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Asymmetric Synthesis of Polyfunctionalized Pyrrolidines *via* a Thiourea Catalyzed Domino Mannich/Aza-Michael Reaction

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Dedicated to Professor Günter Helmchen on the occasion of his 70th birthday.

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Abstract: The domino Mannich/aza-Michael reaction of γ-malonate-substituted α,β-unsaturated esters with *N*-protected arylaldimines has been achieved. Catalyzed by bifunctional thioureas, 2,5-*cis*-configured polysubstituted pyrrolidines are obtained in good to excellent yields (76–99%), enantioselectivities (75–94%) and excellent diastereoselectivities (*de* >95%). The pure stereoisomers are available by crystallization and removal of the racemates.

Keywords: bifunctional thioureas; domino reaction; Mannich/aza-Michael reaction; organocatalysis; pyrrolidines

In the last decade the research area of asymmetric organocatalysis has grown rapidly and became a third brand of asymmetric catalysis besides the well established bio- and metal catalysis.[1] Recently, organocatalytic domino/cascade reactions came into focus allowing the synthesis of complex molecules economically in fewer steps.[2] Applying this strategy to nitrogen-containing heterocycles, such structural motifs as piperidines[3] and isoquinuclidines[4] have been efficiently generated *via* sequential Mannich/aza-Michael reactions.

Due to the involvement of pyrrolidine structures in many physiological processes such as in interactions with enzymes[5] and receptors[6], the synthesis of these compounds is the focus of much current research. In addition, pharmacological studies of the antiviral[7] and analgesic[8] activities of pyrrolidine derivatives have led to a demand for additional synthetic strategies towards these heterocycles. In addition, proline and its derivatives play a central role in organocatalysis and have been applied successfully in many organocatalytic reactions.[9]

Many syntheses of substituted pyrrolidines have been developed, with initial approaches including the hydrogenation of pyrroles[10] and the Hofmann–Löffler–Freytag cyclization.[11] Current synthetic approaches have significantly broadened the stereoselectivity and diversity in the formation of such nitrogen-containing heterocycles. For instance, pyrrolidines have been obtained by the asymmetric [3+2]-cycloaddition of azomethine ylides to alkenes[12] and by ring-closure of pre-synthesized chiral linear molecules.[13]

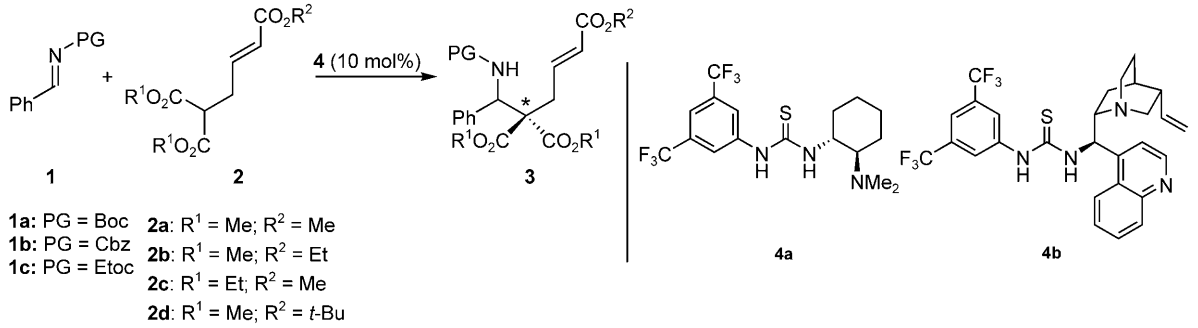
Recently, highly stereoselective Mannich additions of malonic esters to *N*-protected aryl aldimines have been reported.[14] These reactions are usually catalyzed by bifunctional thioureas, although they have also been achieved in the presence of chiral metal-ligand complexes and phase-transfer organocatalysts. Even though the stereoselective addition of α-methyl-substituted malonates to imines has been described in the literature, the use of malonates with other substituents in similar reactions has still remained unsolved.[14f,i]

In the course of our ongoing research on organocatalytic cascade reactions[15] we envisaged an asymmetric synthesis of polyfunctionalized pyrrolidines *via* a thiourea-catalyzed domino Mannich/aza-Michael reaction of *N*-protected aryl aldimines with γ-malonate-substituted α,β-unsaturated esters (Scheme 1). The latter have already been used in tandem Michael reactions to generate substituted cyclopentanes.[16]

Therefore we screened a number of α,β-unsaturated esters **2**[17] with carbamate-protected benzaldimines **1**[18] to gauge the potential of the novel pyrrolidine synthesis (Table 1).

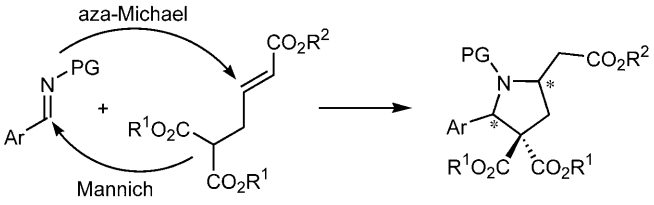
In the first instance we chose the catalysts **4a** and **4b**[19] for the Mannich reaction owing to their excel-

Table 1. Enantioselective Mannich reaction.[a]



Entry	Product	Imine	Malonate	Catalyst	Yield [%][b]	*ee* [%][c]
1	**3a**	**1a**	**2a**	**4a**	95	83
2	**3b**	**1b**	**2a**	**4a**	95	58
3	**3c**	**1c**	**2a**	**4a**	94	15
4	**3d**	**1a**	**2b**	**4a**	92	85
5	**3e**	**1a**	**2c**	**4a**	56	85
6	**3f**	**1a**	**2d**	**4a**	61	84
7	**3a**	**1a**	**2a**	**4b**	50	68

[a] *Reaction conditions:* **1** (1.6 mmol), **2** (0.8 mmol), absolute DCM (4 mL), **4** (10 mol%), 5 d, room temperature.
[b] Yield of isolated **3**.
[c] Determined by chiral stationary phase HPLC analysis.

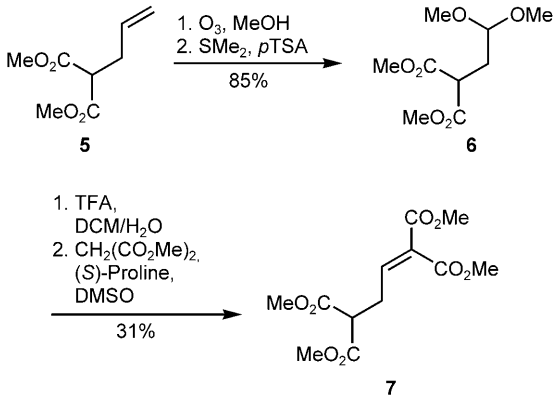


Scheme 1. Envisaged domino Mannich/aza-Michael reaction.

lent results in the previously published organocatalytic Mannich reactions between *N*-protected arylaldimines and malonates.[14b,e]

We found that the Takemoto catalyst **4a** allowed the formation of the Mannich products **3** in moderate to very good yields and good enantiomeric excesses, whereas the more bulky cinchonine-thiourea catalyst **4b** showed both lower enantioselectivity and activity (Table 1, entry 7). The *N*-Boc-protected benzaldimine and γ-malonate-substituted α,β-unsaturated ester **2** bearing small methyl ester groups turned out to be the best substrate combination for the desired Mannich reaction (Table 1, entries 1 and 4).

Even though it was not possible to isolate the envisaged pyrrolidine derivatives, the Mannich reaction could be performed efficiently. It was assumed that the Michael acceptor nature of **2** was not sufficiently electrophilic to enable a direct subsequent aza-Michael addition with the generated secondary amine. The attempt to cyclize products **3** with bases such as K_2CO_3, Cs_2CO_3, DBU, DBN either gave no product or resulted in complex mixtures.Therefore we decided to enhance the electrophilicity of the Michael system by introducing an additional ester function to the double bond. The required γ-malonate-substituted α,β-unsaturated methyl ester **7** was prepared using standard synthetic procedures starting from commercially available dimethyl allylmalonate **5** (Scheme 2). Ozonolysis and subsequent acetal protection furnished dimethyl 2,2-dimethoxyethylmalonate **6**. After treatment with TFA followed by a proline-catalyzed Knoevenagel condensation with dimethyl malonate the tetramethyl ester **7** was obtained.



Scheme 2. Synthesis of the γ-malonate-substituted α,β-unsaturated methyl ester **7.**

In the first test reactions between the *N*-protected benzaldimines **1** and the γ-malonate-substituted α,β-unsaturated ester **7** we were able to isolate the domino Mannich/aza-Michael product **8** exclusively (Table 2). To our delight, excellent diastereoselectivities along with moderate to good enantioselectivities and yields were achieved. The best result with regard to reaction time, yield and stereoselectivity was obtained using the Takemoto catalyst **4a** and the *N*-Boc-protected benzaldimine **1a** (Table 2, entry 1) in accordance with the previous results (Table 1). Catalyst **4b**, cinchonine **4c** and the tryptophan-derived thiourea **4d**[14g] were not as selective or active as catalyst **4a** (Table 2, entries 4–6).

Based on these first results we investigated the optimal catalyst loading. Increasing the catalyst loading to 20 mol% showed no further improvement, while lowering it to 5 mol% caused a slight drop in stereoselectivity and yield. The use of only 1 mol% showed the same enantiomeric excess of 82% with a significantly lower yield though.

Running the reaction without catalyst proved that a possible background reaction could be excluded (Table 3, entry 5). All following reactions were performed with a catalyst loading of 10 mol%. The screening of several solvents showed that the reaction tolerates other solvents besides dichloromethane, such as THF, toluene and chloroform, without any noticeable change in reaction time, yield or stereoselectivity (Table 4, entries 1–4). Interestingly, the addition of molecular sieves (3 Å) caused a significant drop of the enantiomeric excess to 53% (Table 4, entry 5). Therefore we set out to verify the proposed catalytic activity of the molecular sieves in the same reaction and obtained product **8a** in good yield as a racemate (Table 4, entry 6). Decreasing the temperature to 2 °C

Table 3. Optimization of the catalyst loading.[a]

Entry	**4a** [mol%]	Time [d]	Yield[b] [%]	*ee*[c] [%]
1	20	4	94	83
2	10	5	95	84
3	5	5	93	82
4	1	6	57	82
5[d]	–	10	–	–

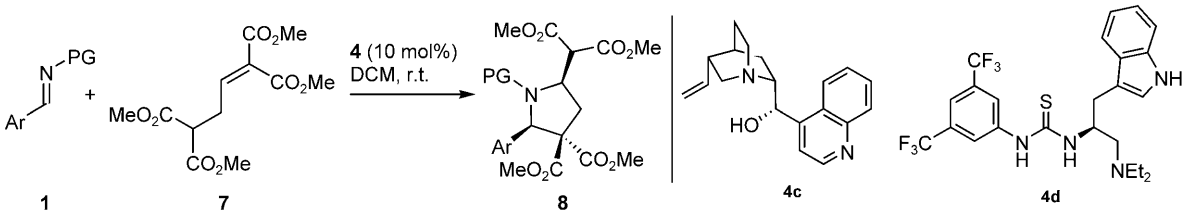
[a] The *de* of every product was found to be >95% as determined by ^{1}H NMR spectroscopy.
[b] Yield of isolated **8a**.
[c] Determined by chiral stationary phase HPLC analysis.
[d] Carried out without the addition of any catalyst.

Table 4. Influence of the solvent on the Mannich/aza-Michael reaction.[a]

Entry	Solvent	Time [d]	Yield [%][b]	*ee* [%][c]
1	THF	5	94	84
2	toluene	5	93	82
3	$CHCl_3$	6	89	83
4	DCM	5	95	84
5	DCM[d]	6	89	53
6	DCM[e]	4	85	–
7	DCM[f]	5	71	85
8	DCM[g]	13	38	91

[a] The *de* of every product was found to be >95% as determined by ^{1}H NMR spectroscopy.
[b] Yield of isolated **8a**.
[c] Determined by chiral stationary phase HPLC analysis.
[d] 3 Å molecular sieves were added.
[e] 3 Å molecular sieves were added without the presence of a catalyst.
[f] The reaction was performed at 2 °C.
[g] The reaction was performed at −26 °C.

Table 2. Screening of protecting groups and catalysts for the Mannich/aza-Michael reaction.[a]



1 7 8 4c 4d

Entry	Product	Catalyst	Imine	Time [d]	Yield[b] [%]	*ee*[c] [%]
1	**8a**	**4a**	**1a**	5	95	84
2	**8b**	**4a**	**1b**	7	52	70
3	**8c**	**4a**	**1c**	6	89	60
4	**8a**	**4b**	**1a**	6	95	78
5	**8a**	**4c**	**1a**	6	39	−69
6	**8a**	**4d**	**1a**	6	33	−79

[a] The *de* of every product was found to be >95% as determined by ^{1}H NMR spectroscopy.
[b] Yield of isolated **8**.
[c] Determined by chiral stationary phase HPLC analysis.

Table 5. Substrate scope of the organocatalytic domino Mannich/aza-Michael reaction.[a,b]

Entry	Product	Aryl Substituent	Time [d]	Yield [%][c,d]	*ee* [%][e,f]
1	**8a**	Phenyl	5	95 (76)	84 (99)
2	**8d**	2-Me-C_6H_4	6	91 (77)	75 (99)
3	**8e**	4-F-C_6H_4	5	91 (75)	83 (>99)
4	**8f**	4-MeO-C_6H_4	5	99 (75)	78 (>99)
5	**8g**	1-naphthyl	11	85 (77)	83 (97)
6	**8h**	2-furyl	3	95	94
7	**8i**	2-thiophenyl	4	76	83

[a] The *de* of every product was found to be >95% as determined by ^{1}H NMR spectroscopy.
[b] *Reaction conditions:* **1** (0.7 mmol), **7** (0.7 mmol), absolute DCM (3 mL), **4a** (10 mol%), room temperature.
[c] Yield of isolated **8**.
[d] The values in brackets are the yields after removal of the racemate.
[e] Determined by chiral stationary phase HPLC analysis.
[f] The values in brackets refer to the enantiomeric excesses after removal of crystalline racemate.

led to a slightly higher *ee* but a notably lower yield (Table 4, entry 7). The highest *ee* of 91% was obtained at −26 °C albeit with a significantly lower yield (Table 4, entry 8).

Next we investigated the substrate scope using different *N*-Boc-protected aryl aldimines **1a**, **d–i**[18] under the optimized conditions. The results are presented in Table 5. Thus, we were able to synthesize a variety of polysubstituted pyrrolidines in good to excellent yields (76–99%), enantiomeric excesses (75–94%) and excellent diastereoselectivities (*de* >95%). In the case of product **8g** a longer reaction time was necessary, likely due to the bulky naphthyl substituent (entry 5). A faster reaction was observed using five-membered heterocycles, with product **8h** formed after 3 days in excellent yield and stereoselectivity. In several cases the virtually stereoisomerically pure pyrrolidines **8** (*de* >95%, *ee* = 97 to >99%) were obtained by crystallization of the racemates from *n*-heptane and dichloromethane and removal of the crystals.

The relative configuration of the product pyrrolidines could be determined to be 2,5-*cis* by X-ray structure analyses in the case of *rac*-**8a** and **8d**. The latter allowed us to assign the absolute configuration as (2*R*,5*R*) (Figure 1).[20]

In conclusion, we have developed an efficient domino Mannich/aza-Michael reaction between carbamate-protected aryl aldimines and γ-malonate-substituted α,β-unsaturated methyl esters promoted by a bifunctional thiourea catalyst. The new method furnishes 2,5-*cis*-configured polysubstituted pyrrolidines in good to excellent yields, enantioselectivities and excellent diastereoselectivities.

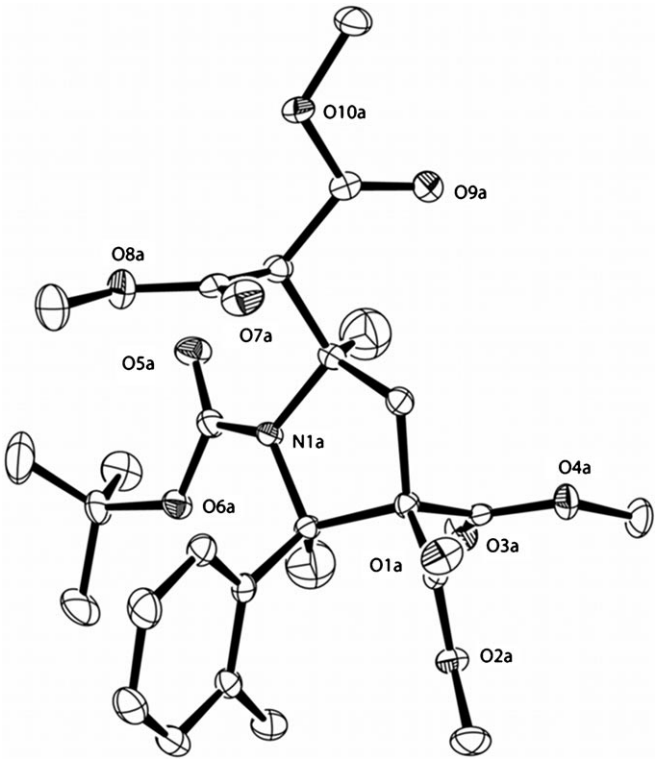


Figure 1. X-ray crystal structure of (*R*,*R*)-**8d**. The Flack parameter[21] for the data collected at 100 K is 0.01(15).

The virtually pure single stereoisomers are available by removal of the crystalline racemates.

Experimental Section

General Procedure for the Mannich Reaction

In a dry, argon-flushed one-necked flask, the carbamate-protected benzaldimine **1** (1.6 mmol), the γ-malonate-substituted α,β-unsaturated methyl ester **2** (0.8 mmol) and the thiourea catalyst **4** (10 mol%) were dissolved in absolute dichloromethane (4 mL) and stirred at room temperature for 5 days. After removal of the solvent under vacuum the mixture was dissolved in toluene and purified *via* flash chromatography over silica gel (diethyl ether/*n*-pentane = 1:3 to 1:1). The Mannich products **3** were obtained as colourless oils. Racemic samples were prepared using a 1:1 mixture of cinchonine:cinchonidine as catalysts applying the same reaction conditions.

General Procedure for the Domino Mannich/Aza-Michael Reaction

In a dry, argon-flushed one-necked flask, the carbamate-protected aryl aldimine **1** (0.7 mmol), the γ-malonate-substituted α,β-unsaturated methyl ester **7** (0.7 mmol) and the catalyst **4** (10 mol%) were dissolved in absolute dichloromethane (3 mL) and stirred at room temperature for 3–11 days. After removal of the solvent under vacuum the mixture was

dissolved in toluene and purified via flash chromatography over silica gel (diethyl ether/*n*-pentane = 1:3 to 1:2). The pyrrolidine derivatives **8** were obtained as colourless oils. Racemic samples were prepared using tetrabutylammonium fluoride (1 M in THF) as catalyst applying the same reaction conditions.

Crystallization Procedure

The domino Mannich/aza-Michael products were dissolved in *n*-heptane/dichloromethane at 60 °C and cooled to 0 °C leading to the crystallization of the racemate.

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References

[1] For recent reviews on organocatalysis, see: a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2004**; b) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; c) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; d) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600; e) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; f) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 493–529; g) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 757–797; h) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857–7870; i) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; j) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; k) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614; l) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058–11076; for special issues on organocatalysis, see: m) K. N. Houk, B. List, (guest editors), *Acc. Chem. Res.* **2004**, 37, 487; n) B. List, (guest editor), *Adv. Synth. Catal.* **2004**, *346*, 1021; o) C. Bolm, (guest editor), *Adv. Synth. Catal.* **2004**, *346*, 1022; p) B. List, (guest editor), *Chem. Rev.* **2007**, *107*, 5413–5415.

[2] For reviews on organocatalytic domino reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; b) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; c) C. Grondal, M. Jeanty, D. Enders, *Nature Chemistry* **2010**, *2*, 167–178.

[3] a) H. Kunz, W. Pfrengle, *Angew. Chem.* **1989**, *101*, 1041–1042; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1067–1068; b) H. Waldmann, M. Braun, *J. Org. Chem.* **1992**, *57*, 4444–4451; c) M. Weymann, W. Pfrengle, D. Schollmeyer, H. Kunz, *Synthesis* **1997**, 1151–1160; d) S. Kirschbaum, H. Waldmann, *Tetrahedron Lett.* **1997**, *38*, 2829–2832; e) Y. Wang, S. R. Wilson, *Tetrahedron Lett.* **1997**, *38*, 4021–4024; f) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2003**, *5*, 4301–4304; g) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1533–1535; h) M. S. Khaliel, M. V. Nandakumar, H. Krautscheid, C. Schneider, *Synlett* **2008**, 2705–2707.

[4] a) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955–4958; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877–4880; b) M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996–7999; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832–7835.

[5] For selected examples, see: a) P. L. Feldman, M. F. Brackeen, D. J. Cowan, B. E. Marron, F. J. Schoenen, J. A. Stafford, E. M. Suh, P. L. Domanico, D. Rose, M. A. Leesnitzer, E. S. Brawley, A. B. Strickland, M. W. Verghese, K. M. Connolly, R. Batemanfite, L. S. Noel, L. Sekut, S. A. Stimpson, *J. Med. Chem.* **1995**, *38*, 1505–1510; b) E. A. A. Wallen, J. A. M. Christiaans, S. M. Saario, M. M. Forsberg, J. I. Venalainen, H. M. Paso, P. T. Mannisto, J. Gynther, *Bioorg. Med. Chem.* **2002**, *10*, 2199–2206.

[6] For selected examples, see: a) N. K. Lin, G. M. Carrera, D. J. Anderson, *J. Med. Chem.* **1994**, *37*, 3542–3553; b) R. L. Elliott, K. B. Ryther, D. J. Anderson, J. L. Raszkiewicz, J. E. Campbell, J. P. Sullivan, D. S. Garvey, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 991–996; c) K. H. Kim, N. H. Lin, D. J. Anderson, *Bioorg. Med. Chem.* **1996**, *4*, 2211–2217; d) R. L. Elliott, K. B. Ryther, D. J. Anderson, M. Piattoni-Kaplan, T. A. Kuntzweiler, D. Donnelly-Roberts, S. P. Arneric, M. W. Holladay, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2703–2708; e) C. Sonesson, H. Wikstrom, M. W. Smith, K. Svensson, A. Carlsson, N. Waters, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 241–246; f) K. H. Ahn, S. J. Lee, C. H. Lee, C. Y. Hong, T. K. Park, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1379–1384; g) M. Gerasimov, D. Marona-Lewicka, D. M. Kurrasch-Orbaugh, A. M. Qandil, D. E. Nichols, *J. Med. Chem.* **1999**, *42*, 4257–4263; h) A. P. Guzikowski, A. P. Tamiz, M. Acosta-Burruel, S. Hong-Bae, S. X. Cai, J. E. Hawkinson, J. F. W. Keana, S. R. Kesten, C. T. Shipp, M. Tran, E. R. Whittemore, R. M. Woodward, J. L. Wright, Z. L. Zhou, *J. Med. Chem.* **2000**, *43*, 984–994.

[7] For selected examples, see: a) N. Kolocouris, A. Kolocouris, G. B. Foscolos, G. Fytas, J. Neyts, E. Padalko, J. Balzarini, R. Snoeck, G. Andrei, E. De Clercq, *J. Med. Chem.* **1996**, *39*, 3307–3318; b) C. L. Lynch, J. J. Hale, R. J. Budhu, A. L. Gentry, S. G. Mills, K. T. Chapman, M. MacCoss, L. Malkowitz, M. S. Springer, S. L. Gould, J. A. DeMartino, S. J. Siciliano, M. A. Cascieri, A. Carella, G. Carver, K. Holmes, W. A. Schleif, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. Miller, E. A. Emini, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3001–3004.

[8] For selected examples, see: a) J. F. Cavalla, R. Jones, M. Welford, J. Wax, C. V. Vinder, *J. Med. Chem.* **1964**, *7*, 412–415; b) R. E. Bowman, H. O. J. Collier, P. J. Hattersley, I. M. Lockhart, D. J. Peters, C. Schneider, N. E. Webb, M. Wright, *J. Med. Chem.* **1973**, *16*, 1177–1180.

[9] For reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748; b) P. I. Dalko, L. Moisan, *Angew.*

Chem. **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) B. List, *Synlett* **2001**, 1675–1686; d) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; e) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; f) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591.

[10] M. Padoa, *Gazz. Chim. Ital.* **1906**, *36*, 317.

[11] a) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558–560; b) K. Löffler, C. Freytag, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427–3431.

[12] For reviews, see: a) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428–6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272–6276; b) S. Husinec, V. Savic, *Tetrahedron: Asymmetry* **2005**, *16*, 2047–2061; c) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235–3285. For selected organocatalytic examples, see: e) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873–9877; f) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653; g) J. Xie, K. Yoshida, K. Takasu, Y. Takemoto, *Tetrahedron Lett.* **2008**, *49*, 6910–6913; h) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691–694.

[13] For recent examples, see: a) D. Enders, C. Thiebes, *Pure Appl. Chem.* **2001**, *73*, 573–578; b) M. M. Martínez, D. Hoppe, *Eur. J. Org. Chem.* **2005**, 1427–1443; c) F. A. Davis, M. Song, A. Augustine, *J. Org. Chem.* **2006**, *71*, 2779–2786; d) S. Saito, T. Tsubogo, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5364–5365; e) C. Taillier, M. Lautens, *Org. Lett.* **2007**, *9*, 591–593; f) S. Jackson, A. Karadeolian, A. Driega, M. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201; g) M. E. Scott, M. Lautens, *J. Org. Chem.* **2008**, *73*, 8154–8162; h) S. G. Davies, R. L. Nicholson, P. D. Price, P. M. Roberts, A. J. Russell, E. D. Savory, A. D. Smith, J. E. Thomson, *Tetrahedron: Asymmetry* **2009**, *20*, 758–772; i) C. Enkisch, C. Schneider, *Eur. J. Org. Chem.* **2009**, 5549–5564.

[14] a) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; b) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1991–1993; c) F. Fini, L. Bernardi, R. P. Herrera, D. Pettersen, A. Ricci, V. Sgarzani, *Adv. Synth. Catal.* **2006**, *348*, 2043–2046; d) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338–8351; e) Y. Yamaoka, H. Miyabe, Y. Yasui, Y. Takemoto, *Synthesis* **2007**, *22*, 2571–2575; f) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171; g) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem.* **2009**, *121*, 7740–7743; *Angew. Chem. Int. Ed.* **2009**, *48*, 7604–7607; h) K. Takada, S. Tanaka, K. Nagasawa, *Synlett* **2009**, 1643–1646; i) T. Poisson, T. Tsubogo, Y. Yamashita, S. Kobayashi, *J. Org. Chem.* **2010**, *75*, 963–965; j) for a recent review on the *N*-acylimine chemistry, see: M. Petrini, E. Torregiani, *Synthesis* **2007**, 159–186.

[15] a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; b) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471–473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467–469; c) D. Enders, A. A. Narine, T. R. Benninghaus, G. Raabe, *Synlett* **2007**, 1667–1670; d) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267–279; e) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649–7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542; f) D. Enders, C. Wang, J. W. Bats, *Synlett* **2009**, 1777–1780; g) D. Enders, C. Wang, G. Raabe, *Synthesis* **2009**, 4119–4124; h) D. Enders, M. Jeanty, J. W. Bats, *Synlett* **2009**, 3175–3178; i) D. Enders, R. Krüll, W. Bettray, *Synthesis* **2010**, 567–572; j) D. Enders, C. Wang, M. Mukanova, A. Greb, *Chem. Commun.* **2010**, *46*, 2447–2449; k) D. Enders, B. Schmid, N. Erdmann, G. Raabe, *Synthesis* **2010**, 2271–2277.

[16] a) R. A. Bunce, E. J. Wamsley, J. D. Pierce, A. J. Shellhammer Jr, R. E. Drumright, *J. Org. Chem.* **1987**, *52*, 464–466; b) L. Zu, H. Li, H. Xie, J. Wang, W. Jiang, Y. Tang, W. Wang, *Angew. Chem.* **2007**, *119*, 3806–3808; *Angew. Chem. Int. Ed.* **2007**, *46*, 3732–3734.

[17] For the synthesis of malonate-α,β-unsaturated esters **2a–c** we used a modified procedure from: a) A. Padwa, S. H. Watterson, Z. Ni, *Org. Synth.* **1997**, *74*, 147. For the synthesis of malonate-α,β-unsaturated ester **2d** we used a modified procedure from: b) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* **1994**, *116*, 3167–3168. Experimental details are provided in the Supporting Information.

[18] For the synthesis of carbamate-protected arylaldimines, see: a) A. M. Kanazawa, J.-N. Denis, A. Greene, *J. Org. Chem.* **1994**, *59*, 1238–1240; b) Z. Xu, X. Lu, *J. Org. Chem.* **1998**, *63*, 5031–5041; c) A. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; d) A. L. Tillmann, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191–1193. Unfortunately, aliphatic alidimines did not give satisfactory results with our protocol.

[19] For the synthesis of thiourea catalysts **4**, see: (**4a**) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (**4b**) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483.

[20] Crystallographic data for *rac*-**8a** and (*R*,*R*)-**8d** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 789982 (*rac*-**8a**) and CCDC 790099 (**8d**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

[21] H. D. Flack, *Acta Crystallogr. A:* **1983**, *39*, 876–881.

