DOI: 10.1002/chem.200801082

One-Pot Catalytic Enantioselective Domino Nitro-Michael/Michael Synthesis of Cyclopentanes with Four Stereocenters

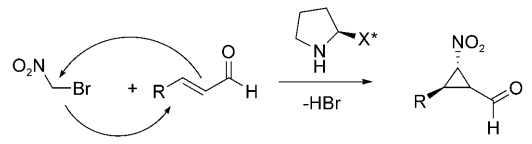
Gui-Ling Zhao,[a] Ismail Ibrahem,[a, c] Pawel Dziedzic,[a, c] Junliang Sun,[b, c] Charlotte Bonneau,[b, c] and Armando Córdova*[a, c]

Abstract: A highly enantioselective organocatalytic one-pot synthesis of nitro-, formyl-, and ester-functionalized cyclopentanes with four stereocenters is presented. The cyclopentanes were formed as a predominant diasteroisomer and isolated in high yields with 97–99% *ee*.

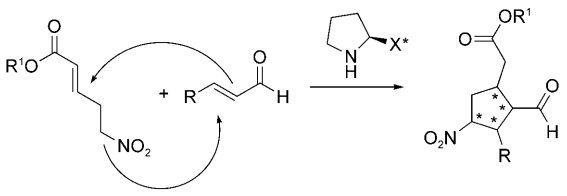
Keywords: aldehydes · asymmetric catalysis · conjugate additions · cyclopentanes · domino reactions · organocatalysis

Introduction

Domino, tandem, or cascade reactions, that involve the formation of multiple carbon–carbon bonds and stereocenters in one-pot, is a rapidly growing research field within the synthesis of small molecules with complex molecular architectures.[1] Domino reactions, a concept introduced by Tietze,[1a,b] have the advantages of including "green chemistry" parameters, such as atom economy,[2] reduction of synthetic steps, and reduction of waste and solvents.[3] In this context, it is challenging and even more economic to develop catalytic asymmetric domino reactions. Therefore, there is intense research into the development of new catalytic enantioselective domino and cascade transformations. The development of organocatalytic asymmetric one-pot domino reactions is a rapidly growing research area.[4–5] For example, the construction of highly functionalized carbocycles, such as cyclohexanes by Enders,[6a,c] Jørgensen,[6b,d] and Hayashi,[6e] as well as cyclopentanes by Wang[6f,g] and our group[6h] have recently been achieved by the employment of enantioselective amine catalysis.[6] Inspired by these elegant reports, and our recently developed nitrocyclopropanation of enals [Eq. (1)],[7] we became intrigued as to whether it would be possible to assemble highly functionalized cyclopentanes by a catalytic cascade nitro-Michael/Michael reaction by using α,β-unsaturated aldehydes as acceptors [Eq. (2)]. Heteroatom functionalized cyclopentanes are valuable synthetic building blocks and are present in several natural products, such as prostaglandins.[8] Herein, we present a highly diastereo- and enantioselective one-pot synthesis of nitrogen-, formyl-, and ester-functionalized cyclopentane derivatives with four stereocenters (97–99% *ee*).



(1)



(2)

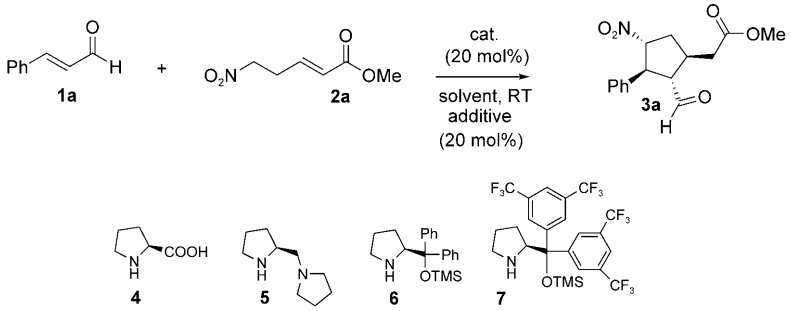
[a] Dr. G.-L. Zhao, Dr. I. Ibrahem, P. Dziedzic, Prof. Dr. A. Córdova
Department of Organic Chemistry
Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)
Fax: (+46) 8154908
E-mail: acordova@organ.su.se
acordova1a@netscape.net

[b] J. Sun, Dr. C. Bonneau
Department of Structural Chemistry
Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)

[c] Dr. I. Ibrahem, P. Dziedzic, J. Sun, Dr. C. Bonneau, Prof. Dr. A. Córdova
Berzelii Center EXSELENT on Porous Materials
Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801082.

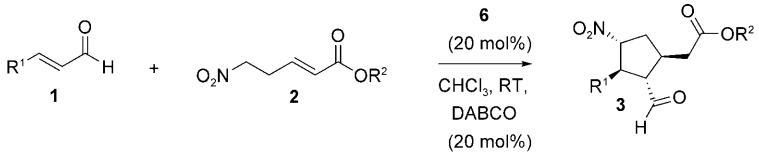
Table 1. Catalyst screening for the reaction between **1a** and ester **2a**.[a]

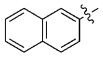
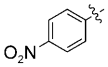
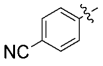


Entry	Cat.	Solvent	Additive	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4**	$CHCl_3$	none	48	15	4:1:2:0	38:nd
2	**5**	$CHCl_3$	none	48	30	3:0:1:0	70:nd
3	**6**	$CHCl_3$	none	96	67	3:1:1:1	94:86:95:99
4	**7**	$CHCl_3$	none	48	traces	nd	nd
5	**6**	$CHCl_3$	benzoic acid	16	89	2:1:1:1	68:94:91:99
6	**6**	CH_2Cl_2	none	68	82	4:1:1:1	99:84:91:99
7	**6**	CH_3CN	none	120	86	3:1:1:2	92:61:86:97
8	**6**	toluene	none	120	67	3:1:2:1	92:61:86:97
9	**6**	$CHCl_3$	DABCO	48	70	7:1:1:1	99:nd
10	**6**	CH_2Cl_2	DABCO	48	84	6:1:1:1	99:nd
11	**6**	$CHCl_3$	TEA	48	64	7:0:1:1	97:nd
12	**6**	$CHCl_3$	NaOAc	48	97	4:1:1:1	98:>10:86:93

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), **2a** (0.30 mmol), and catalyst (20 mol%) in solvent (0.5 mL) was stirred at the temperature and conditions displayed in the table. [b] Isolated yield of **3a** and its diastereoisomers after silica-gel chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis. nd = not determined; TMS = trimethylsilyl.

Table 2. Catalytic asymmetric domino reactions between crude **1** and ester **2**.[a]



Entry	R^1	R^2	Product	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1		Me	**3a**	48	70	7:1:1:1	99
2		Et	**3b**	40	80	10:0:1:2	99
3		Me	**3c**	24	60	6:1:1:1	97
4		Me	**3d**	40	81	10:0:1:1	99
5		Me	**3e**	24	88	7:1:1:1	99
6		Me	**3f**	24	75	7:0:1:1	98
7		Me	**3g**	24	80	7:0:1:1	99
8		Me	**3h**	26	72	12:0:1:2	99
9		Me	**3i**	40	81	10:1:1:2	99
10		Me	**3j**	24	73	12:1:1:2	99

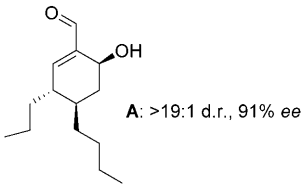
[a] Experimental conditions: A mixture of enal **1** (0.25 mmol), **2a** (0.30 mmol), catalyst (20 mol%), and DABCO (20 mol%) in $CHCl_3$ (0.5 mL) was stirred at room temperature for the time displayed in the table. [b] Isolated yield of **3** after silica-gel chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis on the major isomer.

Results and Discussion

In an initial catalyst screening, we found to our delight that amines **4**–**7** catalyzed the asymmetric domino reaction between cinnamic aldehyde (**1a**) and methyl 5-nitro-pentenoate (**2a**), which is simply derived by a Horner–Wadsworth–Emmons reaction of 3-nitropropanal in $CHCl_3$ (Table 1).

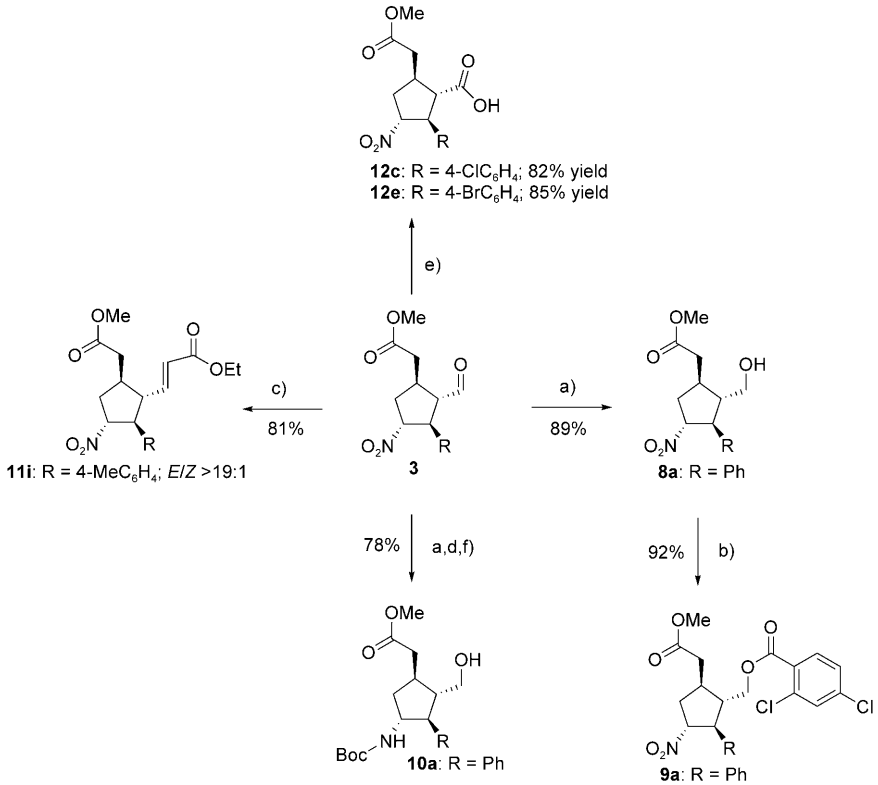
The transformation resulted in the assembly of the corresponding cyclopentane derivative **3a** with moderate diastereoselectivity and 38–94% *ee* (entries 1–4). The protected chiral diarylprolinol **6**[9] exhibited the highest reactivity and enantioselectivity. Thus, amine **6** was chosen as the catalyst for further investigations. High enantioselectivity was also achieved in other solvents (entries 6–8). The presence of an acid additive increased the reactivity but decreased the diastereoselectivity of the reaction (entry 5). Thus, we decided to investigate the addition of a small amount of base (entries 9–12). To our satisfaction, the rate and diastereo- and enantioselectivity of the reaction increased. In particular, the employment of organic bases 1,4-diazabicyclo-[2.2.2]octane (DABCO) and triethylamine (TEA) allowed for the formation of **3a** with high diastereo- and enantioselectivity (entries 9–11). The highest stereoselectivity (7:1 d.r. and 99% *ee*; d.r. = diasteromeric ratio) was achieved when DABCO was used as the additive (entry 9). Based on these results, we decided to investigate the chiral amine **6**-catalyzed enantioselective domino reactions between enals **1** and 5-nitro-pentenoate esters **2** in $CHCl_3$ by using a small amount of DABCO as an additive (Table 2).

The organocatalytic asymmetric domino reactions gave the corresponding cyclopentanes **3a–j** in high yields (60–88%) as a predominant diastereoisomer, which was readily separated from the other minor diastereoisomers by silica-gel column chromatography. The enantioselectivity of the reaction was excellent (97–99% *ee*). Thus, the one-pot procedure allows for the construction of four stereocenters with very high stereocontrol. Notably, when 2-heptenal was employed as the acceptor enal, the corresponding chiral cyclohexane derivative **A** with three stereocenters was formed with >19:1 d.r. and 91% *ee* by a formal [3+3] cycloaddition.[10]



To show the synthetic utility of the transformation and the possibility of employing it in diversity-oriented synthesis,[11] we further modified the cyclopentane derivatives **3** (Scheme 1). Consequently, reduction and oxidation gave the corresponding alcohols and acids **8** and **12**, respectively, in high yields. Both of these transformations can also be performed as one-pot operations. The alcohol moiety of **8** can be esterified to give functional cyclopentanes **9** and a Wittig reaction of aldehyde **3** gave the corresponding cyclopentane **11**. Reduction of the nitro group and Boc protection (Boc = *tert*-butoxycarbonyl) gave access to amine-functionalized cyclopentane **10a**. The relative stereochemistry of **3c** was established by NOE NMR spectroscopic experiments, which confirmed a *trans* relationship between all the neighboring substituents. This was also confirmed by X-ray analysis (Figure 1) of **12c** (1*R*,2*R*,3*S*,4*S*).[12]

Based on these results and the chiral amine **6**-catalyzed reactions with enals,[9e] we propose the following domino reaction mechanism to account for the observed stereochemistry of the reaction (Scheme 2).



Scheme 1. a) $NaBH_4$, MeOH, 0 °C; b) 2,4-$Cl_2C_6H_3COCl$, TEA, CH_2Cl_2; c) $Ph_3P{=}CHCO_2Et$, $CHCl_3$; d) cat. Pd/C, H_2, MeOH; e) $NaClO_2$ KH_2PO_4, $(CH_3)_2C{=}CHCH_3$, *t*BuOH/H_2O 5:1; f) $(Boc)_2O$, TEA.

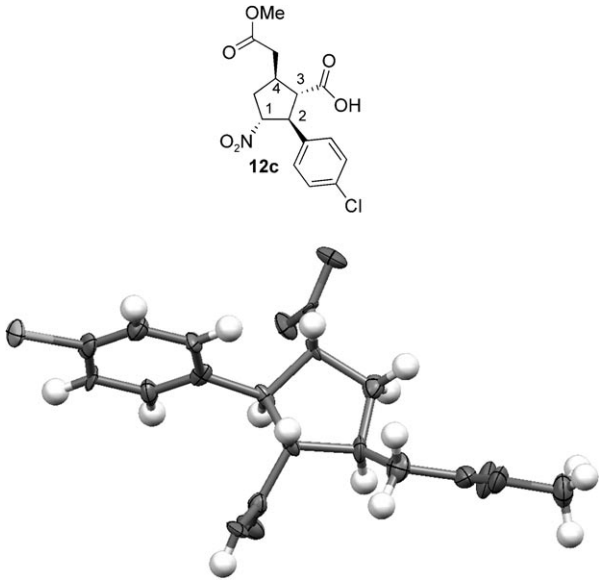
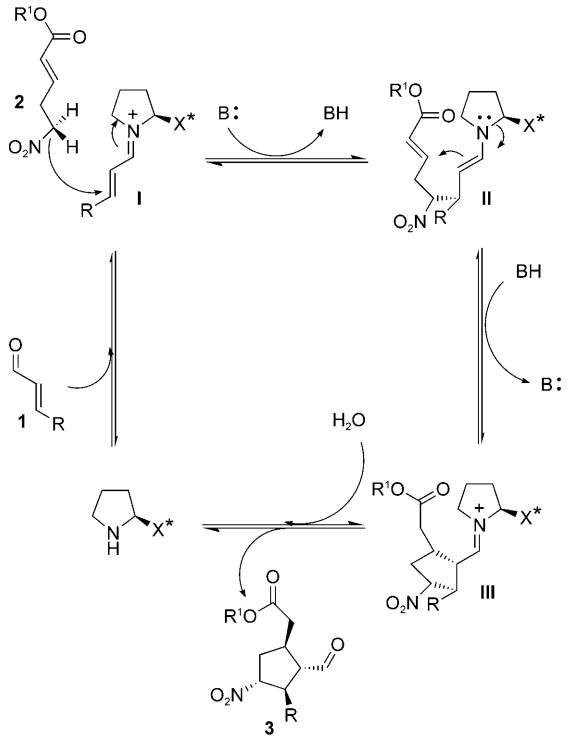


Figure 1. ORTEP picture of the crystalline compound **12c**.



Scheme 2. Proposed reaction pathway.

Thus, efficient shielding of the *Re* face of the chiral iminium intermediate **I** by the bulky aryl groups of **6** leads to stereoselective *Si*-facial nucleophilic conjugate attack on the β-carbon by 5-nitro-butanoate ester **2** from its *pro-R* face at C-5 (Scheme 1). Next, the generated chiral enamine intermediate **II** performs a perfectly aligned intermolecular conjugate attack on the α,β-unsaturated ester moiety and the iminium intermediate **III** is formed. Hydrolysis gives the corresponding cyclopentane product **3** and releases the chiral amine catalyst. The role of the organic base additive is possibly to enhance the deprotonation and proton-transfer in the conjugate addition steps.

Conclusion

In summary, we have developed a highly diastereo- and enantioselective one-pot cascade nitro-Michael/Michael reaction for the synthesis of amino-, formyl-, and ester-functionalized cyclopentanes with four stereocenters (97–99% *ee*). These compounds can be used as scaffolds for further diversification. The importance of the transformation is additionally highlighted in that it correlates to the elegant protocols for cyclohexene and cyclohexane synthesis reported by the groups of Enders,[6a,c] Jørgensen,[6b,d] and Hayashi,[6e] as well as the cyclopentane synthesis developed by Wang's[6f,g] and our group[6h].

Acknowledgement

We gratefully acknowledge the Swedish National Research Council (VR) and the Lars Hierta and Carl Trygger Foundations for financial support. The Berzelii Center EXSELENT is financially supported by VR and the Swedish Governmental Agency for Innovation Systems (VINNOVA).

[1] For reviews on this concept, see: a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, p. 672; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; d) H. Guo, J. Ma, *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem. Int. Ed.* **2006**, *45*, 354; e) H. Pellieser, *Tetrahedron* **2006**, *62*, 2143; f) D. J. Ramon, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.

[2] a) B. M. Trost, *Science* **1991**, *254*, 1471. b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 258.

[3] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **2000**, p. 135; b) for an excellent paper on combining one-pot, step reduction and atom economy in organic chemistry, see: P. A. Clarke, S. Santos, W. H. C. Martin, *Green Chem.* **2007**, *9*, 438.

[4] For an excellent review on organocatalytic domino reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) see also: X. Yu, W. Wang, *Org. Biom. Chem.* **2008**, *6*, 2037.

[5] For selected examples of organocatalytic asymmetric domino and cascade reactions, see: a) N. Halland, P. S. Aburell, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272. b) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051. c) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036; d) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; e) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962; f) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem.* **2003**, *115*, 4365; *Angew. Chem. Int. Ed.* **2003**, *42*, 4233; g) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877; h) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, *47*, 4928; i) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354; j) R. Rios, H. Sunden, I.

Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8547; k) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, *17*, 1763; l) H. Sundén, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574; m) H. Sundén, R. Rios, Y. Xu. L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 2549; n) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267; o) J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Cordova, *Angew. Chem.* **2007**, *119*, 792; *Angew. Chem. Int. Ed.* **2007**, *46*, 778; p) H. Sundén, R. Rios, I. Ibrahem. G.-L. Zhao, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 827; q) B.-C. Hong, R. Y. Nimje, M.-F. Wu, A. A. Sadani, *Eur. J. Org. Chem.* **2008**, 1449; r) H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*. 1833; s) D. Enders, A. Narine, T. R. Benninghaus, G. Raabe, *Synlett* **2007**, 1667.

[6] For selected examples, see: a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; b) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; c) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471; *Angew. Chem. Int. Ed.* **2007**, *46*, 467; d) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 9362; *Angew. Chem. Int. Ed.* **2007**, *46*, 9202; e) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; f) J. Wang, H. Li, H. Xie, L. Zu, X. Shen, W. Wang, *Angew. Chem.* **2007**, *119*, 9208; *Angew. Chem. Int. Ed.* **2007**, *46*, 9050; g) L. Zu, H. Li, H. Xie, J. Wang, W. Jiang, Y. Tang, W. Wang, *Angew. Chem.* **2007**, *119*, 3806; *Angew. Chem. Int. Ed.* **2007**, *46*, 3732; h) R. Rios, J. Vesely, H. Sundén, I. Ibrahem, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5835.

[7] J. Vesely, G.-L. Zhao, A. Bartoszewicz, A. Córdova, *Tetrahedron Lett.* **2008**, *49*, 4201; for nitrocyclopropanation of cyclohexanone, see: M. Hansen, D. A. Longbottom, S. V. Ley, *Chem. Commun.* **2006**, 4838.

[8] a) S. Bergström, *Science* **1967**, *157*, 382; b) P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533; c) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, Weinheim, **1996**, p. 65; d) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, *91*, 5675; e) E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, *97*, 6908; f) M. Suzuki, A. Yanagisawa, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 4718; for a recent example, see: J. Yamaguchi, I. B. Seiple, I. S. Young, D. P. O'Malley, M. Mau, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3634; *Angew. Chem. Int. Ed.* **2008**, *47*, 3578.

[9] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; see also: c) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608; d) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431; for an excellent review, see: e) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922.

[10] B.-C. Hong, M.-F. Wu, H.-C. Tseng, J.-H. Liao, *Org. Lett.* **2006**, *8*, 2217.

[11] a) S. L. Schreiber, *Science* **2000**, *287*, 1964; b) S. L. Schreiber, *Nat. Chem. Biol.* **2005**, *1*, 64.

[12] CCDC-687212 contains the supplementary crystallographic data for 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.

Received: June 4, 2008
Published online: October 1, 2008

