrofurans **10** in good yields (54–76%) *via* an intramolecular oxa-Michael addition (Table 3). In most cases high diastereoselectivities (*dr*: >95:5) were obtained. A relatively low diastereomeric ratio of *dr* >90:10 was observed when the alcohol **9f** bearing a benzyl group was used as substrate.

The relative configuration of the main diastereomers of the tetrahydrofurans **10** was determined by NOE measurements on compound **10b**. It turned out that the ethyl and the nitromethylene groups of **10b** have a *cis*-relationship, whereas the ester-bearing substituent is *trans* to the other two groups (Figure 1).

Table 3. Asymmetric synthesis of 2,3,4-trisubstituted tetrahydrofurans **10**.[a]



10	R	Yield [%][b]	*dr*[c]	*ee* [%][d]
b	Et	54	>95:5	>99
c	*n*-Pr	71	>95:5	98
d	*i*-Pr	76	>95:5	98
e	*n*-Bu	63	>95:5	−99
f	Bn	58	>90:10	−>99
g	*c*-Hex	62	>95:5	99

[a] For the reaction conditions, see Supporting Information.
[b] Yield of the isolated product after flash chromatography after two steps.
[c] Determined by ^{1}H NMR spectroscopy on the isolated product.
[d] Based on the results of nitroaldehyde **3**.

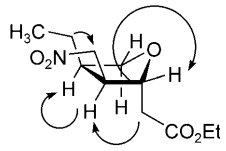


Figure 1. Results of the NOE mesurements of **10b**.

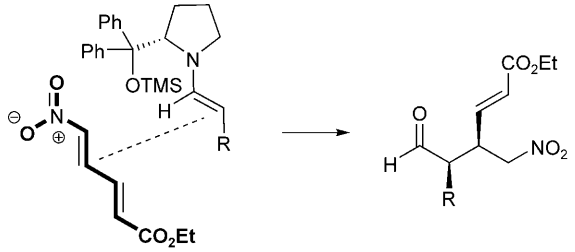


Figure 2. Proposed transition state explaining the (*R*,*R*)-configuration of the Michael products **3**.

Based on these results, the Michael adducts **3** must have the *syn*-configuration.

According to the obtained results in other (*S*)-diphenylprolinol TMS ether [*S*-(**4**)] catalysed Michael additions to nitroalkenes,[3–5] the absolute configuration of the α-C stereogenic centre of the aldehyde was always assigned to be *R*, if the α-substituent has the minor priority according to the CIP rules. A proposed transition state is illustrated in Figure 2, in which (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate (**2**) approaches the *Si*-face of the enamine, while its *Re*-face is effectively shielded by the bulky side chain of the catalyst. In accordance with all previous results the absolute configuration of the γ-nitroaldehydes **3** is assigned as *R*,*R*.

In summary, we have developed an organocatalytic Michael addition of various aldehydes to ethyl 5-nitropenta-2,4-dienoate under diphenyl-prolinol silyl ether catalysis providing the functionalized nitroaldehydes in good to excellent yields (61–94%) and high stereoselectivities (*dr*: up to >98:2, *ee*: >97%). Furthermore, the Michael adducts have been successfully converted to 2,3,4-trisubstituted tetrahydrofurans by means of an aldehyde reduction and subsequent intramolecular oxa-Michael addition in good yields (54–76%) and stereoselectivities (*dr*: up to >95:5, *ee* = 97 to >99%).

Experimental Section

General Procedure of the Organocatalytic Michael Addition

To a solution of diphenylprolinol TMS ether (**4**) (0.05 mmol, 5 mol%) and (2*E*,4*E*)-ethyl 5-nitropenta-2,4-dienoate (**2**) (1.0 mmol, 1 equiv.) in toluene (2 mL) was added aldehyde **1** (3.0 mmol, 3 equiv.) at the temperature displayed in Table 2. The reaction mixture was then stirred for the time given in the Supporting Information. The crude product was purified by flash chromatography on silica gel (pentane:ether mixture) affording the corresponding γ-nitroaldehyde **3** as a yellow oil or solid.

General Procedure of the Borane Reduction

To a solution of γ-nitroaldehyde **3** (1.0 mmol, 1 equiv.) in chloroform (4 mL) was added borane (1 M in THF, 1.7 mmol, 1.7 equiv.) at −13 °C. After stirring for 2 h, the reaction was quenched with acetic acid (5 mmol, 5 equiv.) and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (pentane:ether mixture) affording the corresponding δ-nitro alcohol **9** as a colourless oil.

General Procedure of the Intramolecular Oxa-Michael Addition

To a solution of the δ-nitro alcohol **9** (1.0 mmol, 1 equiv.) in THF (10 mL) was added KO-*t*-Bu (1.4 mmol, 1.4 equiv-) at −55 °C. After stirring for 2.5 h, the reaction was quenched with saturated NH_4Cl (10 mL) and the mixture was extracted three times with ether (40 mL). The combined organic phases were dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (pentane:ether mixture) affording the corresponding tetrahydrofurans **10** as a colourless oil.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (priority program Organocatalysis) and the Fonds der Chemischen Industrie. We thank the former Degussa AG and BASF AG for the donation of chemicals.

References

[1] For recent reviews on organocatalysis, see: a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; b) P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, **2007**; c) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; d) Special issue organocatalysis, *Chem. Rev.* **2007**, *107*, 5413–5883, guest editor B. List; e) R. M. De Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600; f) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; g) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739.; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; h) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857–7870; i) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 757–797; j) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 493–529; k) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew.*

Chem. Int. Ed. **2008**, *47*, 6138–6171; l) K. A. Jørgensen, S. Bertelsen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; m) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614; n) C. Grondal, M. Jeanty, D. Enders, *Nature Chemistry* **2010**, *2*, 167–178.

[2] 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) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441–4444; d) D. Enders, A. Seki, *Synlett* **2002**, 26–28;.

[3] For recent reviews on organocatalyzed 1,4-additions, see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; b) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135; c) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065–2092; d) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; e) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058–11076.

[4] For selected examples of organocatalytic Michael additions to nitroalkenes *via* enamine intermediates, see: a) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527–2530; b) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809; c) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371; d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; e) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599–602; f) D. Enders, S. Chow, *Eur. J. Org. Chem.* **2006**, 4578–4584; g) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514–6518; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366–6370; h) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555–558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548; i) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897–1900; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871–1874; j) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609; k) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611; l) P. García-García, A. Ladépêche, R. Hadler, B. List, *Angew. Chem.* **2008**, *120*, 4797–4799; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721; m) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800–4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722–4724; n) N. Ruiz, E. Reyes, J. L. Vicario, D. Badía, L. Carrillo, U. Uria, *Chem. Eur. J.* **2008**, *14*, 9357–9367; o) T. Mandal, C.-G. Zhao, *Angew. Chem.* **2008**, *120*, 7828–7831; *Angew. Chem. Int. Ed.* **2008**, *47*, 7714–7717; p) S. Belot, A. Massaro, A. Tenti, A. Mordoni, A. Alexakis, *Org. Lett.* **2008**, *10*, 4557–4560; q) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660–4663; r) L. Guo, Y. Chi, A. M. Almeida, I. A. Guzei, B. K. Parker, S. H. Gellman, *J. Am. Chem. Soc.* **2009**, *131*, 16018–16020; s) T. He, J.-Y. Qian, H.-L. Song, X.-Y. Wu, *Synlett* **2009**, 3195–3197; t) H. Uehara, C. F. Barbas III, *Angew. Chem.* **2009**, *121*, 10032–10036; *Angew. Chem. Int. Ed.* **2009**, *48*, 9848–9851.

[5] For selected examples of organocatalytic domino or tandem reactions involving Michael addition to nitroalkenes via enamine intermediates, see: a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; b) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471–473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467–469; c) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010–5013; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922–4925; d) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267–279; e) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649–7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542; f) F.-L. Zhang, A.-W. Xu, Y.-F. Gong, M.-H. Wei, X.-L. Zhang, *Chem. Eur. J.* **2009**, *15*, 6815–6818; g) C.-L. Cao, Y.-Y. Zhou, J. Zhou, X.-L. Sun, Y. Tang, Y.-X. Li, G.-Y. Li, J. Sun, *Chem. Eur. J.* **2009**, *15*, 11384–11389; h) D. Zhu, M. Lu, L. Dai, G. Zhong, *Angew. Chem.* **2009**, *121*, 6205–6208; *Angew. Chem. Int. Ed.* **2009**, *48*, 6089–6092; i) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7332–7335; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196–7199; j) S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem.* **2009**, *121*, 9085–9088; *Angew. Chem. Int. Ed.* **2009**, *48*, 8923–8926; k) S. T. Scroggins, Y. Chi, J. M. Fréchet, *Angew. Chem.* **2009**, *121*, DOI: 10.1002/ange.200902945; l) D. Enders, R. Krüll, W. Bettray, *Synthesis* **2010**, 567–572.

[6] A. Bermejo, B. Figadere, M.-C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269–303.

[7] M. Saleem, H. J. Kim, M.-S. Ali, Y. S. Lee, *Nat. Prod. Rep.* **2005**, *22*, 696–716.

[8] M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407–2474.

[9] E. J. Kang, E. Lee, *Chem. Rev.* **2005**, *105*, 4348–4378.

[10] For recent reviews on the stereoselective synthesis of tetrahydrofurans, see: a) J. P. Wolfe, M. B. Hay, *Tetrahedron* **2007**, *63*, 261–290; b) G. Jalce, X. Franck, B. Figadère, *Tetrahedron: Asymmetry* **2009**, *20*, 2537–2581.

[11] For recent selected examples of stereoselective syntheses of tetrahydrofurans, see ref.[5j] and: a) J. P. Wolfe, M. A. Rossi, *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621; b) T. K. Sarkar, S. A. Haque, A. Basak, *Angew. Chem.* **2004**, *116*, 1441–1443; *Angew. Chem. Int. Ed.* **2004**, *43*, 1417–1419; c) H. Y. Jang, F. W. Hughes, H. Gong, J. Zhang, J. S. Brodbelt, M. J. Kirsche, *J. Am. Chem. Soc.* **2005**, *127*, 6174–6175; d) P. D. Pohlhaus, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015; e) T. J. Donohoe, S. Butterworth, *Angew. Chem.* **2005**, *117*, 4844–4846; *Angew. Chem. Int. Ed.* **2005**, *44*, 4766–4768; f) J. S. Nakhla, J. W. Kampf, J. P. Wolfe, *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901; g) C. G. Nasveschuk, N. T. Jui, T. Rovis, *Chem. Commun.* **2006**, 3119–3121; h) S. N. Chavre, H. Choo, J. H. Cha, A. N. Pae, K. I. Choi, Y. S. Cho, *Org. Lett.* **2006**, *8*, 3617–3619; i) Z. Zhang, A. S. Widenhoefer, *Angew. Chem.* **2007**, *119*, 287–289; *Angew. Chem. Int. Ed.* **2007**, *46*, 283–285; j) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 3122–2123.

[12] For first applications of diphenylprolinol TMS ether catalysis, see ref.[4d] and M. Marigo, T. C. Wabnitz, D.

Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797.
[13] For reviews on diphenylprolinol TMS ether catalysis, see: a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042–8046; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880; b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922–948.
[14] Review: D. Enders, M. Klatt, *Synthesis* **1996**, 1403–1418.
[15] D. Enders, H. Kipphardt, P. Gerdes, L. J. Breña-Valle, V. Bhushan, *Bull. Soc. Chim. Belg.* **1988**, *97*, 691–704.

