DOI: 10.1002/chem.200902449

Enantioselective Michael Addition to α,β-Unsaturated Aldehydes: Combinatorial Catalyst Preparation and Screening, Reaction Optimization, and Mechanistic Studies

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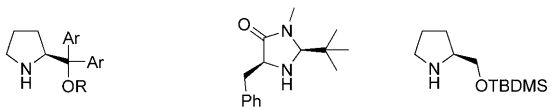
Organocatalysis is one of the fastest growing fields of current research in organic chemistry.[1] Many of the known organocatalysts are readily prepared and easily modified, making it possible to synthesize large catalyst libraries without too much effort. Therefore, considerable efforts have been made to develop efficient screening methods for catalyst development and optimization.[2] We have recently reported a new screening method for chiral catalysts, based on mass-labeled quasi-enantiomeric substrates and electrospray mass spectrometry (ESI-MS).[3–5] This method allows the determination of the intrinsic enantioselectivity of a catalyst by mass spectrometric monitoring of catalytic intermediates. In contrast to conventional screening methods, which are based on product analysis, simultaneous screening of catalyst mixtures in homogeneous solution is possible. As we have shown, our method allows rapid screening of chiral organocatalysts for Diels–Alder reactions.[4d,5]

Herein, we report the successful application of our methodology to the organocatalyzed Michael reaction of malonates **2** to α,β-unsaturated aldehydes **1** (Scheme 1).[6,7] Based on the principle of microscopic reversibility, it is possible to determine the enantioselectivity of a catalyst by screening the intermediates in the *retro*-Michael reaction of a pair of quasienantiomeric Michael adducts **3a** and **3b**.[8] Because the transition states of the forward and back reaction are identical, the ratio of the signal intensities of intermediates **6a** and **6b** with masses M_a and M_b reflects the enantioselectivity of the catalyst.

Based on the above concept, ESI-MS screening of different prolinol-derived organocatalysts **4a–f** and **8**,[9a,b] and imidazolidinone **7**[9c] was conducted (see Table 1). A 1:1 mixture of Et- and *i*Pr-substituted quasi-enantiomers **3a** and **3b** and a catalyst (10 mol%) in a 1:9 CH_2Cl_2/EtOH mixture was stirred for 5 min, then diluted with MeCN and analyzed by ESI-MS. The signals of the iminium derivatives of the Michael adducts **5a** and **5b** and the *retro*-Michael products **6a** and **6b** were clearly visible in the spectra (Scheme 1). Because the reaction is reversible, it is important to take samples after a short time, as longer reaction times will result in racemization of the quasi-enantiomeric Michael adducts. Several very selective catalysts were identified, with the TBDMS derivative **4d** being the catalyst of choice. The results were validated both by screening of the inversely labeled quasi-enantiomers and by comparison with the preparative forward reaction under the same conditions (Table 1, column A). Preparative reactions were also carried out at 0°C (Table 1, column B) and under these conditions, enantiomeric ratios of ≥99:1 were obtained with catalysts **4d** and **4e**. As a further control, both enantiomers of catalysts **4a** and **4d** were tested and, as expected, they gave identical results within the margin of error.[10] No intermediates were observed in the reaction with catalyst **4f**, possibly due to the formation of an inactive cyclic species.



4a Ar = 3,5-$(CF_3)_2$-C_6H_3 R = TMS
4b Ar = Ph R = TMS
4c Ar = Ph R = TES
4d Ar = Ph R = TBDMS
4e Ar = Ph R = TIPS
4f Ar = Ph R = H

7 **8**

This procedure was then extended to multi-catalyst screening.[11] To demonstrate the potential of our method for combinatorial catalyst development, we synthesized a small library of six catalysts in three steps without isolation of the intermediates and purification of the resulting proline derivatives **4b**, **4d**, **4h**, **4j**, and **4g**/**4h**, which were formed as mixtures of diastereomers (Scheme 2). Grignard reaction

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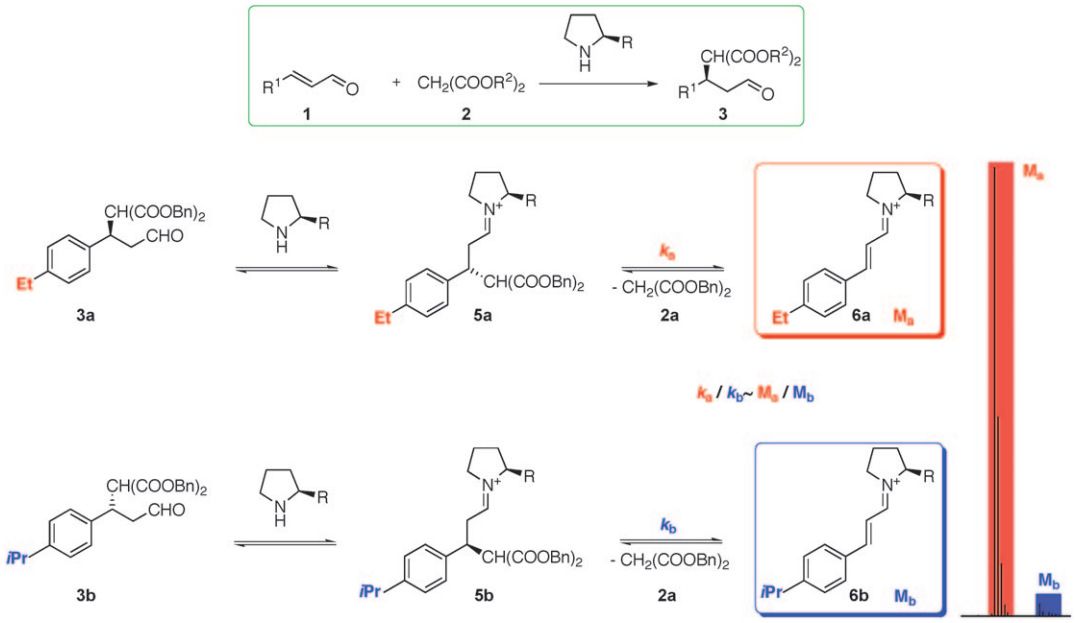
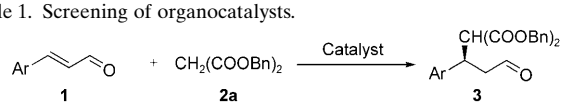
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902449.



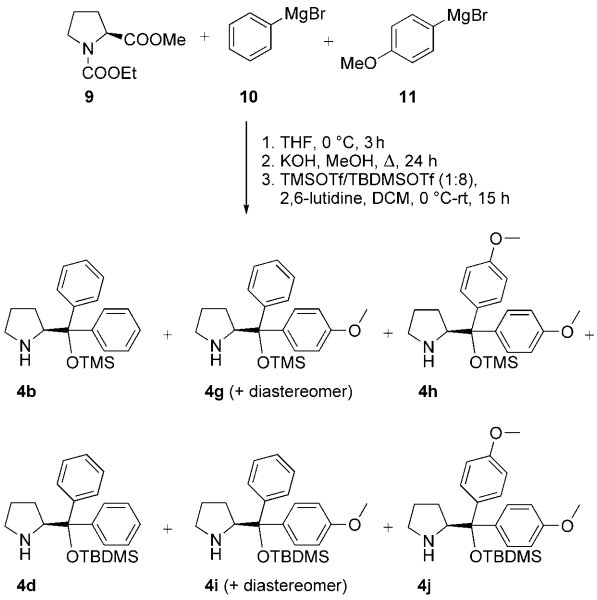
Scheme 1. Principle of the mass spectrometric screening.

Table 1. Screening of organocatalysts.



Entry	Catalyst	ESI-MS screening		Enantiomeric ratio (preparative reaction)	
		(*R*)-**3a**+(*S*)-**3b**	(*S*)-**3a**+(*R*)-**3b**	A[a,f]	B[b,f]
1	(*S*)-**4a**	90:10	10:90	90:10	95:5
2	(*R*)-**4a**	11:89	89:11	nd[g]	95:5
3	(*S*)-**4b**	93:7	7:93	93:7	96:4
4	(*S*)-**4c**	94:6	6:94	95:5	96:4
5	(*S*)-**4d**	97:3	4:96	97:3	99:1
6	(*R*)-**4d**	3:97	97:3	nd[g]	1:99
7	(*S*)-**4e**	96:4	3:97	97:3	99.5:0.5
8	(*S*)-**4f**	nr[c,d]	nr[c]	nr[c]	nd[g]
9	(2*S*,5*S*)-**7**	66:34[e]	nd[g]	nd[g]	nd[g]
10	(*S*)-**8**	59:41	40:60	62:38	nd[g]

[a] Performed with **1a** (Ar = 4-Et-Ph) and **2a** in EtOH/DCM 9:1 at room temperature, stopped after 2 h. [b] Performed with **1a** (Ar = 4-Et-Ph) and **2a** in EtOH at 0 °C. [c] No reaction (nr). [d] No intermediates observed. [e] Very low intensity. [f] Determined by chiral-stationary-phase HPLC. [g] Not determined (nd).



Scheme 2. Synthesis of catalyst mixture **4b/4d/4g–j**.

with a 1:1 mixture of reagents **10** and **11** led to a mixture of alcohols, which was subjected to hydrolysis in refluxing KOH solution to remove the N-protecting group. The resulting crude mixture of pyrrolidine derivatives was treated with a 1:8 mixture of Me_3SiOTf and tBuMe$_2$OTf, which was used in excess to account for its lower reactivity. After aqueous workup, ESI-MS screening was performed directly on the crude mixture of catalysts (Figure 1).

The intermediates derived from the six catalysts were all readily identified in the spectrum. Although the accuracy was somewhat lower than in single catalyst screens due to signal overlap and interfering signals from impurities, the selectivity order of the six catalysts could be unambigously established. The most selective catalyst in this series was **4d** with an enantiomeric ratio of 97:3, which was identical to the value determined in single catalyst screening (Table 1). The results demonstrate that combinatorial library synthesis combined with ESI-MS screening allows rapid and reliable structural optimization of a catalyst. By avoiding laborious isolation and purification steps in the library synthesis, this strategy can considerably accelerate catalyst development.

After identification of the most selective catalysts, the preparative reaction with catalyst **4d** was then further investigated. It is well known that additives such as acids, bases,

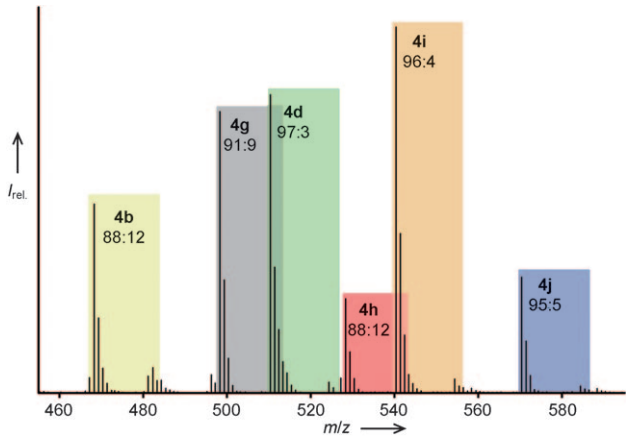


Figure 1. Mass spectrometric screening of catalyst mixture **4b/4d/4g–j**.

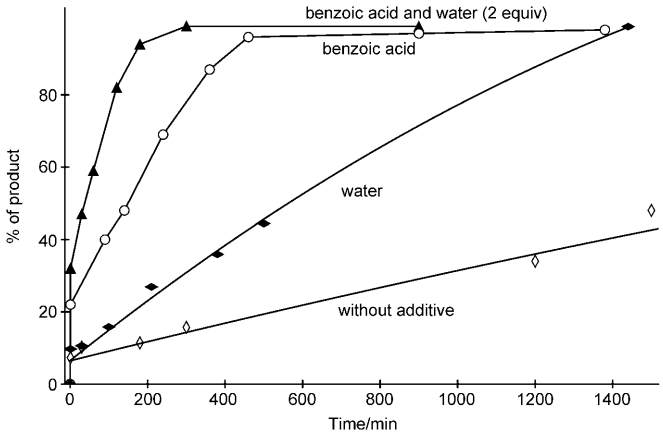
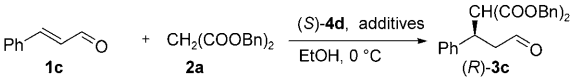


Figure 2. The dependence of product formation on time in the presence of additives at 0 °C.

or water can strongly affect the enantioselectivity and rate of organocatalytic reactions.[1,12,13] In the Michael addition studied here, acids can accelerate the formation of the iminium intermediate from the catalyst and unsaturated aldehyde as well as the conversion of the product enamine to the corresponding iminium salt, which then undergoes hydrolysis to the final product. Indeed, addition of a catalytic amount of a weak acid such as $PhCO_2H$ (1 equiv with respect to catalyst) resulted in a strong rate enhancement (Table 2 and Figure 2). Stronger acids such as CF_3CO_2H completely inhibited the reaction. Addition of sodium benzoate or hydrogencarbonate gave inferior results, in contrast to a recent report on the beneficial effect of carboxylate salts in this reaction.[6d] Stoichiometric experiments showed that benzoic acid strongly accelerates conversion of the aldehyde to the iminium ion (in the absence of acid no iminium ion was observed after 30 min at 0 °C in ethanol). Addition of water (2 equiv relative to malonate) results in further rate increase, whereas water alone has only a weak effect.

Table 2. Effect of additives on the organocatalyzed Michael addition of malonates to α,β-unsaturated aldehydes.[a]

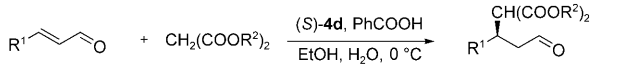


Entry	Additive	Time [h]	Conversion [%][c]	*ee* [%][d]
1	none	84	99	99
		15	30	99
		24	48	99
		48	68	99
2	PhCOOH	15	97	99
3	PhCOOH[b]	6	95	97
4	PhCOONa	15	63	96
5	4-NO_2-(C_6H_4)-COOH	15	97	>99
6	4-OMe-(C_6H_4)-COOH	15	98	99
7	CH_3COOH	15	93	94
8	CH_3COONa	15	77	89
9	CF_3COOH	24	0	nd[e]
10	*p*-CH_3-(C_6H_4)-SO_3H	24	0	nd[e]
11	$NaHCO_3$	24	38	94

[a] Performed with **1c** (0.19 mmol), **2a** (0.13 mmol), **4d** (0.0088 mmol, 7 mol%), and additive (0.0088 mmol) in ethanol (0.5 mL) at 0 °C. [b] Room temperature. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral-stationary-phase HPLC. [e] Not determined (nd).

With optimized conditions in hand, we explored the substrate scope (Table 3). The reaction was found to be general for the malonates tested, however, Meldrum's acid gave 1,2- instead of 1,4-addition (48% yield). High yields and enantioselectivities were obtained with a range of aromatic unsaturated aldehydes. The reaction of the aliphatic unsaturated aldehyde **1g** yielded several unidentified by-products resulting from self-condensation of the aldehyde.[14,15] To suppress this side-reaction, the aldehyde was added slowly to the mix-

Table 3. Michael addition of malonates to α,β-unsaturated aldehydes.[a]



Entry	R^1	R^2	Product	Time [h]	Yield [%]	*ee*[e] [%]
1[b]	4-Et-Ph (**1a**)	Bn (**2a**)	**3a**	6	90	>99 (*R*)
2[b]	4-*i*Pr-Ph (**1b**)	Bn (**2a**)	**3b**	6	89	>99 (*R*)
3	Ph (**1c**)	Bn (**2a**)	**3c**	5	97	99 (*R*)
4	Ph (**1c**)	Me (**2b**)	**3d**	5	92	>99 (*R*)
5	Ph (**1c**)	Et (**2c**)	**3e**	5	95	>99 (*R*)
6	4-MeO-Ph (**1d**)	Me (**2b**)	**3f**	8	95	99 (*R*)
7	4-NO_2-Ph (**1e**)	Me (**2b**)	**3g**	8	96	99 (*R*)
8	2-Furyl (**1f**)	Me (**2b**)	**3h**	6	92	99 (*R*)
9[c]	*n*Bu (**1g**)	Bn (**2a**)	**3i**	24	55[f]	96 (*R*)
10[d]	Ph (**1c**)	Bn (**2a**)	**3c**	8	90	>99 (*R*)

[a] Performed with **1c–g** (0.19 mmol), **2a–c** (0.13 mmol), **4d** (0.0088 mmol), PhCOOH (0.0088 mmol), and water (0.25 mmol) in ethanol (0.5 mL) at 0 °C. [b] Performed with **1a** or **1b** (1.00 mmol), **3c** (0.67 mmol), **4d** (0.047 mmol), PhCOOH (0.047 mmol), and water (1.34 mmol) in ethanol (2.5 mL) at 0 °C. [c] Compound **1g** was added to **4d** and **2a** during 3 h. [d] Performed at room temperature with **2a** (2.50 mmol), **4d** (2 mol%) and benzoic acid, in technical EtOH, yield and *ee* after one recrystallization. [e] Determined by chiral-stationary-phase HPLC (see the Supporting Information). [f] Isolated product contained 10% of **2a**.

ture of catalyst and malonate. Under these conditions, product **3i** was formed in high enantiomeric purity but only moderate yield (Table 3, entry 9). The reaction of dibenzyl malonate and cinnamaldehyde was also conducted on a gram scale with only 2 mol% of catalyst (Table 3, entry 10) in ethanol at room temperature. After 8 h and one recrystallization, pure product was obtained in 90% yield and >99% *ee*.

In addition, we examined the reaction for nonlinear effects.[16] As shown in Figure 3, experiments with samples of

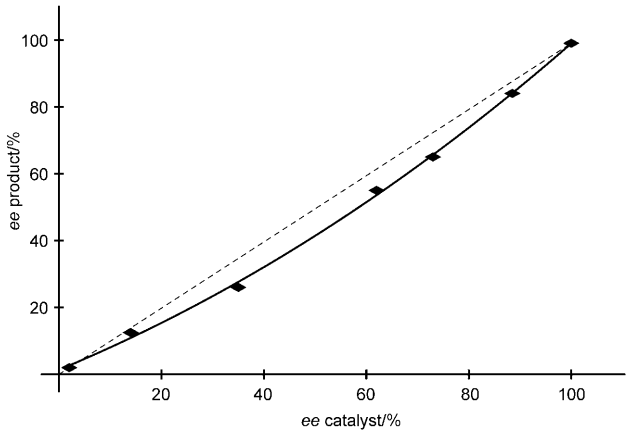
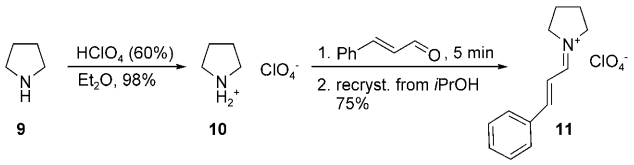


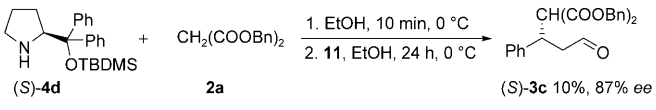
Figure 3. Nonlinear effect in the Michael addition of malonate **2a** to aldehyde **1c** catalyzed by **4d**.

catalyst **4d** of varying enantiomeric purity showed a clear negative nonlinear effect. As a possible explanation we considered the involvement of two catalyst molecules in the enantioselective step, one forming the iminium intermediate, the other forming a chiral nucleophilic species by hydrogen bonding to the enol form of malonate. To test this hypothesis, iminium salt **11** was prepared according to a known procedure (Scheme 3)[17] and allowed to react with equimolar



Scheme 3. Synthesis of iminium perchlorate **11**.

amounts of dibenzyl malonate and catalyst (*S*)-**4d**. After 24 h at 0°C, the Michael adduct **3c** was obtained as the *S* enantiomer in 87% *ee*, as opposed to the *R* enantiomer formed in the catalytic reaction with (*S*)-**4d** (Scheme 4; Table 3, entry 3).



Scheme 4. Effect of (*S*)-**4d** in the addition of malonate **2a** to iminium salt **11**.

Thus, there appears to be a mismatch between the chiral induction by the chiral iminium group and that of the chiral catalyst–malonate adduct. However, control by the iminium group strongly dominates such that high enantioselectivities are still possible. This mismatch between the action of the two catalyst molecules explains the observed negative nonlinear effect. If a non-enantiopure catalyst is used, four pairs of activated species are involved in the enantioselective step: two mismatched and, accordingly, less reactive homochiral combinations and two matched, more reactive heterochiral combinations. The two heterochiral pairs [(*R*)-iminium/(*S*)-malonate and (*S*)-iminium/(*R*)-malonate] are present in equal amounts and, therefore, produce racemic product. Because these heterochiral pairs are more reactive, formation of racemic product will be faster than the corresponding enantioselective process and, as a consequence, the proportion of racemate in the product will be higher compared to the catalyst.

In conclusion, we have developed an efficient combinatorial strategy for the development and structural optimization of organocatalysts for the Michael addition to α,β-unsaturated aldehydes. In contrast to conventional parallel screening methods, simultaneous evaluation of a mixture of catalysts is possible without the need to isolate and purify the individual catalysts. Thus, our method should greatly facilitate the search for more efficient catalysts for substrates, which give unsatisfactory results with known catalysts. A strong accelerating effect of added carboxylic acid and water was observed, which allows considerably shorter reaction times and much lower catalyst loadings. In addition, a distinct nonlinear effect was observed that was rationalized by a double nucleophilic–electrophilic activation mechanism involving two catalyst molecules.

Experimental Section

Experimental details are included in the Supporting Information.

Acknowledgements

Financial support by the Swiss National Science Foundation is gratefully acknowledged. We appreciate the helpful discussions with Dr. Matthias Maywald.

Keywords: asymmetric catalysis · conjugate addition · high-throughput screening · mass spectrometry · organocatalysis

[1] For recent reviews on asymmetric organocatalysis, see: a) B. List, *Chem. Commun.* **2006**, 819–824; b) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; c) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; d) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8–27; e) *Chem. Rev.* **2007**, *107*(12), special issue; f) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; g) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–

4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; h) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.
[2] For a review, see: a) M. H. Fonseca, B. List, *Curr. Opin. Chem. Biol.* **2004**, *8*, 319–326; for selected examples, see: b) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474–2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; c) P. Krattiger, R. Kovàsy, J. D. Revell, H. Wennemers, *QSAR Comb. Sci.* **2005**, *24*, 1158–1163.
[3] For selected examples of the use of mass spectrometry in the measurement of enantiomeric excesses, see: a) A. Horeau, A. Nouaille, *Tetrahedron Lett.* **1990**, *31*, 2707–2710; b) J. Guo, J. Wu, G. Siuzdak, M. G. Finn, *Angew. Chem.* **1999**, *111*, 1868–1871; *Angew. Chem. Int. Ed.* **1999**, *38*, 1755–1758; c) M. T. Reetz, M. H. Becker, H.-W. Klein, D. Stöckigt, *Angew. Chem.* **1999**, *111*, 1872–1875; *Angew. Chem. Int. Ed.* **1999**, *38*, 1758–1761; d) M. G. Finn, *Chirality* **2002**, *14*, 534–540; and references therein.
[4] a) C. Markert, A. Pfaltz, *Angew. Chem.* **2004**, *116*, 2552–2554; *Angew. Chem. Int. Ed.* **2004**, *43*, 2498–2500; b) C. Markert, P. Rösel, A. Pfaltz, *J. Am. Chem. Soc.* **2008**, *130*, 3234–3235; c) C. A. Müller, A. Pfaltz, *Angew. Chem.* **2008**, *120*, 3411–3414; *Angew. Chem. Int. Ed.* **2008**, *47*, 3363–3366; d) C. A. Müller, C. Markert, A. M. Teichert, A. Pfaltz, *Chem. Commun.* **2009**, 1607–1618.
[5] A. Teichert, A. Pfaltz, *Angew. Chem.* **2008**, *120*, 3408–3410; *Angew. Chem. Int. Ed.* **2008**, *47*, 3360–3362.
[6] For organocatalyzed Michael additions of malonates to aldehydes, see: a) M. Yamaguchi, N. Yokota, T. Minami, *J. Chem. Soc. Chem. Commun.* **1991**, 1088–1089; b) S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411–4415; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309; c) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583–8587; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435; d) Y. Wang, P. Li, X. Liang, J. Ye, *Adv. Synth. Catal.* **2008**, *350*, 1383–1389; e) A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075–3077.
[7] For recent reviews on organocatalyzed 1,4-additions, see: a) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; c) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065–2092.
[8] For a review on quasi-enantiomers, see: Q. S. Zhang, D. P. Curran, *Chem. Eur. J.* **2005**, *11*, 4866–4880.
[9] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; c) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.
[10] The results are in accord with those reported in literature, see reference [6].
[11] P. Chen, *Angew. Chem.* **2003**, *115*, 2938–2954; *Angew. Chem. Int. Ed.* **2003**, *42*, 2832–2847.
[12] For an example, see: N. Halland, M. A. Lie, A. Kjærsgaard, M. Marigo, B. Schiøtt, K. A. Jørgensen, *Chem. Eur. J.* **2005**, *11*, 7083–7090.
[13] For a discussion on effect of water, see: a) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102; b) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104; c) D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem.* **2007**, *119*, 3872–3874; *Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800; d) N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101.
[14] J. M. McIntosh, H. Khalil, D. W. Pillon, *J. Org. Chem.* **1980**, *45*, 3436–3439.
[15] B. J. Bench, C. Liu, C. R. Evett, C. M. H. Watanabe, *J. Org. Chem.* **2006**, *71*, 9458–9463.
[16] For recent reviews on nonlinear effects, see: a) D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402–411; b) H. B. Kagan, *Synlett* **2001**, 0888–0899; c) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369–3400.
[17] a) N. J. Leonard, J. V. Paukstelis, *J. Org. Chem.* **1963**, *28*, 3021–3024; b) D. Seebach, U. Grošelj, M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999–2034; c) U. Grošelj, D. Seebach, M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru, *Helv. Chim. Acta* **2009**, *92*, 1225–1259.

Received: September 4, 2009
Published online: November 13, 2009

