Asymmetric Organocatalysis

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How to Make Five Contiguous Stereocenters in One Reaction: Asymmetric Organocatalytic Synthesis of Pentasubstituted Cyclohexanes**

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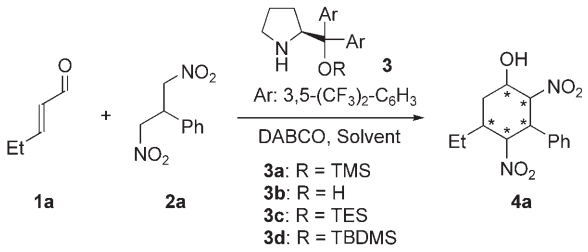
Asymmetric synthesis of complex molecules containing multiple stereocenters is a well-known research area used for the synthesis of a variety of natural products and other molecules of interest.[1] In this field, strategies which reduce the number of chemical steps for the final assembly of the desired products are highly demanded, thereby decreasing the formation of waste products and increasing the economy of the processes.[2] One of the most important goals in this area is the generation of more than one bond in a multistep reaction concomitant with the creation of multiple stereocenters in a one-pot fashion.[1] Recently, asymmetric one-pot syntheses of complex organic molecules have been achieved with the generation of up to eight new stereocenters by employing different methodologies.[3] In the field of organocatalysis, Enders et al. have performed the synthesis of substituted cyclohexenes by applying a three-component domino reaction,[3a] and Hayashi et al. have described a two-component multistep Michael/Henry sequence for the synthesis of cyclohexane derivatives by using pentane-1,5-dial and 2-substituted nitroalkenes.[3c] To the best of our knowledge, the generation of five or more stereocenters by one intermolecular reaction of two compounds in an asymmetric fashion has not so far been reported.

In the course of our efforts to develop organocatalytic methodologies to gain rapid access to complex molecules, we recently achieved the synthesis of cyclohexenals containing three contiguous stereocenters in good yields and excellent stereoselectivities by using a multicomponent reaction.[4] In fact, it has been demonstrated with this and other examples[5] that organocatalysis can be a very valuable tool for controlling diverse asymmetric syntheses. Herein we describe the first one-pot asymmetric formation of five stereocenters by an intermolecular two-component reaction, which leads in this particular case to the formation of highly substituted optically active cyclohexanols. Furthermore, this reaction represents one of the few examples of organocatalytic conjugate addition of nitroalkanes to α,β-unsaturated aldehydes.[3a,6a,b]

Our studies started with the discovery of a novel nitro-Michael[6]/Henry[7] reaction promoted by a 1,3-dinucleophile.[8] This transformation allows the straightforward synthesis of pentasubstituted cyclohexanes in a one-pot fashion. In the reaction between aldehyde **1a** and dinitroalkane **2a**, in the presence of (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)(trimethylsilyloxymethyl)]pyrrolidine (**3a**),[9] we observed that the initially formed Michael adduct cyclized in situ to furnish the cyclohexanol derivative **4a** as the only product (Scheme 1).



Scheme 1. Reaction of 2-pentenal **1a** with the 1,3-dinitroalkane **2a** in the presence of the catalyst **3** and an external base. DABCO = 1,4-diazabicyclo[2.2.2]octane, TMS = trimethylsilyl, TES = triethylsilyl, TBDMS = *tert*-butyldimethylsilyl.

During the screening of this reaction, we discovered a low dependence on the solvent used and in all cases obtained good stereoselectivities (1 major out of 32 possible stereoisomers) (Table 1). In fact, in many of the solvents tested and in the presence of DABCO as the base additive (Table 1, entries 1–4), the major diastereoisomer could be isolated after column chromatography in moderate yields with up to 80% *ee*.[10] The best enantioselectivities were obtained using CH_2Cl_2 as the solvent. In these cases, the use of 10 mol% of DABCO was found to be more efficient with respect to yield and enantioselectivity (Table 1, entries 5 and 6). It is important to note that no epimerization occurs during the purification. The diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture is maintained after isolation of the single isomers. The reaction temperature was decreased to 4 °C to improve the stereoselectivity of the process (Table 1, entry 7). However, it was observed that decreasing the reaction temperature gave no improvement in the enantioselectivity. Other catalysts

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Table 1: Screening of the organocatalytic nitro-Michael/Henry reaction of α,β-unsaturated aldehyde **1a** with dinitro compound **2a**.[a]

Entry	Solvent	3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	*i*PrOH	**3a**	n.d.[f]	4:2:1	80
2[e]	AcOEt	**3a**	n.d.[f]	4:2:1	80
3[e]	DMF	**3a**	n.d.[f]	4:1:1	46
4[e]	$CHCl_3$	**3a**	n.d.[f]	4:2:1	80
5[e]	CH_2Cl_2	**3a**	45 (74)	4:2:1	84
6[g]	CH_2Cl_2	**3a**	45	4:2:1	90
7[e,h]	CH_2Cl_2	**3a**	23	4:2:1	89
8[g]	CH_2Cl_2	**3b**[i]	n.d.[f]	4:2:1	−58[j]
9[g]	CH_2Cl_2	**3c**[i]	41	4:2:1	89
10[g]	CH_2Cl_2	**3d**[i]	35	4:2:1	93

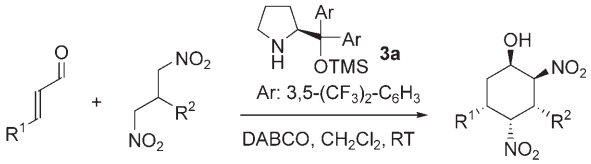
[a] The reaction was carried out on a 0.2-mmol scale of **1a** and **2a**, using 20 mol% of the catalyst **3** and DABCO in a vial containing 0.25 mL of the appropriate solvent. [b] Yield of the isolated major stereoisomer (combined yield of the three stereoisomers). [c] Determined by NMR spectroscopy of the reaction mixture. [d] Determined by HPLC on a chiral stationary phase. [e] 20 mol% of DABCO was used. [f] Not determined. [g] 10 mol% of DABCO was used. [h] Reaction performed at 4°C. [i] 10 mol% of **3** was used. [j] The opposite enantiomer was obtained.

(**3b–d**) were also tested for this transformation. It should be noted that derivative **3b** with a free OH group led to the formation of the opposite enantiomer (Table 1, entry 8). This is one of the first examples where opposite induction has been observed using the pair of catalysts **3a** and **3b**.[6b] This result can be rationalized by a possible hydrogen-bonding interaction between the free OH group of catalyst **3b** and the incoming dinitro compound. The more bulky substituted pyrrolidine catalysts **3c** and **3d** also gave good enantioselectivities (Table 1, entries 9 and 10). However, the yield observed in these cases showed that the use of the common catalyst **3a** was recommended.

Having established the best protocol to extend the reaction, we studied the possibility of using different aldehydes as well as different 1,3-dinucleophiles to synthesize various pentasubstituted cyclohexane derivatives. Thus, a broad spectrum of β-alkyl-substituted aldehydes (**1a–g**)[11] could be used as the electrophile reacting with **2a**, with a general high preference for one diastereoisomer. The major isomer was in all cases isolated in good yields and with high enantioselectivity (Table 2, entries 1–8, in which the yields given are for the major diastereoisomer). The substituent in the β position of the aldehyde was found to have a strong effect on the stereoselectivity of the process. Reactions with more bulky alkyl substituents proceeded with better enantioselectivity (Table 2, entries 2–4). The scope of the reaction could also be extended to functionalized aldehydes bearing a protected alcohol (Table 2, entry 6) as well as an alkenyl moiety (Table 2, entry 7). In both cases the enantioselectivity is maintained at high levels.

Other 1,3-dinucleophiles were compatible with this methodology. As Table 2 shows, aromatic and heteroaromatic substituted nucleophiles **2b–i** could be used in this reaction, with the desired products formed with similar yields and stereoselectivities (Table 2, entries 9–19). Again, the more bulky isopropyl-substituted aldehyde **1d** gave the best results in terms of diastereoselectivity (Table 2, compare entries 9 and 10). Consequently, the scope of the reaction was

Table 2: Scope of the organocatalytic nitro-Michael/Henry reaction.[a]



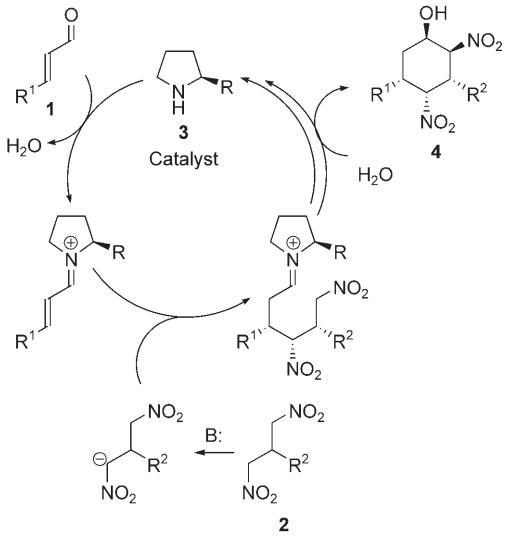
1a-h **2a-i** **4a-s**

Entry	1 (R^1)	2 (R^2)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a** (Et)	**2a** (Ph)	**4a**: 45	4:2:1	90
2	**1b** (Me)	**2a** (Ph)	**4b**: 43 (61)	4:1:1	75
3	**1c** (*n*-Pr)	**2a** (Ph)	**4c**: 44	4:2:1	86
4	**1d** (*i*Pr)	**2a** (Ph)	**4d**: 38 (60)	3:1:1	90
5	**1e** (*n*Bu)	**2a** (Ph)	**4e**: 43	4:2:1	87
6	**1f** (CH_2OTIPS)	**2a** (Ph)	**4f**: 56[e]	3:1:0	94
7	**1g** (*cis*-C_6H_{11})	**2a** (Ph)	**4g**: 52	4:2:1	86
8	**1h** (C_7H_{16})	**2a** (Ph)	**4h**: 50	4:2:1	87
9	**1a** (Et)	**2b** (*p*-$MeOC_6H_4$)	**4i**: 48	4:2:1	92
10[f]	**1d** (*i*Pr)	**2b** (*p*-$MeOC_6H_4$)	**4j**: 53	5:1:1	89
11	**1d** (*i*Pr)	**2c** (*m*-$MeOC_6H_4$)	**4k**: 65	12:2:3	90
12	**1d** (*i*Pr)	**2d** (*o*-MeC_6H_4)	**4l**: 48 (71)	5:2:1	90
13	**1d** (*i*Pr)	**2e** (*p*-MeC_6H_4)	**4m**: 40	5:1:1.2	84
14	**1d** (*i*Pr)	**2f** (*p*-ClC_6H_4)	**4n**: 47	5:1:1	88
15	**1d** (*i*Pr)	**2g** (naphth-2-yl)	**4o**: 61	5:0:1	88
16	**1a** (Et)	**2h** (furan-2-yl)	**4p**: 60	4:2:1	86
17	**1d** (*i*Pr)	**2h** (furan-2-yl)	**4q**: 43 (52[e])	6:1:0	88
18	**1a** (Et)	**2i** (thiophen-2-yl)	**4r**: 42	4:0:1	80
19	**1d** (*i*Pr)	**2i** (thiophen-2-yl)	**4s**: 43	5:1:1	90

[a] The reaction was carried out on a 0.2-mmol scale of **1a** and **2a**, using 20 mol% of the catalyst **3a** and DABCO (10 mol%) in a vial containing 0.25 mL of CH_2Cl_2. [b] Yield of the isolated major stereoisomer (combined yield of the three stereoisomers). [c] Determined by NMR spectroscopy of the reaction mixture. The minor diastereoisomers were also characterized for **4a**. [d] Determined by HPLC on a chiral stationary phase. [e] Combined yield of the two stereoisomers. [f] Reaction carried out on a 0.1-mmol scale. TIPS = triisopropylsilyl.

evaluated by treating **1d** with the different dinitro compounds **2b–i**. Changing the electronic properties of the aromatic substituent in the nucleophile had no major effect on the stereoselectivity of the reaction. Electron-withdrawing as well as electron-donating groups could be attached to the aromatic moiety, and gave rise to the cyclohexanols **4j–o** with comparable diastereoselectivities and enantioselectivities in the range of 88–90% *ee*. Only in the case of the *p*-tolyl-substituted nucleophile **2e** was a slight decrease in enantioselectivity observed (Table 2, entry 13). Finally, furanyl- and thiophenyl-substituted nucleophiles **2h** and **2i** were also shown to be compatible in this reaction, and provided the corresponding cyclohexanol derivatives **4p–s** with yields and diastereoselectivities within the ranges observed before, and with enantioselectivities of up to 90% *ee*. Similar results were obtained from reactions giving **4a** and **4c** performed on a 1-mmol scale.

The asymmetric domino organocatalytic nitro-Michael/Henry reaction for the synthesis of the cyclohexanol derivatives **4** can be explained by an initial iminium activation of the α,β-unsaturated aldehyde **1** by catalyst **3**, followed by an intramolecular nitro-aldol reaction as outlined in Scheme 2. In the first step, an activation of the aldehyde as an iminium



Scheme 2. Proposed mechanism for the organocatalyzed asymmetric nitro-Michael/Henry domino reaction.

ion occurs, which allows the formation of the Michael adduct by attack of the nucleophile from the less hindered face. After hydrolysis of the iminium ion, the nitroaldehyde intermediate undergoes a subsequent intramolecular Henry reaction which generates the final product **4** with five contiguous stereocenters.

The absolute configuration of the major stereoisomer was assigned by single-crystal X-ray analysis of the *p*-chlorobenzoate derivative of **4a** (Figure 1).[12] The structure leads to a 1*R*,2*S*,3*R*,4*R*,5*R* assignment of the formed stereocenters, which indicates that the initial addition takes place from the *Re* face through the control of the catalyst. From the absolute configuration at C-1 and C-2, we assume that the final assembly takes place from the *Si* face of the carbonyl group, which suggests no catalyst involvement during this bond formation.

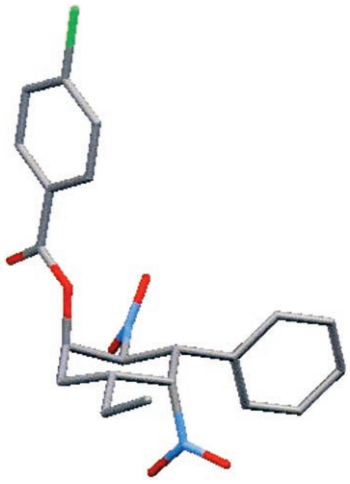


Figure 1. X-ray structure of the *p*-chlorobenzoate derived from **4a**. C gray, N blue, O red, Cl green. H atoms are omitted for clarity.

In conclusion, we have developed the addition of nitroalkanes to α,β-unsaturated aldehydes followed by an intramolecular Henry reaction which leads to the formation of highly substituted cyclohexanols with control over five contiguous stereocenters. This novel domino reaction catalyzed by the commercially available diarylprolinol silyl ether **3a** proceeds with moderate to good yields and with high diastereo- and enantioselectivity. The optically active cyclohexanols arising from this domino process constitute valuable chiral building blocks since they contain the β-amino alcohol functional motif which is ubiquitous in biologically active compounds.[13]

Experimental Section

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **3a** (0.04 mmol, 20 mol%), DABCO (0.02 mmol, 10 mol%), and CH_2Cl_2 (0.25 mL). Then, **2** (0.2 mmol) and the α,β-unsatured aldehyde **1** (0.2 mmol) were added. The stirring was maintained at room temperature until completion of the reaction and the crude reaction mixture was directly charged on to silica gel and subjected to flash chromatography.

Representative example: (1*R*,2*S*,3*R*,4*R*,5*R*)-5-Ethyl-2,4-dinitro-3-phenylcyclohexanol (**4a**) was isolated by flash chromatography (*n*-hexane/AcOEt gradient from 9.5:0.5 to 8:2) in 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53$–7.08 (m, 5H), 5.93 (dd, $J = 12.4$, 2.5 Hz, 1H), 5.02 (t, $J = 4.4$ Hz, 1H), 4.79 (brs, 1H), 4.17 (dd, $J = 12.4$ Hz, 1H), 2.58 (brs, 1H), 2.53–2.42 (m, 1H), 2.20 (td, $J = 13.5$, 2.0 Hz, 1H), 2.06 (td, $J = 14.5$, 4.2 Hz, 1H), 1.45–1.20 (m, 2H), 1.01 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 134.3$, 129.3, 128.6, 127.0, 92.1, 85.9, 67.5, 41.7, 34.7, 32.1, 24.6, 11.3 ppm; HRMS: calcd for $[C_{14}H_{18}N_2O_5Na]^+$: 317.1113; found: 317.1122. M.p. 153–155 °C (*n*-hexane/AcOEt). The *ee* value was determined by HPLC on a Chiralpak AS column (hexane/*i*PrOH 95:5); flow rate 1.0 mL min^{-1}; $\tau_{major} = 20.8$ min, $\tau_{minor} = 24.4$ min (90% *ee*). $[\alpha]_D^{RT} = -49.8$ ($c = 0.75$, $CHCl_3$).

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[1] a) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

[2] For recent reviews on tandem and domino strategies for enantioselective synthesis, see a) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1, and references therein; b) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; c) T. J. J. Muller, *Metal Catalysed Cascade Reactions*, Wiley-VCH, Weinheim, **2006**; d) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; e) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; f) L. F. Tietze, *Chem. Rev.* **1996**, *96*,

115; g) L. F. Tietze, F. Haunert, in *Stimulating Concepts in Chemistry* (Eds.: F. Vögtle, J. F. Stoddart, M. Shibasaki), Wiley-VCH, Weinheim, **2000**.

[3] a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; b) D. Enders, M. R. M. Hüttl, J. Runsink, C. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471; *Angew. Chem. Int. Ed.* **2007**, *46*, 467; c) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; d) H. Y. Kim, A. E. Lurain, P. Garcia-Garcia, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 13138; e) D. M. Hodgson, A. H. Labande, F. Y. T. M. Pierard, *Synlett* **2003**, 59; f) H. A. Dondas, C. W. G. Fishwick, X. Gai, R. Grigg, C. Kilner, N. Dumrongchai, B. Kongkathip, N. Kongkathip, C. Polysuk, V. Sridharan, *Angew. Chem.* **2005**, *117*, 7742; *Angew. Chem. Int. Ed.* **2005**, *44*, 7570; g) C. Lim, J.-E. Kang, J.-E. Lee, S. Shin, *Org. Lett.* **2007**, *9*, 3539.

[4] A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101.

[5] For recent reviews on organocatalytic cascade reactions, see for example: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693; c) M. Yus, D. J. Ramón, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602; d) F. Liéby-Muller, C. Simon, T. Constantieux, J. Rodriguez, *QSAR Comb. Sci.* **2006**, *25*, 432; for a recent review on organocatalytic enantioselective conjugate additions, see for example: e) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065; for examples, see f) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496; g) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; h) G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas III, *J. Am. Chem. Soc.* **1997**, *119*, 8131; i) B. List, R. A. Lerner, C. F. Barbas III, *Org. Lett.* **1999**, *1*, 59; j) T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951; k) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2003**, *5*, 4301; l) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272; m) J. Pukkinen, P. S. Aburel, N. Halland, K. A. Jørgensen, *Adv. Synth. Catal.* **2004**, *346*, 1077; n) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962; o) Y. Huang, A. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; p) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036, and references therein; q) E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, *Org. Lett.* **2006**, *8*, 6135; r) H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.* **2007**, *13*, 9068.

[6] a) D. Enders, A. A. Narine, T. Benninghaus, *Synlett* **2007**, 1667; b) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, DOI: 10.1002/ange.200703261; *Angew. Chem. Int. Ed.* **2007**, DOI: 10.1002/anie.200703261 (this paper was available on the internet during the reviewing of this mansucript); for recent reviews with extensive references, see c) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**; d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933; for examples, see e) M. Yamaguchi, T. Shiraishi, Y. Igarashi, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 8233; f) M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi, M. Hirama, *Tetrahedron* **1997**, *53*, 11223; g) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; h) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; i) K. Funabashi, Y. Saida, M. Kanai, T. Arai, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7557; j) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; k) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; l) S. Hanessian, Z. Shao, J. S. Warrier, *Org. Lett.* **2006**, *8*, 4787; m) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897; n) C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 2039.

[7] For reviews, see for example: a) G. Rosini in *Comp. Org. Synth.* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**; b) M. Shibasaki, H. Groger, in *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; c) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915; d) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561; e) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315; for examples, see f) C. Christensen, K. Juhl, K. A. Jørgensen, *Chem. Commun.* **2001**, 2222; g) T. Risgaard, K. V. Gothelf, K. A. Jørgensen, *Org. Biomol. Chem.* **2003**, *1*, 153; h) D.-M. Du, S-F. Lu, T. Fang, J. Xu, *J. Org. Chem.* **2005**, *70*, 3712; i) D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392; j) T. Arai, M. Watanabe, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 3595.

[8] For the synthesis of the 1,3-dinitroderivative, see R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, *Synthesis* **2004**, 1938.

[9] For design and mechanistic insights with this catalyst, see a) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjarsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; for the characterization and synthesis of the catalyst, see b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 795.

[10] Other base additives tested led to lower enantioselectivities. The reaction rate is considerably lower in the absence of DABCO and in the presence of acids.

[11] For the synthesis of aldehyde **1 f**, see S. Cardani, C. De Toma, C. Gennari, C. Scolastico, *Tetrahedron* **1992**, *48*, 5557.

[12] CCDC-662261 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.

[13] For a review, see G. M. Coppola, H. F. Schuster, *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*, Wiley-VCH, New York, **1987**.

