Organocatalysis

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Organocatalytic Conjugate Addition of Malonates to α,β-Unsaturated Aldehydes: Asymmetric Formal Synthesis of (−)-Paroxetine, Chiral Lactams, and Lactones**

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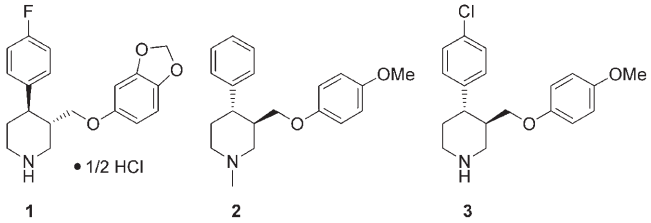
Chiral lactones and lactams are endowed with a large spectrum of biological properties[1] including very important pharmaceutical activities.[2] The chiral piperidines (−)-paroxetine hydrochloride **1**, marketed as paxil/seroxat, and (+)-femoxetine **2** are selective serotonin reuptake inhibitors and are used in the treatment of depression, obsessive-compulsive disorder, and panic (Figure 1).[3] The nonpeptide



1 2 3

Figure 1. Antidepressants (−)-paroxetine **1**, (+)-femoxetine **2**, and peptidomimetic inhibitor Roche-1 **3**.

peptidomimetic type III inhibitor of renin, the piperidine Roche-1 **3**, was found to stabilize an enzyme conformation not previously observed for this enzyme.[4] All these compounds consist of a phenyl piperidine core structure with two *trans*-related substituents at C3 and C4. However, (−)-paroxetine **1** possesses the opposite enantiomeric configuration relative to (+)-femoxetine **2** and Roche-1 **3**.

The synthesis of the antidepressants (−)-paroxetine **1** and (+)-femoxetine **2** is focused on enzymatic asymmetric desymmetrization,[3a,5] chiral auxiliary-assisted,[6] or asymmetric

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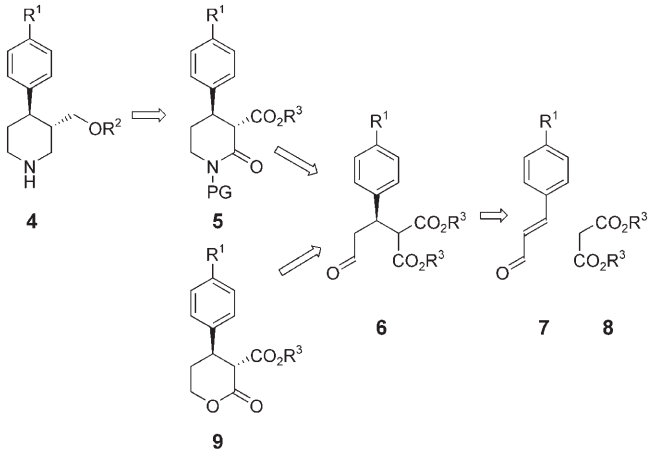
deprotonation[7] reactions. The total synthesis of these chiral compounds consists of approximately 12–14 steps. Herein we present a novel approach, based on organocatalysis employing chiral proline-derived catalysts, for a new, short, and simple methodology for the synthesis of chiral lactams and lactones of which the former can be converted to the phenyl piperidine serotonin reuptake inhibitors.

The retrosynthetic analysis of (−)-paroxetine **1** and (+)-femoxetine **2** leads to the phenyl piperidinone core structure **5**, which can be synthesized by a reductive amination sequence, starting from the optically active aldehyde **6** (Scheme 1). Moreover, compound **6** is also a precursor for



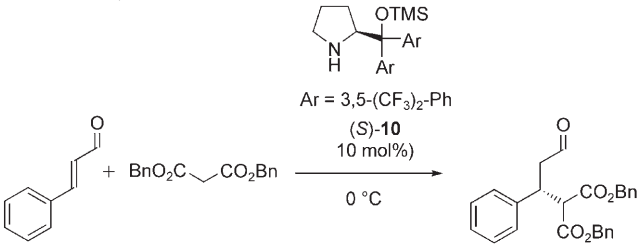
Scheme 1. Retrosynthetic analysis.

the formation of chiral lactones **9**, which are accessible through a reductive cyclization sequence. The formation of optically active **6** is derived from a conjugate addition reaction of malonates **8** to α,β-unsaturated aldehydes **7**. To date, no asymmetric organocatalytic reaction is reported for the conjugate addition of malonates to α,β-unsaturated aldehydes.[8,9]

The field of organocatalysis is a rapidly progressing area[10] and a large number of new asymmetric reactions have been developed. For the addition of nucleophiles to α,β-unsaturated compounds, a variety of different nucleophiles have been added to, for example, α,β-unsaturated aldehydes.[11] However, according to our knowledge, nucleophiles such as malonates that use iminium ion activation have only been added enantioselectively to α,β-unsaturated ketones.[12] Herein we will present the development of the first organocatalytic enantioselective addition of malonates to aromatic α,β-unsaturated aldehydes[13] with the purpose of creating a simple approach to optically active lactams and lactones, and also to show the potential of this new reaction for the formation of very important pharmaceutical compounds.

The organocatalytic enantioselective addition of malonates to aromatic α,β-unsaturated aldehydes was initially developed by reaction of cinnamaldehyde **7a** with dibenzyl malonate **8a** in different solvents at 0 °C by using the L-proline derivative (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine (*S*)-**10**[11c,d,m,14] as the catalyst (Table 1).

Table 1: Solvent screening for the addition of dibenzyl malonate **8a** to cinnamaldehyde **7a**.



7a **8a** **6a**

Entry	Solvent	Conversion [%][b]	Yield [%][c]	*ee* [%][d]
1	CH_2Cl_2	0	–	-
2	Et_2O	0	–	-
3	CH_3CN	45	–	–
4	DMSO	46	28[e]	81
5	*n*-hexane	26	–	–
6	H_2O	12	–	–
7	$(CH_3)_2CO$	<5	–	–
8	MeOH	70	46[e]	92
9	EtOH	100	80	91
10	*n*PrOH	48	24[e]	86
11	*i*PrOH	<5	–	–

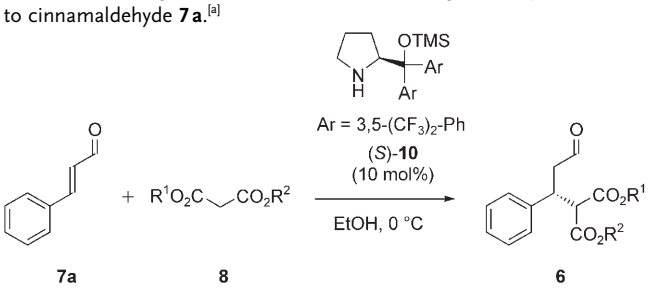
[a] All reactions were performed on a 0.25 mmol scale. [b] The conversion of **7a** into **6a** was estimated by ^{1}H NMR spectroscopy after 4 days at 0 °C. [c] Yield of the isolated product. [d] Determined by chiral HPLC after oxidation to the corresponding methyl ester. [e] Yield after oxidation.

The screening of the reaction conditions in Table 1 shows that the reaction is very solvent dependent. Primary alcohols are the optimal solvent and the best results are obtained in MeOH and EtOH; in the latter solvent, full conversion is found after 4 days giving an 80 % yield of the addition product **6a** with an enantiomeric excess of 91 % *ee* (Table 1, entry 9). A slightly higher enantioselectivity (92 % *ee*) is obtained in MeOH (Table 1, entry 8); however, the conversion is much lower compared to EtOH. In *n*PrOH, a high enantioselectivity is also found (86 % *ee*) (Table 1, entry 10), but in this solvent a low conversion and yield have also been observed. It is notable that in all the other solvents, with the exception of dimethylsulfoxide (DMSO; Table 1, entry 4), no or low conversion is observed.

The reaction proceeds especially well for malonate derivatives with benzyl and methyl esters, **8a**,**b** (Table 2, entry 1, 2). For the ethyl ester **8c**, a lower yield is obtained (Table 2, entry 3), whereas no conversion is observed for the isopropyl ester **8d** (Table 2, entry 4). For the unsymmetrical malonate **8e** in Table 2, entry 5, a nondiastereoselective reaction takes place. The scope of the organocatalytic enantioselective addition of the dibenzyl **8a** and dimethyl malonates **8b** to a number of different aromatic α,β-unsaturated aldehydes **7a**–**k** catalyzed by (*S*)-**10** and (*R*)-**10** is presented in Table 3.

The results in Table 3 show the generality of this conjugate addition reaction with regard to aromatic α,β-unsaturated aldehydes. Very good to excellent enantioselectivities were obtained for all the addition products **6** ranging from 86–95 % *ee*. The addition of malonates to the aromatic α,β-unsaturated

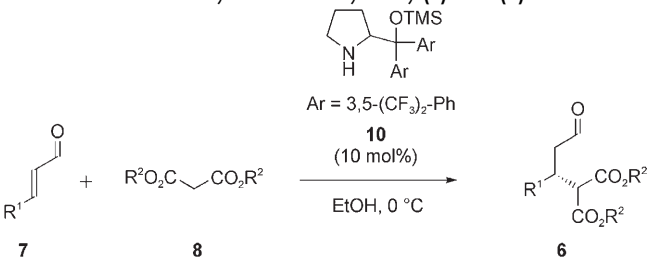
Table 2: Screening of various malonates for the organocatalytic addition to cinnamaldehyde **7a**.[a]



Entry	R^1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Bn	Bn—**8a**	**6a**—80	–	91
2	Me	Me—**8b**	**6b**—85	–	94
3	Et	Et—**8c**	**6c**—42	–	89
4	*i*Pr	*i*Pr—**8d**	**6d**—0	–	–
5	Bn	Me—**8e**	**6e**—nd[e]	1:1	nd

[a] All reactions were performed on a 0.25 mmol scale. [b] Yield of the isolated product. [c] Estimated by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC after oxidation to the corresponding methyl ester. [e] No full conversion after 96 h.

Table 3: Reaction of dibenzyl **8a** and dimethyl malonates **8b** with different aromatic aldehydes **7a-k** catalyzed by ***(S)***- and ***(R)*-10**.[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	Ph—**7a**	Bn—**8a**	**6a**—80	91
2	Ph—**7a**	Bn—**8a**	**6a**—75	(−)90[d]
3	Ph—**7a**	Me—**8b**	**6b**—85	94
4	*p*-BrPh—**7b**	Bn—**8a**	**6f**—84	90
5	*p*-BrPh—**7b**	Me—**8b**	**6g**—31	95
6	*o*-BrPh—**7c**	Bn—**8a**	**6h**—34	88
7	*p*-MeOPh—**7d**	Bn—**8a**	**6i**—93	92
8	*p*-MeOPh—**7d**	Me—**8b**	**6j**—73	90
9	*p*-ClPh—**7e**	Bn—**8a**	**6k**—85	86
10	*p*-PhPh—**7f**	Bn—**8a**	**6l**—76	89
11	*p*-FPh—**7g**	Bn—**8a**	**6m**—72	86
12	*p*-CHOPh—**7h**	Bn—**8a**	**6n**—95	86
13	*p*-CH_3Ph—**7i**	Bn—**8a**	**6o**—95	88
14	2-Np—**7j**	Bn—**8a**	**6p**—69	88
15	2-Thiophene—**7k**	Bn—**8a**	**6q**—83	92

[a] All reactions were performed on a 0.25 mmol scale. [b] Yield of the isolated product. [c] Determined by chiral HPLC after oxidation to the corresponding methyl ester. [d] (*R*)-2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine (*R*)-**10** used as the catalyst.

aldehydes tolerates many functional groups in the *p*- or *o*-position of the aromatic ring, however, owing to steric interaction of the *o*-substituent (**7c**) to the malonate during the addition, a lower yield of **6h** is obtained (Table 3, entry 6). It is important to notice that aside from halogens, ethers, phenyl, and alkyl substituents, heteroaromatics and additional aldehydes are tolerated well in this reaction giving the addition products in high yields up to 95% and enantioselectivities up to 92% *ee* (Table 3, entry 12, 15). Use of the catalyst (*R*)-**10** for the addition of dibenzyl malonate **8a** to cinnamaldeyde **7a** afforded the enantiomeric (*S*)-configurated product **6a** in 75% yield and with an enantiomeric excess of 90% *ee* (Table 3).

The absolute configuration of the addition products **6** was confirmed by a single-crystal X-ray analysis of the methyl ester **11k** obtained by oxidation of **6k** (Figure 2).[15] The

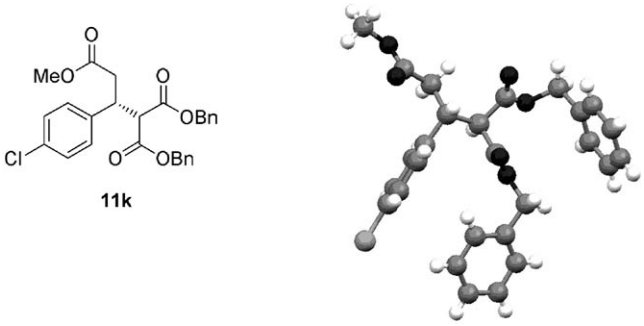
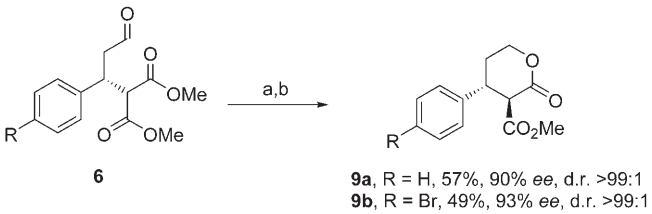


Figure 2. X-ray crystal structure of (*R*)-2-benzyloxycarbonyl-3-(4-chlorophenyl)petanedioic acid 5-benzyl ester 1-methyl ester, **11k**.

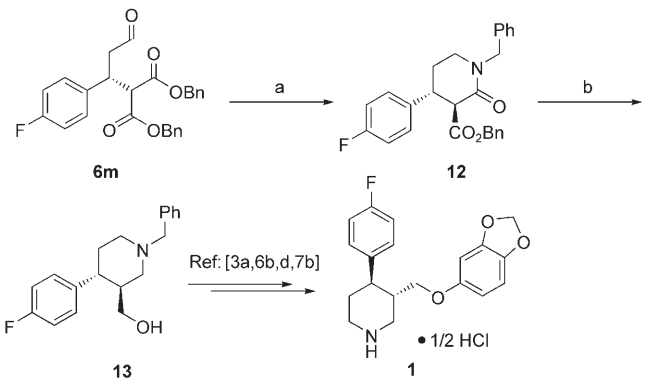
optically active compounds **6**, which are formed by the organocatalytic addition of dimethyl malonate **8b** to α,β-unsaturated aldehydes **7**, are valuable precursors for the formation of chiral lactones **9** (Scheme 1). In a reduction–cyclization procedure, the aldehyde function is reduced with $NaCNBH_3$ to the alcohol and then, in the presence of silica, a stereoselective cyclization reaction to the desired lactone takes place (Scheme 2).[16] We obtained the diastereomeri-



Scheme 2. Synthesis of chiral lactones **9**. Reagents: a) $NaCNBH_3$, AcOH, THF; b) SiO_2, CH_2Cl_2.

cally pure *trans*-lactones **9** in good yields and excellent enantioselectivities of up to 93% *ee*. However, we observed a minor loss of chirality of up to 2% *ee* during these reactions. The *trans* relationship of the substituents at C2 and C3 was confirmed by the ^3J coupling constants of the protons at C2 and C3 in the ^{1}H NMR spectra, showing a value of 10.5 Hz (**9a**) and 10.9 Hz (**9b**), respectively.

Compound **6** is also the building block for chiral lactam **12**, which can be easily synthesized by a reductive amination–cyclization sequence (Scheme 3).[17] We applied a tandem procedure of three reaction steps: imine formation, reduction, and lactamization, yielding the lactam **12** in 70% overall yield with an excellent diastereomeric ratio of 13:1 referring to the



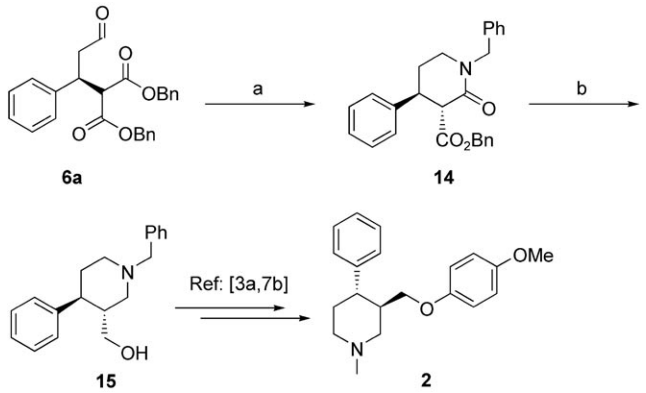
6m 12 13 1

Scheme 3. Synthesis of (−)-paroxetine **1**. Reagents: a) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 70%; b) $LiAlH_4$, THF, Δ, 85%.

trans-lactam. The *trans* position of the substituents at C3 and C4 was confirmed by ^1H NMR spectroscopy. Lactam **12** has previously been transformed to (−)-paroxetine hydrochloride **1** in four steps (Scheme 3):[3a,6b,d,7b] Reduction of **12** with $LiAlH_4$ to give **13** in 85% yield as one diastereomer, etherification with sesamol, and hydrogenolysis of the benzyl group furnished (−)-paroxetine hydrochloride **1**. The 2-step asymmetric synthesis of **12** leads to (−)-paroxetine hydrochloride **1** in six steps overall.

Changing the catalyst for the malonate addition from (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine, (*S*)-**10**, to (*R*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine, (*R*)-**10**, yields the Michael adduct **6a** and gives us the opportunity to synthesize the precursor for the chiral piperidine (+)-femoxetine **2** (Scheme 4) and (+)-paroxetine hydrochloride **1**. For the synthesis of (+)-femoxetine **2**, **6a** was transformed in a one-pot procedure to the *trans*-lactam **14** in 68% overall yield and with a diastereomeric ratio of 12:1. It has been reported that (+)-femoxetine **2** can be formed by subsequent reduction with $LiAlH_4$ in THF to give the piperidine **15** in 75% yield and as one diastereomers that can be converted to the desired product (+)-femoxetine **2**.[3a,7a]

In summary we reported the first organocatalytic enantioselective conjugate addition of malonates to aromatic α,β-unsaturated aldehydes resulting in the addition products in good yields and very good to excellent enantioselectivities. Furthermore, we developed new procedures for the formation of chiral lactones and lactams. These reactions proceed in a highly stereoselective manner leading to a simple synthesis of (−)-paroxetine in six steps overall and (+)-femoxetine in seven steps overall.



6a 14 15 2

Scheme 4. Synthesis of (+)-femoxetine **2**. Reagents: a) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 68%; b) $LiAlH_4$, THF, Δ, 75%.

Experimental Section

General procedure for the organocatalytic addition of malonates to α,β-unsaturated aldehydes: **10** (15.0 mg, 0.025 mmol, 0.1 equiv) was added to a stirred ice-cooled (0 °C) solution of the α,β-unsaturated aldehyde **6** (0.50 mmol, 2.0 equiv) in solvent (1.0 mL) followed by the addition of malonate (0.25 mmol, 1.0 equiv). The reaction mixture was stirred for 96 h at 0 °C and then filtered through 1–2 cm bed of silica that was then washed through with Et_2O and CH_2Cl_2. The solvents were evaporated under vacuum. The crude product was subjected to flash chromatography on silica gel (Et_2O/*n*-pentane/CH_2Cl_2 1:10:0.1) to yield the desired addition product.

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[1] For an example, see: a) S. E. De Laszlo, B. L. Bush, J. J. Doyle, W. J. Greenlee, D. G. Hangauer, T. A. Halgren, R. J. Lynch, T. W. Schorn, P. K. S. Siegl, *J. Med. Chem.* **1992**, *35*, 833–846; b) H. Ebel, S. Knör, W. Steglich, *Tetrahedron* **2003**, *59*, 123–129; c) Z. H. Peng, K. A. Woerpel, *Org. Lett.* **2001**, *3*, 675–678; d) J. D. Connolly, R. A. Hill, *Dictionary of Terpenoids*, *Vol. 1*, Chapman and Hall, London, **1991**, pp. 476–541.

[2] For an example, see: a) P. Wei, G. W. Kaatz, R. J. Kerns, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3093–3097; b) P. E. Reed, J. A. Katzenellenbogen, *J. Med. Chem.* **1991**, *34*, 1162–1176; c) K. Bush, M. Macielag, M. Weidner-Wells, *Curr. Opin. Microbiol.* **2004**, *7*, 466–476; d) M. I. Konaklieva, B. J. Plotkin, *Med. Chem.* **2004**, *4*, 721–729; M. Kidwai, P. Sapra, K. R. Bhuskan, *Curr. Med. Chem.* **1999**, *6*, 195–215; e) D.-R. Hwang, Y.-S. Wu, C.-W. Chang, T.-W. Lien, W.-C. Chen, U.-K. Tan, J. T. A. Hsu, H.-P. Hsieh, *Bioorg. Med. Chem.* **2006**, *14*, 83–91.

[3] For an example, see: a) M. S. Yu, I. Lantos, Z.-Q. Peng, J. Yu, T. Cacchio, *Tetrahedron Lett.* **2000**, *41*, 5647–5651; b) G. M. Shutske, *Expert Opin. Ther. Pat.* **1994**, *4*, 335; c) J. A. Christensen, R. F. Squires, US Patent 3912743, **1975**; d) J. A. Christensen, R. F. Squires, US Patent 4007196, **1977**; e) E. A. Frank, R. T. Martin, US Patent 4902801, **1990**; f) I. Borza, L. Czibula, L. Dobay, K. Harsanyi, I. Hegedues, J. Kreidl, A. Nemes, E. Werkne Papp, I. Deutschne Juhasz, J. Nagyne Bagdy, WO Patent 98/01424, **1998**; g) C. M. Zepp, Y. Gao, D. L. Heefner, US Patent 5258517, **1993**; h) K. S. K. Murthy, A. W. Rey, US Patent 5962689, **1999**; i) B. M. Adger, M. E. Fox, G. A. Potter, US Patent 6066737, **2000**.

[4] For an example, see: M. G. Bursavich, D. H. Rich, *J. Med. Chem.* **2002**, *45*, 541–558.

[5] For an example, see: a) C. M. Zepp, Y. Gao, D. L. Heefner, *Chem. Abstr.* **1993**, *120*, 217289; b) G. de Gonzalo, R. Brieva, V. M. Sánchez, M. Bayod, V. Gotor, *J. Org. Chem.* **2001**, *66*, 8947–8953; c) J. M. Palomo, G. Fernández-Lorente, C. Mateo, R. Fernández-Lafuente, J. M. Guisan, *Tetrahedron: Asymmetry* **2002**, *13*, 2375–2381.

[6] See *e.g.*: a) M. Amat, J. Hidalgo, J. Bosch, *Tetrahedron: Asymmetry* **1996**, *7*, 1591 – 1594; b) M. Amat, J. Hidalgo, J. Bosch, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem.* **2000**, *65*, 3074 – 3084; c) J. Cossy, O. Mirguet, D. G. Pardo, J.-R. Desmurs, *Eur. J. Org. Chem.* **2002**, *42*, 3543 – 3551; d) L. Czibula, A. Nemes, F. Sebök, C. Szántay, Jr., M. Mák, *Eur. J. Org. Chem.* **2004**, *44*, 3336 – 3339.

[7] a) T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtius, P. Beak, *J. Am. Chem. Soc.* **2002**, *124*, 11689 – 11698; b) D. A. Greenhalgh, N. S. Simpkins, *Synlett* **2002**, *12*, 2074 – 2076; c) L. T. Liu, P.-C. Hong, H.-L. Huang, S.-F. Chen, C.-L. J. Wang, Y.-S. Wen, *Tetrahedron: Asymmetry* **2001**, *12*, 419 – 426; d) T. A. Johnson, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 1004 – 1005.

[8] For the addition of malonates to α,β-unsaturated aldehydes catalyzed by lewis acids, see, for example: a) S. Narasimhan, S. Velmathi, *Molecules* **2003**, *8*, 256 – 262; b) S. Velmathi, S. Swarnalakshmi, S. Narasimhan, *Tetrahedron: Asymmetry* **2003**, *14*, 113 – 117; c) K. A. Kochetkov, S. R. Harutyunyan, N. A. Kuz"mina, T. F. Savel"eva, V. I. Maleev, A. S. Peregudov, S. Vyskočil, A. S. Sagiyan, *Russ. Chem. Bull.* **2001**, *50*, 1620 – 1624.

[9] For a nonstereoselective organocatalytic addition of malonates to α,β-unsaturated aldehydes, see: M. Yamaguchi, N. Yokota, T. Minami, *J. Chem. Soc. Chem. Commun.* **1991**, 1088 – 1089.

[10] For reviews on organocatalysis, see, for example: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248 – 5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138 – 5175; b) B. List, *Tetrahedron* **2002**, *58*, 5573 – 5590; c) A. Berkessel, H. Gröger, *Metal-Free Organic Catalysts in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2004**; d) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; e) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035 – 1050; f) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580 – 591; g) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719 – 724; h) B. List, *Chem. Commun.* **2006**, 819 – 824.

[11] For recent examples of organocatalyzed additions to α,β-unsaturated aldehydes, see: a) R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240 – 3241; b) H. Sunden, I. Ibrahem, A. Cordova, *Tetrahedron Lett.* **2005**, *47*, 99 – 103; c) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710 – 15711; d) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964 – 6965; e) W. Wang, H. Li, J. Wang, *Org. Lett.* **2005**, *7*, 1637 – 1639; f) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 6829 – 6832; *Angew. Chem. Int. Ed.* **2004**, *43*, 6660 – 6662; g) S. G. Ouellet, J. B. Tuttle, D. W. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32 – 33; h) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051 – 15053; i) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036 – 15037; j) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894 – 7895; k) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482 – 5487; l) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192 – 1194; m) M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, published online. For the synthesis of the α,β-unsaturated aldehydes, see: G. Battistuzzi, S. Cacchi, G. Fabrizi, *Org. Lett.* **2003**, *5*, 777 – 780.

[12] a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *42*, 685 – 689; *Angew. Chem. Int. Ed.* **2003**, *42*, 661 – 665; b) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66 – 68; c) A. Kawara, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 8805 – 8808; d) M. Yamaguchi, T. Shiraish, M. Hirama, *Angew. Chem.* **1993**, *105*, 1243 – 1245; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176 – 1178; e) M. Yamaguchi, T. Shiraisi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520 – 3530.

[13] Notably, aliphatic α,β-unsaturated aldehydes did not react with only malonates, but reacted with both the malonates and EtOH (solvent) under the present reaction conditions.

[14] For the use of this catalyst in organocatalysis, see, for example: a) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296 – 18304; See also: b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284 – 4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215.

[15] X-ray crystal structure analysis of **10h**: Formula $C_{27}H_{25}ClO_6$, weight 480.92 g mol^{-1}, colorless crystal. CCDC-601775 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.

[16] E. Alvarez, T. Cuvigny, C. Harvé du Penhoat, *Tetrahedron* **1988**, *44*, 119 – 126.

[17] For the reductive amination see: A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Marynoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849 – 3862.

