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A temperature study on a stereoselective organocatalyzed aldol reaction *in water*

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ABSTRACT

We report the first temperature study on the stereoselectivity of the 'in-water' aldol reaction between nicotinaldehyde (3-pyridinecarbaldehyde) and cyclohexanone catalyzed by morpholine and *trans*-4-*tert*-butyldimethylsilyloxy-L-proline. Eyring plots of diastereomeric ratio *anti*/*syn* gave a constant diastereoselectivity with respect to reaction temperature using morpholine as catalyst. With O(TBS)-L-proline we observed a non-linear behaviour of the Eyring plot with the presence of an inversion temperature (T_{inv}), which disclosed dynamic solvation effects in water.

1. Introduction

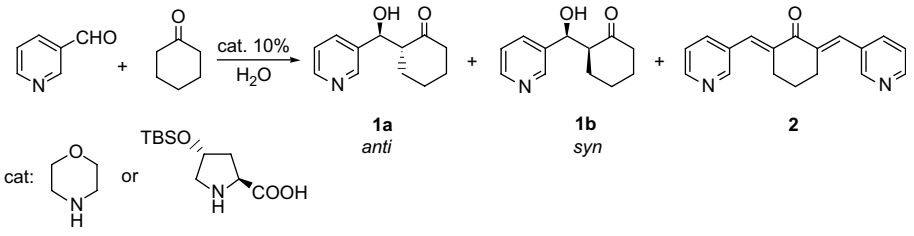
Organocatalysis has been receiving much attention by the chemical community,[1] especially aqueous-phase organocatalysis, in light of the development of environmental friendly chemical processes and to study an analogue of enzyme catalysis. Water was demonstrated to be a suitable solvent for organocatalyzed cross-aldol reactions,[2] but it gives heterogeneous reaction mixtures with the need of surfactant agents.[3] In recent years, we have been involved in studying the effect of solvent and temperature on diastereofacial selectivity in nucleophilic addition to α-chiral aldehydes[4] and imines.[5] Concerning the aldol reaction, we found that solute–solvent interactions are able to affect the stereochemical outcome of an aldol reaction even in the case of hydrocarbon solvents in which only weak and non-specific interactions are involved.[6]

We report here our results on the temperature dependence of diastereo- and enantio-selectivity of an 'in-water' cross-aldol reaction between nicotinaldehyde and cyclohexanone catalyzed by morpholine or *trans*-4-*tert*-butyldimethylsilyloxy-L-proline (O(TBS)-proline). The reaction was studied upon temperature variation from 2 to 80 °C and an Eyring plot of ln(*anti*/*syn*) versus 1/*T* revealed the presence of an inversion temperature (T_{inv}).

2. Results and discussion

Taking into account the 'in-water' and 'on-water' debate in organocatalysis,[7] we initially spent efforts to design a truly 'in-water' condition with all species soluble and forming a homogeneous phase with the aqueous solvent. In these conditions effective solvation effects could be revealed.

We chose 3-pyridinecarbaldehyde and cyclohexanone as partners in a stoichiometric amount, thus avoiding an excess of the ketone, which could act as the reaction solvent.



We initially screened some secondary amines at 10 mol % as catalysts (piperidine, pyrrolidine, morpholine, proline and O(TBS)-proline). Careful examination of water-solubility, reaction time and conversion led us to focus our study on two catalysts: one achiral, morpholine, and one chiral, O(TBS)-proline.

Reactions proceeded smoothly to give *anti* (**1a**) and *syn* (**1b**) aldols. The *anti* and *syn* configurations were determined by NMR

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Table 1
Aldol reaction in water between 3-pyridinecarbaldehyde and cyclohexanone catalyzed by morpholine 10 mol %

Entry	Time (h)	T (°C)	**1a/1b**	**1a**+**1b** (Y%)	**2**[a] (*Y*%)
1	24	30	60:40	57	—
2	0.5	37	64:36	21	—
3	1	37	63:37	37	—
4	2	37	60:40	57	—
5	3	37	58:42	60	—
6	5.5	37	50:50	88	Traces
7	7	37	50:50	89	Traces
8	24	55	51:49	78	21
9	24	70	45:55	47	40

[a] Compound **2** was obtained from crude reaction mixtures by filtration.

analysis by comparison and in analogy with the known products.[8] The *anti*/*syn* ratio (**1a/1b**) within the crude reaction mixture was determined in each experiment by ^{1}H NMR analysis. To test for the presence of equilibration phenomena we followed the variation of the diastereomeric ratio (dr) with reaction time and temperature (Table 1). A preliminary study at 37 °C with 10 mol % morpholine revealed that the *anti*/*syn* ratio was almost constant within 2 h, but for reaction times exceeding 3 h a significant reequilibration occurred. For a longer reaction time and for higher temperature values, a considerable amount of the double eliminated adduct **2** appeared and eroded the diastereomeric ratio. The double condensed aldol or a mono-eliminated product was never observed. Due to the constant diastereomeric ratio after 1 h, we choose to extend the reaction time only for reactions performed at lower temperatures. With O(TBS)-proline as catalyst we never observed eliminated products.

The diastereomeric ratio *anti*/*syn* was then determined in a reaction temperature range of 80 °C with morpholine and O(TBS)-proline (Table 2). The dr data were analyzed according to the differential Eyring equation:[9]

$$\ln(anti/syn) = -\Delta\Delta G^{\neq}/RT = -(\Delta\Delta H^{\neq}/RT) + (\Delta\Delta S^{\neq}/R) \quad (1)$$

where $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{anti} - \Delta H^{\neq}_{syn}$ and $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{anti} - \Delta S^{\neq}_{syn}$.

The temperature dependence of dr values is illustrated in Figure 1, where the natural logarithm of *anti*/*syn* is plotted against the reciprocal temperature. The catalyst has a significant influence on the temperature profile of diastereoselectivity. This accounts for an effective and determining presence of the catalyst within the stereoselective step.[10] Data were then analyzed by least squares fitting to Eq. 1 to obtain linear correlations. For each data set we applied a residual statistical analysis to evaluate the number of linear trends. At all temperature values and with both catalysts there was a predominance of the *anti* isomer and O(TBS)-proline was found to be a better catalyst than morpholine in terms of diastereoselectivity.

With O(TBS)-proline the Eyring plot showed a non-linear behaviour with two linear trends and the presence of an inversion temperature (T_{inv}),[11] with morpholine the dr remained constant at all temperatures.

With morpholine as catalyst there is only one temperature domain with its activation parameters ($\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$), whereas with O(TBS)-proline the presence of a T_{inv} in the Eyring plot determines the existence of two temperature domains characterized by two sets of activation parameters one for $T>T_{inv}$ and one for $T<T_{inv}$. Activation parameters were calculated according to Eq. 1 and reported in Table 3.

In previous papers, we demonstrated that the presence of a T_{inv} in temperature-dependent studies of enantio- and diastereoselectivity depends on dynamic solvation effects.[12] In our interpretation, an Eyring plot featuring a T_{inv} is the result of two

Table 2
anti and *syn* % in the aldol reaction between 3-pyridinecarbaldehyde and cyclohexanone catalyzed by morpholine or O(TBS)-proline 10% in water

Entry	Catalyst	Time (h)	T (°C)	**1a**[a] (%) *anti*	**1b**[a] (%) *syn*
1	Morpholine	16	2	61.9	38.1
2		17	4	61.4	38.6
3		16	8	61.4	38.6
4		6	14	61.3	38.7
5		2	26	60.7	39.3
6		2	34	61.1	38.9
7		2	37	60.5	39.5
8		1	45	60.3	39.7
9		1	47	59.9	40.1
10		1	55	61.3	38.7
11		15 min	65	59.9	40.1
13		5 min	71	60.0	40.0
14		3 min	81	50.8	41.2
15	O(TBS)-Proline	48	8	74.0	26.0
16		25	13	73.7	26.3
17		22	18	73.4	26.6
18		12	31	72.5	27.5
19		23	34	72.4	27.6
20		21	40	71.8	28.2
21		22	45	71.2	28.8
22		24	50	70.7	29.3
23		18	51	70.9	29.1
24		17	55	70.4	29.6
25		21	60	68.1	31.9
26		22	65	65.4	34.6
27		16	70	63.1	36.9
28		22	75	61.7	38.3
29		24	80	59.8	40.2

[a] The reaction yields in **1a**+**1b** ranged from 15 to 60% depending on time and temperature. The average standard deviation on **1a** and **1b** is 0.8% (see Section 4).

intersecting linear trends produced by two distinct solvation clusters. These solute–solvent clusters are the real reacting species in solution and they have specific thermodynamic properties and hence distinct stereoselectivities. The solvent effect on selectivity reflects its different influence on the two diastereomeric paths through distinct contributions to $\Delta\Delta G^{\neq}$. This interpretation can be extended even in this case. In the O(TBS)-proline-catalyzed reaction the reactive intermediate, presumably the enamine,[10] presents two solvation regimes, which are temperature dependent, one for $T>T_{inv}$ and one for $T<T_{inv}$ at the inversion temperature there is an equilibrium between the two.

To understand the nature of the present temperature effect it is necessary to consider the activation parameters in more detail. In the case of morpholine, $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ have very low values, the two diastereomeric reaction paths are so little differentiated by activation enthalpy (−0.2 kcal/mol) that low diastereomeric ratios

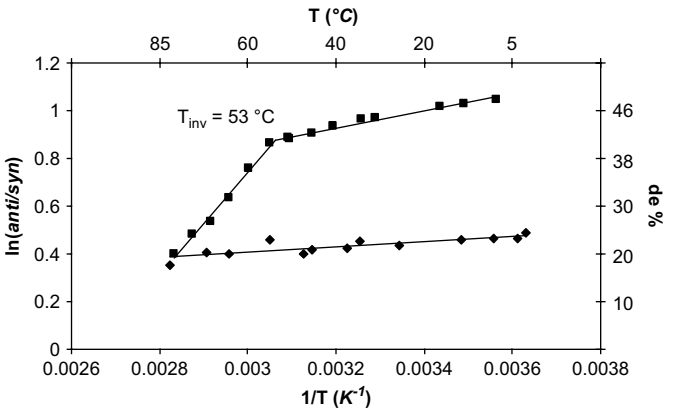

Figure 1. Eyring plots of the diastereomeric ratios *anti*/*syn* in the aldol reaction between 3-pyridinecarbaldehyde and cyclohexanone catalyzed by morpholine (◆) or O(TBS)-proline (■).

Table 3
Differential activation parameters

catalyst		$\Delta\Delta H^{\neq}$ (kcal/mol)	$\Delta\Delta S^{\neq}$ (cal/mol K)
Morpholine		−0.20±0.04	0.1±0.1
O(TBS)-proline	T_{inv}=53 °C		
	$T>T_{inv}$	−4.3±0.2	−11.5±0.6
	$T<T_{inv}$	−0.71±0.03	−0.4±0.1

are obtained, moreover a low differential activation entropy diminished the effect of temperature. With O(TBS)-proline we have to consider the two T domains: for $T>T_{inv}$ the activation enthalpy favours the *anti* isomer (a negative $\Delta\Delta H^{\neq}$ derives from $\Delta H^{\neq}_{syn}>\Delta H^{\neq}_{anti}$), whereas the negative value of activation entropy favours the *syn* one because a greater loss in activation entropy for the *anti* isomer occurred (a negative $\Delta\Delta S^{\neq}$ derives from $|\Delta S^{\neq}_{anti}|>|\Delta S^{\neq}_{syn}|$).[11a] This counteracting action of the two activation parameters does not allow great dr values even if there is a considerable temperature effect for $T>T_{inv}$ essentially due to the enthalpy factor.

One of the crucial arguments for the aldol reaction in water with secondary amines as catalysts is that the reaction could proceed by an enamine mechanism or by a base-catalyzed mechanism. In our case, the nicotinaldehyde, which possesses the pyridine moiety, could act itself as a catalyst. By mixing nicotinaldehyde and cyclohexanone in water without a catalyst, the pH is 5.9 and the reaction does not proceed in 24 h reaction time (Table 4, entry 1), thus excluding the hypothesis of autocatalysis by the aldehyde. In buffered aqueous solution at pH 4.8 and 10.8 (the same pH values of the organocatalyzed reaction with O(TBS)-proline and morpholine, respectively) in the absence of an amine, the aldol reaction takes place only at pH 10.8 but with a low diastereomeric ratio (cf. entries 2 and 3). In the morpholine catalyzed reaction the pH results at 10.8 and the conversion % and dr are quite similar to entry 3, thus suggesting general base catalysis.[13] With morpholine in buffered solution at lower pHs the conversion is lower and the dr is only slightly higher. In the proline-catalyzed reaction the pH is 4.8, the reaction is slow but with an enhanced diastereomeric ratio (entry 8), whereas with buffered solutions at pH 6 and 4 (entries 9 and 10) the dr decreases and at low pH the conversion is very low. The temperature profile in Eyring plots and the pH profile indicate that in unbuffered aqueous solution morpholine generates a basic pH and the reaction has a general base catalysis by hydroxide ion, whereas O(TBS)-proline proceeds by an enamine mechanism subjected to temperature-dependent solvation effects.

We also analyzed the temperature dependence of the enantiomeric excesses of the *syn* and *anti* isomers (Supplementary data). In the aldol reaction catalyzed by O(TBS)-proline, the T dependence of ee_{anti} and ee_{syn} is almost null. The enantiomeric ratios ranged from 0.8 to 2.4 (see Supplementary data) with a high level of scattering, which prevented the possibility of a data analysis via the Eyring Eq. 1. It is known that organocatalyzed aldol reactions in water as reaction solvent give poor results in terms of enantioselectivity except for the use of a low amount of water.[2] Our result strengthens the hypothesis that a better enantioselectivity in organocatalyzed aldol reaction could be achieved in an 'on-water' condition with the reaction taking place at the interfacial hydrophobic region.[14]

Table 4
Control of pH in the aldol reaction between 3-pyridinecarbaldehyde and cyclohexanone

Entry	Time (h)	T (°C)	Catalyst 10%	Buffer (20 mM)	pH[a]	Y (%)	**1a/1b**
1	24	45	—	—	5.9	—	—
2	1	50	—	Acetate	4.8	—	—
3	1	50	—	Carbonate	10.8	57	58:42
4	1	50	Morpholine	—	10.8	47	57:43
5	1	50	Morpholine	Phosphate	6	2	60:40
6	1	55	Morpholine	Phosphate	7.5	13	62:38
7	1	50	Morpholine	Borate	8	14	60:40
8	12	50	Proline	—	4.8	15	70:30
9	12	50	Proline	Phosphate	6	14	58:42
10	24	50	Proline	Citrate	4	4	53:47

[a] pH was measured in the reaction tube.

3. Conclusions

In conclusion, we have reported the first temperature study on an aldol reaction catalyzed by morpholine or O(TBS)-proline with the reactants, nicotinaldehyde and cyclohexanone, solubilized in water as the true reaction solvent. Treatment of data according to Eyring equation allowed us to calculate the differential activation parameters $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$. With morpholine we had a constant diastereoselectivity with temperature. With silyloxyproline we observed a non-linear behaviour with the presence of an inversion temperature, which disclosed the presence of dynamic solvation effects in water. Discussions on water-based organocatalysis contribute once more to a better understanding of the role of water on these processes.

4. Experimental section

4.1. General

TLC: Merck 60 F_{254}. Column chromatography: Merck silica gel 200–300 mesh. FT-IR: Nicolet 205 measured as films or Nujol mull between NaCl plates and reported in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained on a Varian INOVA 300 with a 5 mm probe. All chemical shifts have been quoted relative to deuterated solvent signals, δ in parts per million, J in hertz. The *anti* and *syn* ratios were determined by ^1H NMR analysis of the crude and 64–128 scans were collected for each experiment. After establishment of an equal T_1 relaxation time, the resonance signals at 5.42 ppm (*syn* isomer) and 4.84 ppm (*anti* isomer) of the protons C*H*–OH were manually integrated. A standard deviation of 0.8% on the integrals was calculated.[15] In the O(TBS)-proline-catalyzed reactions, the enantiomeric ratio was determined by HPLC on a chiral stationary phase: Chiracel OJ 25×0.46 isocratic elution 90:10 hexane–isopropanol, 0.5 ml/min. To set and maintain temperature in the range of ±1 °C, a Techne TE-10D Tempunit and Fison Haake K15 were used. *trans*-4-*tert*-Butyldimethylsilyloxy-L-proline was prepared according to Ref. 2.

HPLC-MS: Agilent Technology HP1100, column ZOBRAX-Eclipse XDB-C8 Agilent Technologies coupled with Agilent Technologies MSD1100 single-quadrupole mass spectrometer, full-scan mode from m/z 50 to 2600, scan time 0.1 s in positive ion mode, ESI spray voltage 4500 V, nitrogen gas 35 psgi, drying gas flow 11.5 ml/min, fragmentor voltage 20 V. The compounds were eluted with CH_3CN/H_2O, gradient: from 30% to 80% of CH_3CN in 8 min, then 80% of CH_3CN for 15 min.

4.2. General procedure for the organocatalyzed aldol reaction

In a typical experiment, 5 ml of water (HPLC grade) was placed in a 20 ml test tube equipped with screw-cap and magnetic bar. The desired temperature was reached and kept constant by use of a temperature control apparatus. Freshly distilled cyclohexanone (1.2 mmol), catalyst (morpholine or O(TBS)-proline) (0.1 mmol) and 3-pyridinecarbaldehyde (1.0 mmol) were added to the test tube under constant stirring. After the time indicated in Tables 1 and 2, the reaction mixture was extracted with dichloromethane (3×20 ml). The combined organic layers were dried over anhydrous sodium sulfate. After removal of solvent, the crude was analyzed for dr determination (^1H NMR). The residue was purified by flash-column chromatography on silica gel (cyclohexane/ethylacetate

85:15) to give the mixture of the two aldols **1a** *anti* and **1b** *syn*, which was analyzed by HPLC for determination of enantiomeric ratios. The compounds **1a** and **1b** are known products,[8] however their spectra were never reported.

ν_{max}: 3387, 2937, 2858, 1709 cm^{-1}.

HPLC/ESI-MS: (t_R 2.89 min.): 206.1 $[M+H]^+$, 228.1 $[M+Na]^+$, 433.1 $[2\ M+Na]^+$.

Compound **1b** (*syn*): ^1H NMR (300 MHz, $CDCl_3$) δ 1.49–2.13 (6H, m), 2.31–2.52 (2H, m, CH_2), 2.58–2.66 (1H, m, C*H*), 4.13 (1H, br s, O*H*), 5.42 (1H, s, C*H*OH), 7.25–7.31 (1H, m, arom), 7.68–7.71 (1H, m, arom), 8.48–8.54 (2H, m, arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 27.7, 30.7, 42.6, 56.8, 68.9, 123.2, 133.8, 136.9, 147.5, 148.4, 214.3.

Compound **1a** (*anti*): ^1H NMR (300 MHz, $CDCl_3$) δ 1.49–2.13 (6H, m), 2.31–2.52 (2H, m, CH_2), 2.58–2.66 (1H, m, C*H*), 3.30 (1H, br s, O*H*), 4.84 (1H, d, *J*=8.7 Hz, C*H*OH), 7.25–7.31 (1H, m, arom), 7.68–7.71 (1H, m, arom), 8.48–8.54 (2H, m, arom).

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 27.7, 30.9, 42.6, 57.1, 72.6, 123.5, 134.5, 136.4, 148.8, 149.3, 215.1.

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Supplementary data

Supplementary data contains: ^1H NMR and ^{13}C NMR spectra of **1a** and **1b**. HPLC analysis for the determination of enantiomeric ratios and their temperature dependence. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.059.

References and notes

1. For recent reviews see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Berkssel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005; (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (d) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. C. *Drug Discov. Today* **2007**, *12*, 8–27; (e) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007; (f) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293; (g) List, B. *Chem. Rev.* **2007**, *107*, 5413–5415; (h) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331; (i) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798–3800.
2. For a recent example of organocatalyzed aldol reaction in water, see: Aratake, S.; Itoh, T.; Oakano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem.—Eur. J.* **2007**, *13*, 10246–10256 and references cited therein.
3. (a) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–5529; (b) Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073–9077; (c) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Mi, X.; Zhenga, X.; Chenga, J.-P. *Tetrahedron* **2007**, *63*, 11307–11314.
4. (a) Berardi, R.; Cainelli, G.; Galletti, P.; Giacomini, D.; Gualandi, A.; Muccioli, L.; Zannoni, C. *J. Am. Chem. Soc.* **2005**, *127*, 10699–10706; (b) Cainelli, G.; Galletti, P.; Giacomini, D.; Gualandi, A.; Quintavalla, A. *Tetrahedron* **2005**, *61*, 69–75.
5. Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. *Eur. J. Org. Chem.* **2002**, *18*, 3153–3161.
6. Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* **2001**, *42*, 7383–7385.
7. For what concerns the 'in-water/on-water' debate, see: (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100–8102 and references cited therein; (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103–8104 and references cited therein.
8. (a) Wang, Y.; Wei, S.; Sun, J. *Synlett* **2006**, 3319–3323; (b) Cheng, C.; Wei, S.; Sun, J. *Synlett* **2006**, 2419–2422; (c) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420.
9. Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107–115.
10. (a) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H. Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569; (b) Clemente, F.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766–5768; (c) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16–17.
11. (a) Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.* **1999**, 567–572; (b) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477–515.
12. (a) Cainelli, G.; Galletti, P.; Pieraccini, S.; Quintavalla, A.; Giacomini, D.; Spada, G. P. *Chirality* **2004**, *16*, 50–56; (b) Cainelli, G.; Galletti, P.; Giacomini, D.; Gualandi, A.; Quintavalla, A. *Helv. Chim. Acta* **2003**, *86*, 3548–3559; (c) Cainelli, G.; Giacomini, D.; Galletti, P.; Orioli, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 523–527; (d) Cainelli, G.; Giacomini, D.; Galletti, P.; Marini, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 2849–2852.
13. Chimni, S. S.; Mahajan, D. *Tetrahedron* **2005**, *61*, 5019–5025; Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221; Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970–6979.
14. Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101.
15. Deubner, R.; Holzgrabe, U. *Magn. Reson. Chem.* **2002**, *40*, 762–766.