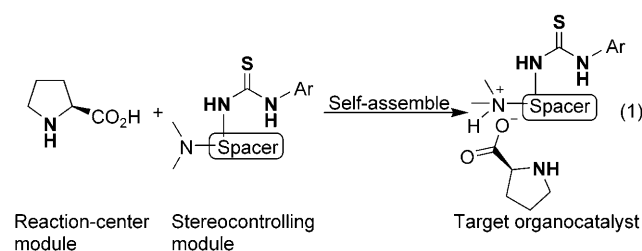


Modularly Designed Organocatalytic Assemblies for Direct Nitro-Michael Addition Reactions**

Tanmay Mandal and Cong-Gui Zhao*

Organocatalysis has developed rapidly in recent years.^[1] Among the catalysts developed for this purpose, proline derivatives have risen to prominence, and have been used to catalyze a wide range of reactions.^[2] While covalent bonds are used to connect the stereocontrolling moiety and the pyrrolidine backbone in most of these derivatives, Clarke and Fuentes recently reported the first example of modularly designed prolinamide-based catalysts that self-assemble under the reaction conditions through hydrogen-bonding interactions.^[3] Although the reported method only affords mediocre enantioselectivities in most cases, the advantage of this approach is obvious: Modification of the catalyst structure only needs simple replacement of the modules, while further chemical synthesis is avoided. Moreover, a library of diverse organocatalysts may be more efficiently obtained for catalyst screening and structure modification.^[4]

During our recent study of quinine derivative-catalyzed enantioselective reactions,^[5,6] we envisioned that ionic interactions may be utilized for the self-assembly of modularly designed organocatalysts. Our hypothesis is shown in Equation (1) with proline as the reaction-center module. When proline and a tertiary amine carrying a thiourea moiety (the stereocontrolling module)^[7] are mixed, an acid–base reaction between the carboxylic acid and the tertiary amine groups should lead to an ammonium salt.^[8] Ionic interactions between the ammonium and the carboxylate should cause these two modules to self-assemble,^[9] forming a potential



organocatalyst incorporating both the proline reaction center and a stereocontrolling moiety.

Michael addition is one of the most important C–C bond-forming reactions in organic synthesis,^[10] and many proline derivatives^[11] have been developed as catalysts for the direct addition of ketones/aldehydes to nitroalkenes since the proline-catalyzed direct nitro-Michael addition was discovered.^[12] To test our hypothesis, the nitro-Michael addition reaction was adopted as a model. Herein we wish to report our preliminary results of using these self-assembled organocatalysts in the direct Michael addition of ketones and aldehydes to nitroalkenes.

Acetone and *trans*- β -nitrostyrene were selected as the model substrates in the preliminary screening. Acetone is one of the most problematic substrates for the nitro-Michael addition. To our knowledge, enantiomeric excesses of over 90% have been obtained for the Michael product with an acetone substrate in only two cases^[11i–j], despite the fact that numerous sophisticated proline derivatives have been reported as the organocatalysts for this reaction.^[11p–q] Readily available α -amino acids, such as proline, glycine, alanine, L-*tert*-leucine, and phenylglycine,^[13] were selected as the reaction-center modules, whereas some readily accessible cinchona alkaloid derivatives were chosen as the stereocontrolling modules (Scheme 1). Some typical results^[13] are summarized in Table 1.

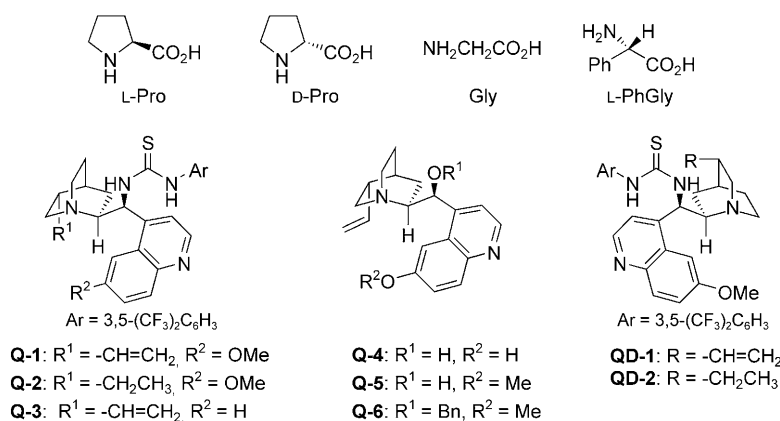
The enantiomers of proline show strong matching and mismatching effects with the thiourea derivative **Q-1** (Scheme 1): No conversion of *trans*- β -nitrostyrene was detected after 72 h when L-proline was used (Table 1, entry 1). In contrast, after only 20 h, the desired product was obtained in 88% yield and 66% *ee* for the *R* enantiomer when D-proline (Table 1, entry 2) was used under the same conditions. Nonetheless, poor conversions were achieved when either **Q-1** (0%) or D-proline (<5%) were used alone.^[13] Thiourea derivatives **Q-2** and **Q-3** (see Scheme 1) generate similar results to **Q-1** with D-proline (Table 1, entries 3 and 4). In contrast, similar precatalyst modules without the thiourea moiety were not effective in promoting enantioselectivity. For examples, **Q-4**, **Q-5**, and **Q-6** (see Scheme 1) and D-proline all lead to much inferior *ee* values (Table 1, entries 5–7). These results indicate that this catalytic system is different from the reported asymmetric counterion-directed catalysis (ACDC),^[8] as, in the case of ACDC, the stereocontrol is achieved mainly through steric effects instead of hydrogen-bonding.

The reaction conditions were then optimized for the self-assembly of **Q-1** and D-proline and we were surprised to find that improved enantioselectivity (78% *ee*) of the product may be obtained by reducing the catalyst loading to 5 mol%.^[13]

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Scheme 1. Structure of representative precatalyst modules.

Table 1: Michael addition of acetone to *trans*- β -nitrostyrene catalyzed by self-assembled catalysts.^[a]

Entry	Module/Lading (mol %)	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c] (configuration)
1	L-Pro/20 Q-1 /20	72	0	–
2	D-Pro/20 Q-1 /20	20	88	66 (<i>R</i>)
3	D-Pro/20 Q-2 /20	22	83	66 (<i>R</i>)
4	D-Pro/20 Q-3 /20	24	83	67 (<i>R</i>)
5	D-Pro/20 Q-4 /20	30	78	11 (<i>S</i>)
6	D-Pro/20 Q-5 /20	40	87	11 (<i>R</i>)
7	D-Pro/20 Q-6 /20	32	79	5 (<i>R</i>)
8 ^[d]	D-Pro/5 Q-1 /5	120	67	86 (<i>R</i>)
9 ^[e]	L-Pro/5 QD-1 /5	72	81	86 (<i>S</i>)
10 ^[d]	L-Pro/5 QD-2 /5	72	75	86 (<i>S</i>)
11 ^[e]	D-Pro/5 QD-1 /5	120	13 ^[f]	40 (<i>R</i>)
12	Gly/20 Q-1 /20	120	13 ^[f]	51 (<i>S</i>)
13	L-Ala/20 Q-1 /20	120	5 ^[f]	6 (<i>S</i>)
14 ^[e]	L-PhGly/5 QD-1 /5	192	63	95 (<i>R</i>)

[a] Unless otherwise indicated, all reactions were conducted with *trans*- β -nitrostyrene (0.1 mmol), acetone (0.7 mmol, 50 μ L), and the precatalyst combinations in CH₂Cl₂ (1.0 mL) at room temperature. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analysis on a ChiralPak AD-H column. Absolute configuration was determined by comparison with the reported optical rotation data. [d] Conducted in benzene (1.0 mL) at 2°C. [e] Conducted in benzene (1.0 mL) at room temperature. [f] Conversion as determined by ¹H NMR analysis.

Through further optimization of the reaction conditions,^[13] a highest *ee* value of 86% of the product may be obtained in benzene at approximately 2°C (Table 1, entry 8).

As expected, quinidine thioureas, such as **QD-1** and **QD-2**, match with L-proline for this reaction. The reaction catalyzed by the organocatalyst assembly of **QD-1** and L-proline yields the anticipated *S* enantiomer in 86% *ee* at room temperature in benzene (Table 1, entry 9). Similar results were obtained for the assembly of **QD-2** and L-proline (Table 1, entry 10). The mismatched assembly of D-proline and **QD-1** again delivered poor results (Table 1, entry 11).

Besides proline, some α -amino acids with a primary amine amine group were also screened, delivering some very interesting

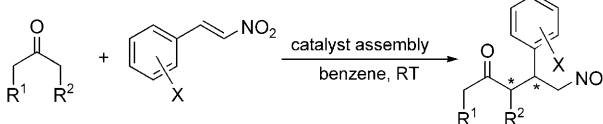
results.^[15] For example, the achiral α -amino acid glycine was found to self-assemble with **Q-1**, too. Although this assembly is not very reactive, the enantioselectivity obtained is a very promising 51% *ee* for the *S*-configured product (Table 1, entry 12). The self-assembly of L-alanine and **Q-1** also reacts, albeit in very low efficiency (Table 1, entry 13). Further such screenings^[13] identified the assembly of L-phenylglycine and **QD-1** as a highly enantioselective catalyst, affording the *R*-configured Michael adduct in 95% *ee* (Table 1, entry 14).

In contrast, proline derivatives that do not self-assemble with **QD-1**, such as methyl L-prolinate and L-prolinamide, fail to generate the desired product in good yields and *ee* values under similar conditions.^[13] These results clearly

evince that catalytic activity and directing effects are, in this case, the result of the self-assembled catalysts instead of synergistic effects.^[14] Moreover, this conclusion is also supported by NMR spectroscopy^[13] of the L-proline and **QD-1** mixture. The scope of this approach was then evaluated, under the optimized conditions, with various ketone, aldehyde, and nitroalkene substrates. Some typical results with ketones and nitrostyrenes are compiled in Table 2.^[15] The reaction of acetone with β -nitrostyrene derivatives, under the catalysis of the assembly of L-phenylglycine and **QD-1**, affords excellent enantioselectivities ($\geq 94\%$ *ee*, Table 2, entries 1–8). However, this assembly is not very reactive for most other ketone substrates, although when reaction does occur, it is with very high enantioselectivity in the product (Table 2, entry 9). While the assembly of L-proline and **QD-1** leads to slightly inferior *ee* values for an acetone substrate,^[15] it is much more reactive under similar conditions. This assembly is a good catalyst for longer-chain ketone substrates, such as methyl ketones (Table 2, entries 10–13) and 3-pentanone (Table 2, entry 14), and cyclic ketones, such as cyclopentanone (Table 2, entry 15) and cyclohexanone derivatives (Table 2, entries 16–18). The *syn* diastereomers were obtained in good diastereoselectivity in all cases, except for 4-methyl-2-pentanone, which produces the kinetic (*anti*) product (Table 2, entry 13). Excellent *ee* values and good diastereoselectivities may also be achieved with aldehyde and aliphatic nitroalkene substrates by using this catalytic system.^[15]

The opposite senses of enantioselectivity and diastereoselectivity for the assemblies of L-proline and L-phenylglycine with **QD-1** may be rationalized by the proposed transition states, as shown in Scheme 2. In the case of L-proline, the *Si*,*Si*-attack of the hydrogen-bonded nitrostyrene on the *anti* rotamer of the *E*-enamine intermediate leads to the (3*R*,4*S*)-configured major *syn* diastereomer (Scheme 2, upper structure). In contrast, in the case of L-phenylglycine, formation of a *Z*-enamine is favored,^[11] and the *Re*,*Si*-attack of the hydrogen-bonded nitrostyrene on this enamine leads to the major (3*R*,4*R*)-configured *anti* product (Scheme 2, lower structure).

In summary, we have demonstrated that ionic interactions between ammonium and carboxylate ions may be utilized for the formation of organocatalytic self-assemblies from readily

Table 2: Direct nitro-Michael addition of ketones to nitrostyrenes catalyzed by the self-assemblies.^[a]


Entry	R ¹	R ²	X	t [d]	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d] (configuration)
1	H	H	H	8	63	—	95 (R)
2	H	H	4-Cl	8	57	—	95 (R)
3	H	H	4-Br	8	59	—	94 (R)
4	H	H	4-Me	8	61	—	94 (R)
5	H	H	4-MeO	8	55	—	96 (R)
6	H	H	3-Cl	8	55	—	95 (R)
7	H	H	2-Br	8	63	—	98 (R) ^[e]
8	H	H	2-NO ₂	8	69	—	97 (R)
9 ^[f]	H	Me	H	8	40	25:75	99 (R,R) ^[g]
10 ^[f,h]	H	Me	H	3.5	78	96:4	90 (R,S) ^[g]
11 ^[f,h]	H	Et	H	3.5	72	90:10	94 (R,S) ^[g]
12 ^[f,h]	H	OMe	H	4	51	82:18	90 (R,S) ^[g]
13 ^[f,h]	iPr	H	H	5	53	—	86 (S)
14 ^[h]	Me	Me	H	7	47	88:12	90 (R,S)
15 ^[h,i]	—	-(CH ₂) ₂ -	H	5	63	77:23	92 (R,S)
16 ^[h,i]	—	-(CH ₂) ₃ -	H	3	92	93:7	84 (R,S)
17 ^[h,i]	—	-CH ₂ OCH ₂ -	H	4	75	90:10	94 (S,S)
18 ^[h,i]	—	-CH ₂ SCH ₂ -	H	3.5	76	96:4	99 (R,S)

[a] Unless otherwise indicated, all reactions were conducted with *trans*- β -nitrostyrene (0.1 mmol), ketone (0.7 mmol), and the catalyst assembly of **QD-1** and L-phenylglycine (5 mol% loading each) in benzene (1.0 mL) at room temperature. [b] Yield of the isolated product after column chromatography. [c] Ratio of *syn/anti* as determined by ¹H NMR analyses of the crude products. [d] Unless otherwise indicated, *ee* values were determined by HPLC analysis on a ChiralPak AD-H column; absolute configurations were determined by comparison with the reported optical rotation data or tentatively assigned on the basis of the reaction mechanism. [e] Separated on a ChiralPak AS column. [f] Only the given regioisomer was obtained in the crude product. [g] Separated on a Chiralcel OD-H column. [h] The catalyst assembly used was L-proline and **QD-1** (5 mol% loading each). [i] 0.15 mmol of ketone was used.

enantioselective direct nitro-Michael addition of ketones and aldehydes to nitroalkenes.

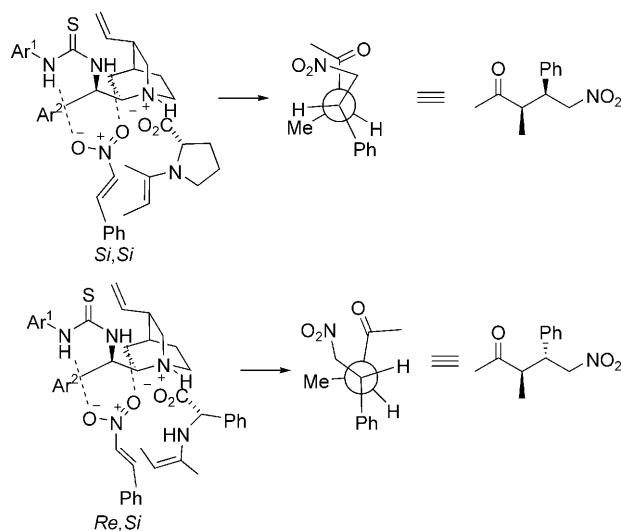
Experimental Section

General Procedure: The precatalysts L-proline (or D-proline, 0.005 mmol, 0.6 mg, or L-phenylglycine, 0.005 mmol, 0.8 mg) and **Q-1** (or **QD-1**, 3.0 mg, 0.005 mmol), *trans*- β -nitrostyrene (0.1 mmol, 14.9 mg) and benzene (1 mL) were added to a capped 8 mL sample vial. The resulting mixture was stirred for 1 min at room temperature before acetone (0.7 mmol, 50 μ L) was added with a Hamilton syringe. The reaction mixture was further stirred at room temperature for the time as specified in Table 1 (monitored by TLC), and then directly transferred to a short column packed with silica gel. The column was eluted with 9:1 hexane/ethyl acetate mixture and the solvent was removed under reduced pressure, affording the direct nitro-Michael addition product as a pure compound.

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Scheme 2. Proposed transition-state structures (see text for details).

available α -amino acids and alkaloid derivatives. These self-assembled organocatalysts are excellent catalysts for the

- [1] For reviews, see: a) A. Berkessel, H. Groeger in *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; b) H. Pellissier, *Tetrahedron* **2007**, 63, 9267–9331.
- [2] For reviews, see: a) S. V. Ley, *Tetrahedron: Asymmetry* **2007**, 201–206; b) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, 37, 580–591; c) B. List, *Tetrahedron* **2002**, 58, 5573–5590.
- [3] M. L. Clarke, J. A. Fuentes, *Angew. Chem.* **2007**, 119, 948–951; *Angew. Chem. Int. Ed.* **2007**, 46, 930–933.
- [4] For reviews, see a) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, 103, 3071–3100; b) M. T. Reetz, *Angew. Chem.* **2001**, 113, 292–320; *Angew. Chem. Int. Ed.* **2001**, 40, 284–310; c) B. Breit, *Angew. Chem.* **2005**, 117, 6976–6986; *Angew. Chem. Int. Ed.* **2005**, 44, 6816–6825. For some leading examples using modular approach in designing transition metal catalysts, see: d) B. Breit, W. Seiche, *Angew. Chem.* **2005**, 117, 1666–1669; *Angew. Chem. Int. Ed.* **2005**, 44, 1640–1643; e) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, 128, 4188–4189; f) F. Chevallier, B. Breit, *Angew. Chem.* **2006**, 118, 1629–1632; *Angew. Chem. Int. Ed.* **2006**, 45, 1599–1602; g) K. Ding, A. Ishii, K. Mikami, *Angew. Chem.* **1999**, 111, 519–523; *Angew. Chem. Int. Ed.* **1999**, 38, 497–501; h) F. W. Patureau, M. Kuil, A. J. Sandee, J. N. H. Reek, *Angew. Chem.* **2008**, 120, 3224–3227; *Angew. Chem. Int. Ed.* **2008**, 47, 3180–3183; i) X.-B. Jiang, L. Lefort, P. E.

- Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245–1249; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223–1227; j) V. F. Slagt, M. Roeder, P. C. J. Kamer, P. W. N. M. Van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2004**, *126*, 4056–4057.
- [5] a) T. Mandal, S. Samanta, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 943–945; b) R. Dodda, J. J. Goldman, T. Mandal, C.-G. Zhao, G. A. Broker, E. R. T. Tiekink, *Adv. Syn. Catal.* **2008**, *350*, 537–541; c) R. Dodda, T. Mandal, C.-G. Zhao, *Tetrahedron Lett.* **2008**, *49*, 1899–1902.
- [6] For some leading examples of quinine derivative-catalyzed reactions, see: a) H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732–733; b) L. Zu, J. Wang, H. Li, H. Xie, W. Jiang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 1036–1037; c) M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 3830–3831; d) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; e) M. Bella, K. A. Jorgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672–5673; f) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri, P. Melchiorre, *Angew. Chem.* **2006**, *118*, 5088–5092; *Angew. Chem. Int. Ed.* **2006**, *45*, 4966–4970.
- [7] For a review, see: A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.
- [8] For leading examples of using chiral ammonium salts for asymmetric counteranion-directed catalysis, see: a) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369; b) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299–4301; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193–4195. For an example of using carboxylic acid as an additive in the quinine derivative-catalyzed nitro-Michael reaction, see: S. H. McCooey, S. J. Cannon, *Org. Lett.* **2007**, *9*, 599–602.
- [9] For examples of self-assembly between amines and acids, see: a) C. Schmuck, W. Wienand, *J. Am. Chem. Soc.* **2003**, *125*, 452–459; b) S. Le Gac, M. Luhmer, O. Reinaud, I. Jabin, *Tetrahedron* **2007**, *63*, 10721–10730.
- [10] For a review, see: P. Perlmutter in *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.
- [11] For some leading examples, see: a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; b) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371; c) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; d) S. V. Pansare, K. J. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625; e) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079; f) C. Palomo, S. Vera, A. Mielgo, E. Goméz-Bengoa, *Angew. Chem.* **2006**, *118*, 6130–6133; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984–5987; g) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042–8046; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880; h) D. Enders, C. Huttli, M. R. M. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; i) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451–1453; j) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; k) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897–1900; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871–1874; l) P. García-García, A. Ladépêche, R. Halder, 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) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611; o) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609. For reviews, see: p) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1706; q) D. Almaši, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.
- [12] a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2424; b) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441–4444; c) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; d) D. Enders, A. Seki, *Synlett* **2002**, 26–28.
- [13] For more details, please see the Supporting Information.
- [14] S. B. Tsogoeva, S. B. Jagtap, *Synlett* **2004**, 2624–2626.
- [15] For a list of additional substrates, please see Tables 6 and 7 in the Supporting Information.