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Highly Diastereo- and Enantioselective Catalytic Domino Thia-Michael/Aldol Reactions: Synthesis of Benzothiopyrans with Three Contiguous Stereocenters

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Abstract: Highly enantioselective organocatalytic domino thia-Michael/aldol reactions between 2-mercaptoacetophenone and α,β-unsaturated aldehydes are presented. The reactions proceed with excellent chemo-, diastereo- and enantioselectivity to give the corresponding benzothiopyran derivatives in high yields with up to >15:1 *dr* and 96 to >99% *ee*.

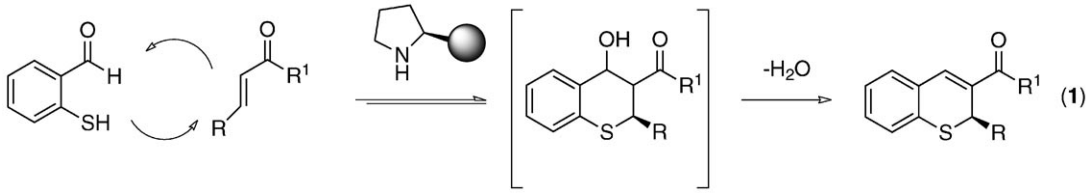
Keywords: asymmetric catalysis; benzothiopyrans; domino reactions; thia-Michael reaction; α,β-unsaturated aldehydes

Hetereocycles are very important in the design and discovery of novel compounds for pharmaceutical applications.[1] In this context, benzothiopyran derivatives are of great importance in the preparation of biologically active compounds.[2] For example, benzothiopyrans exhibit activity against inflammation, bacteria, cancer, and work as analgesics.[2,3] Furthermore, they may also show higher biological activity as compared to the corresponding benzopyran structural motif, which is also very important in the preparation of drugs.[4] Thus, catalytic methods have been developed for the synthesis of racemic benzothiopyrans.[5]

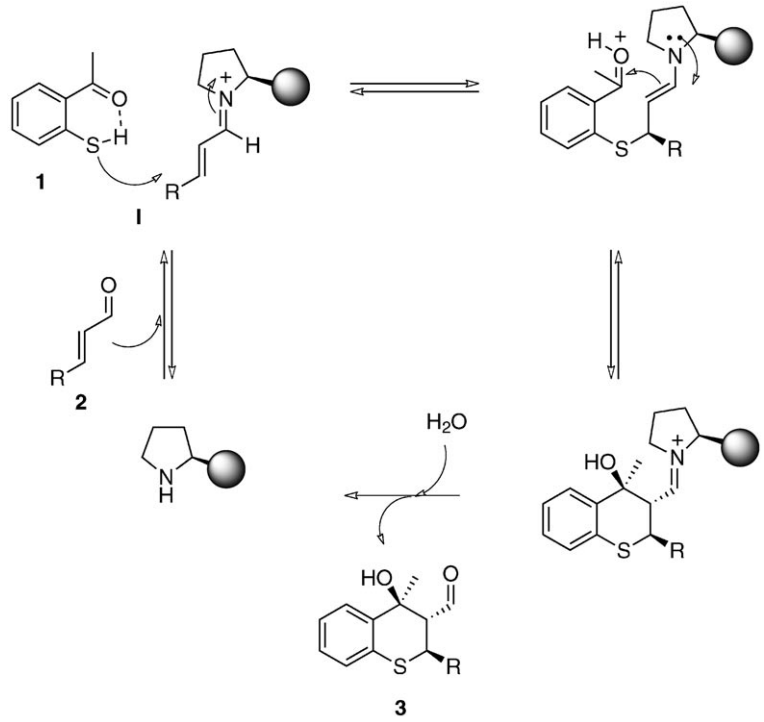
Domino or cascade reactions, that involve the formation of multiple stereocenters in one-pot, comprise a rapidly growing research field within the synthesis of small molecules with complex architectures.[6] The undeniable benefits of domino reactions include "green chemistry" factors such as atom economy,[7] reduction of synthetic steps and minimization of solvents and waste.[8] Thus, significant efforts have been made in the development of asymmetric domino reactions using chiral precursors for stereocontrol. However, the development of catalytic diastero- and enantioselective domino reactions is still a challenging task.[9,10] In this context, the development of organocatalytic asymmetric domino reactions has been intensely pursued.[9a,10]

Recently, Wang[11a] and our group[11b] independently reported a chiral pyrrolidine-catalyzed asymmetric synthesis of 2*H*-1-thiochromenes using 2-mercaptobenzaldehydes and enals as substrates [Eq. (1)].[11] Moreover, we reported the catalytic asymmetric synthesis of tetrahydrothioxanthenones using cyclic enones as substrates.[12] In both of these chiral pyrrolidine-mediated syntheses, the aldol adduct is dehydrated, which results in the loss of two chiral centers.

Based on the lessons learnt from the development of these reactions and our research interest of finding catalytic domino reactions that give useful structures,[10q,13] we envisioned that a reaction between 2-mercaptoacetophenone and enals could be a highly selective novel entry to benzothiopyrans with three contiguous stereocenters and a tertiary aldol structural motif (Scheme 1). These compounds would be very



(1)



Scheme 1. The proposed reaction pathway for a chiral amine-catalyzed enantioselective formation of thiochromenes with three contiguous stereocenters and a tertiary aldol structural motive.

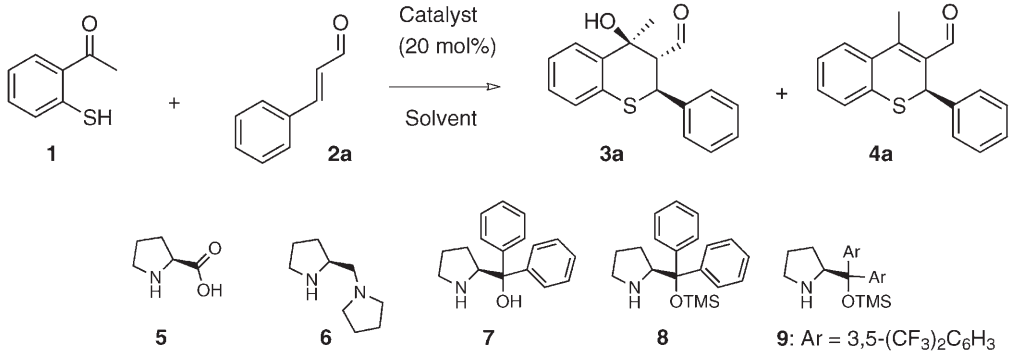
important for chemical, biological and medicinal chemistry studies. However, both the development of a highly selective catalytic asymmetric synthesis of tertiary stereocenters and avoiding subsequent dehydration are very challenging. In fact, controlling the stereochemistry of the intermolecular aldol addition to the acceptor ketone moiety, which would give the tertiary aldol structural motif is not trivial.[14] Herein, we present a highly enantioselective organocatalytic domino thia-Michael/aldol reaction that gives benzothiopyran derivatives in high yields with up to >15:1 *dr* and 96 to >99% *ee*.[15]

In an initial catalyst screen for the reaction between 2′-mercaptoacetophenone **1** (0.30 mmol) and cinnamic aldehyde **2a** (0.25 mmol), we found to our delight that chiral amines **5**, **6**, **8** and **9**[16] were catalysts for the asymmetric domino thia-Michael/aldol reaction (Table 1). For instance, compound **9** catalyzed the asymmetric formation of benzothiopyran **3a** in 44% yield and 83% *ee*, which was the highest of all the investigated catalysts, at room temperature (entry 5). However, the diastereoselectivety was low (2:1 *dr*) and the dehydrated thiopyran was isolated in 40% yield. Thus, we decided to optimize the reaction conditions of the catalytic asymmetric domino thia-Michael/aldol reaction using **9** as the catalyst (Table 1).[17]

We found that performing the asymmetric domino reactions in $CHCl_3$ or toluene gave a higher reaction efficiency and *ee* of the thiochromene derivative **3a** as compared to other solvents. In addition, the employment of an organic acid as an additive increased the efficiency of the domino reaction. Decreasing the reaction temperature improved the diastereoselectivity of the reaction. 2-Nitrobenzoic acid gave the superior results with respect to conversion and diastereoselectivity in toluene at −25 °C (entry 14). Moreover, the dehydration of **3a** was nearly avoided at this temperature. For example, the chiral amine **9** catalyzed the enantioselective formation of the corresponding benzothiopyran **3a** in 98% yield with 10:1 *dr* and 98% *ee* (entry 14). The superior level of enantioselectivity and efficiency encouraged us to choose these reaction conditions for further exploration (Table 2).

The catalytic enantioselective domino reactions were highly chemoselective and the corresponding thiochromenes **3** were isolated in high yields with 96 to 99% *ee*. The diastereoselectivity of the reaction was high and in some cases nearly a single diastereomer was formed with excellent enanioselectivity.[18] Thus, it was possible to control the formation of three new stereocenters in one-pot. Enal substituents such as aryl, alkyl and ester groups are readily tolerated. For example, chiral amine **9** catalyzed the formation of benzothiopyrans **3b** and **3e** in high yields with >15:1 *dr* and 99% *ee*, respectively (entries 2 and 5). Moreover, ester and aliphatic substituted products **3f**–**h** were isolated with 10:1 to >15:1 *dr* and 96% *ee*, re-

Table 1. Catalyst screen for the amine-catalyzed enantioselective domino reactions between **1** and **2a**.[a]

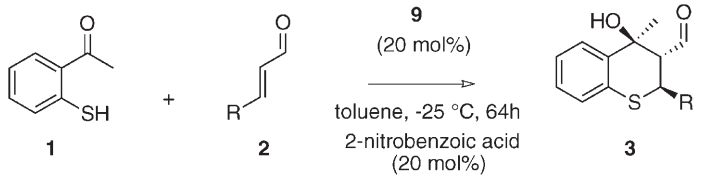


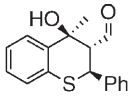
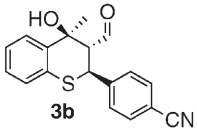
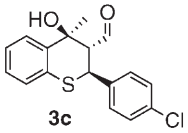
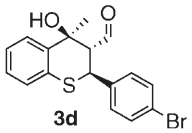
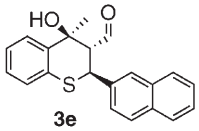
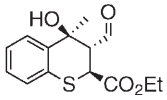
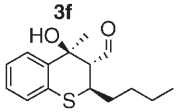
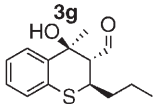
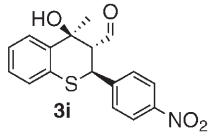
Entry	Additive (20 mol%)	Catalyst	Solvent	Temp (°C)	Time (h)	3a			4a
						Yield (%)[b]	Dr[c]	Ee (%)[d]	Yield (%)[b]
1	none	**5**	$CHCl_3$	rt	24	54	2:1	5	n.d.
2	none	**6**	$CHCl_3$	rt	24	44	2:1	3	n.d.
3	none	**7**	$CHCl_3$	rt	24	trace	n.d.	n.d.	n.d.
4	$C_6H_5CO_2H$	**8**	$CHCl_3$	rt	24	46	1:1	38	n.d.
5	$C_6H_5CO_2H$	**9**	$CHCl_3$	rt	24	44	2:1	83	40
6	none	**9**	$CHCl_3$	rt	21	32	2:1	94	n.d.
7	$C_6H_5CO_2H$	**9**	$CHCl_3$	-15	36	70	3:1	97	traces
8	$C_6H_5CO_2H$	**9**	toluene	-15	24	98	5:1	97	traces
9	2-$O_2NC_6H_4CO_2H$	**9**	toluene	-15	36	82	7:1	97	traces
10	2-$FC_6H_4CO_2H$	**9**	toluene	-15	36	72	4:1	97	traces
11	acetic acid	**9**	toluene	-15	36	96	3:1	96	traces
12	$C_6H_5CO_2H$	**9**	CH_3CN	-15	24	trace	n.d.	n.d.	traces
13	$C_6H_5CO_2H$	**9**	toluene	-25	22	42	4:1	99	traces
14	2-$O_2NC_6H_4CO_2H$	**9**	toluene	-25	64	98	10:1	98	traces

[a] *Experimental conditions:* A mixture of **1** (0.24 mmol), cinnamic aldehyde **2a** (0.20 mmol) and catalyst (20 mol%) in 0.5 mL solvent was stirred at the temperature and conditions displayed in the Table.
[b] Isolated yield of pure compound **3a** and **4a**.
[c] Determined by NMR analysis of the crude reaction mixture.
[d] Determined by chiral HPLC analyses.

spectively (entries 6–8). Notably, the reaction can be readily scaled up and create tertiary alcohols with high selectivity. For example, the reaction run at a 1-mmol scale of cinnamic aldehyde **2a** gave the corresponding benzothiopyran product **3a** in 96% yield with 10:1 *dr* and 97% *ee*. The relative configuration was confirmed by NOESY experiments of benzothiopyran **3d** (Figure 1). The methyl group had a strong interaction with H′ and hydrogen of the aldehyde group. Moreover, H″ interacts with the hydroxy group and *o*-hydrogen of the 4-bromophenyl group. In addition, the coupling constant of H′ and H″ de-

Table 2. Scope of the domino thia-Michael/aldol reaction between 2-mercaptoacetophenone **1** and enals **2**.[a]



Entry	R	Product	Yield[b]	Dr[c]	Ee (%)[d]
1	Ph	 **3a**	98	10:1	98
2	4-CNC_6H_4	 **3b**	63	15:1	99
3	4-ClC_6H_4	 **3c**	88	10:1	99
4	4-BrC_6H_4	 **3d**	71	13:1	>99
5	2-naphthyl	 **3e**	91	>15:1	99
6	CO_2Et	 **3f**	91	>15:1	96
7	*n*-butyl	 **3g**	83	10:1	96
8	*n*-propyl	 **3h**	68	10:1	96
9	4-$NO_2C_6H_4$	 **3i**	75	10:1	99

[a] *Experimental conditions:* A mixture of **1** (0.24 mmol), enal **2** (0.2 mmol), 2-nitrobenzoic acid (20 mol%) and catalyst **9** (20 mol%) in toluene (0.5 mL) was stirred at −25 °C. The crude product **3** obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of pure compounds **3** and **4**.
[c] Determined by NMR analysis of the crude reaction mixture.
[d] Determined by chiral HPLC analyses.

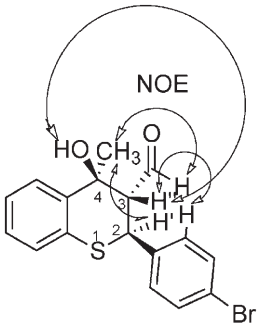


Figure 1. The results from the NOE experiments of **3d**.

rived by ^{1}H NMR analyses was 12.0 Hz, which confirmed that the relative stereochemistry between the aryl group and the formyl group was *trans*.

Based on the relative and absolute stereochemistry of the thiochromenes **3**, which has previously been established by X-ray analyses of 2*H*-thiochromenes derived by **9** catalysis,[11a,b] we propose the following reaction mechanism to account for the stereochemical outcome of the reaction (Scheme 1). Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups of **9** leads to stereoselective *Re*-facial nucleophilic conjugate attack on the β-carbon by the thio group of **1**. Next, the generated resulting chiral enamine intermediate makes a highly diastereoselective intramolecular six-*exo trig* aldol reaction (Scheme 1). Hydrolysis of the resulting iminium intermediate gives the aldol product **3** with three contiguous stereocenters. The addition of a benzoic acid additive possibly increase the efficiency of the reaction by pushing the equilibrium of the catalyst towards iminium formation. The addition of a small amount of water did not significant improve the *ee* or reaction rate.

In summary, we report a highly chemo-, diastereo- and enantioselective organocatalytic asymmetric domino thia-Michael/aldol reaction that gives thiochromenes with three contigous stereocenters in high yields with up to $>15{:}1$ *dr* and 96 to $>99\%$ *ee*. Hence, the reaction constitutes a simple catalytic highly stereoselective entry to pharmaceutically valuable benzothiopyran derivatives. Mechanistic studies, synthetic applications of this transformation as well as development of other enantioselective domino reactions are ongoing in our laboratory.

Experimental Section

General Procedure for the Domino Reaction

A stirred solution of the chiral amine **9** (24 mg, 20 mol%) and 2-$NO_2C_6H_4COOH$ (7 mg, 20 mol%) in toluene (0.5 mL) was cooled to −25 °C. Next, the enal **2** (0.2 mmol) and 2-mercaptoacetophenone **1** (0.24 mmol) were added. After vigorously stirring the reaction for 64 h at −25 °C, the reaction mixture was directly loaded on to a column and purified by silica gel chromatography (pentane/ethyl acetate mixtures) to give the corresponding product **3**. The *ee* of the product was determined by chiral-phase HPLC analysis (For HPLC conditions and NMR analysis see Supporting Information).

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References

[1] a) *Comprehensive Heterocyclic Chemistry*, (Eds.: A. R. Katrizky, C. W. Rees), Pergamon, Oxford, **1984**, Vol. 3, pp 737–883; b) E. A. Couladourous, A. T. Strongilos, *Angew. Chem. Int. Ed.* **2002**, *41*, 3677; c) Z. Gan, P. T. Reddy, S. Quevillon, S. Couve-Bonnaire, P. Arya, *Angew. Chem. Int. Ed.* **2005**, *44*, 1366.

[2] a) J. S. Carter, B. Devadas, J. J. Talley, D. L. Brown, M. J. Graneto, D. J. Rogier, Jr., S. R. Nagarajan, C. E. Hanau, S. J. Hartmann, C. L. Ludwid, S. Metz, D. E. Korte, S. R. Bertenshaw, M. G. Obukowicz, *PCT Int. Appl.* WO 2000023433A1, **2000**; *Chem. Abstr.* **2000**, *132*, 293665; b) J. S. Carter, M. G. Obukowicz, B. Devadas, J. J. Talley, D. L. Brown, M. J. Graneto, S. R. Bertenshaw, D. J. Rogier, Jr., S. R. Nagarajan, C. E. Hanau, S. J. Hartmann, C. L. Ludwig, S. Metz, *PCT Int. Appl.* WO 9847890A1, **1998**; *Chem. Abstr.* **1998**, *129*, 330653; c) B. P. Chekal, E. Freund, C. M. Grill, E. Huthmann, M. Juza, V. Leshchinskaya, M. T. Maloney, L. M. Miller, Jr., Y. Wang, M. Zeng, *US Patent Appl.* A1 20060020022, **2006**; *Chem. Abstr.* **2006**, *144*, 177626.

[3] a) J. F. Geissler, J. L. Roesel, T. Meyer, U. P. Trinks, P. Traxler, N. B. Lydon, *Cancer Res.* **1992**, *52*, 4492; b) A. Bargagna, M. Longobardi, E. Mariani, P. Schenone, C. Losasso, G. Esposito, C. Falzarano, E. Marmo, *Farmaco* **1990**, *45*, 405; c) A. Arnoldi, A. Bonsignori, P. Melloni, L. Merlini, M. L. Quadri, A. C. Rossi, M. Valsecchi, *J. Med. Chem.* **1990**, *33*, 2865; d) M. J. Brown, P. S. Carter, A. E. Fenwick, A. P. Fosberry, D. W. Hamprecht, M. J. Hibbs, R. L. Jaevest, L. Mensah, P. H. Milner, P. J. O'Hanlon, A. J. Pope, C. M. Richardson, A. Ewst, D. R. Witty, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3171; e) W. Quaglia, M. Pigini, A. Piergentili, M. Giannella, F. Gentili, G. Marucci, A. Carrieri, A. Carotti, E. Poggesi, A. Leonardi, C. Melchiorre, *J. Med. Chem.* **2002**, *45*, 1633.

[4] a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939; b) K. C. Nicolaou, J. A. Pfefferkorn, S. Barluenga, H. J. Mitchell, A. J. Roecker, G. Q. Cao, *J. Am. Chem. Soc.* **2000**, *122,* 9968; c) E. E. Schweizer, O. Meeder-Nycz, in: *Chromenes, Chromanes, Chromones*, (Ed.: G. P. Ellis), Wiley-Interscience, New York, **1977**, pp 11–139; d) W. S. Bowers,

T. Ohta, J. S. Cleere, P. A. Marsella, *Science* **1976**, *193*, 542.

[5] a) P. T. Kaye, *S. Afr. J. Sciences* **2004**, *100*, 545; b) P. T. Kaye, X. W. Nocanda, *Synthesis* **2001**, 2389; see also: c) J. Tércio, B. Ferreira, V. Catani, J. V. Comasseto, *Synthesis* **1987**, 149; d) A. Arnoldi, M. Carughi, *Synthesis* **1998**, 155; e) K. Kobayashi, H. Konishi, T. Kitamura, O. Morikawa, R. Nakahashi, *J. Chem. Soc., Perkin Trans; 1* **1999**, 1547; f) G. V. Nenajdenko, A. V. Sanin, A. V. Churakov, J. A. K. Howard, E. S. G. Balenkova, *Chem. Heterocycl. Compd.* **1999**, *35*, 549; g) H. Sunden, I. Ibrahem, R. Rios, G.-L. Zhao, A. Córdova, A. *Chemia* **2007**, *61*, 219.

[6] For reviews on this concept see: a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim **2006**, p 672; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; d) H. Guo, J. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 354; e) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143; f) D. J. Ramon, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.

[7] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *107*, 258.

[8] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **2000**, p 135; b) for an excellent paper on combining one-pot, step reduction and atom economy in organic chemistry, see: P. A. Clarke, S. Santos, W. H. C. Martin, *Green Chem.* **2007**, *9*, 438.

[9] For a review on organocatalytic domino reactions see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; for selected reviews on organocatalysis see: b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; c) B. List, *Chem. Commun.* **2006**, 819; d) P. I. Dalko, L. Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; e) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001.

[10] For selected examples of organocatalytic asymmetric domino reactions see: a) N. Halland, P. S. Aburell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1272; b) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; c) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036; d) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; e) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962; f) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2003**, *42*, 4233; g) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; h) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, *44*, 4877; i) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; j) H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99; k) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, *47*, 4928; l) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; m) D. Enders, M. R. M. Hüttl, J. Runsink, J.; Raabe, B. Wendt, *Angew. Chem. Int. Ed.* **2007**, *46*, 467; n) M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475; o) R. Rios, H. Sundén, J. Vesely, G. L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Cat.* **2007**, *349*, 1028; p) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, *17*, 1763; q) H. Sundén, I. Ibrahem, G. L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574; r) D. Enders, A. A. Narine, T. R. Benninghaus, G. Raabe, *Synlett* **2007**, 1667.

[11] a) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354; b) R. Rios, H. Sunden, I. Ibrahem, G. L. Zhao, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8547; c) For a recent thiourea-catalyzed synthesis see: L. Zu, J. Wang, H. Li, H. Xie, W. Jiang, W. Wang, *J. Am. Chem. Soc.* **2007**, 129, 1036; d) for 2-mercapto-1-phenyl ethanones as nucleophildes see: S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986.

[12] R. Rios, H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2181.

[13] a) I. Ibrahem. R. Rios, J. Vesely, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 6252; b) J. Vesely, I. Ibrahem. G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem. Int. Ed.* **2007**, *46*, 778; c) H. Sundén, R. Rios, I. Ibrahem. G.-L. Zhao, L. Eriksson, A. Córdova, *Adv. Synth. Cat.* **2007**, *349*, 827; d) R. Rios, J. Vesely, H. Sundén, I. Ibrahem. G. L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5835.

[14] D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959.

[15] For an excellent review on the topic of asymmetric thia-Michael additions see: D. Enders, K. Lüttingen, A. A. Narine, *Synthesis* **2007**, 959.

[16] Selected examples of the use of protected diarylprolinols in catalysis see: a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjaersgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703; c) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaersgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; e) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; f) I. Ibrahem, A. Córdova , *Chem. Commun.* **2006**, 1760; g) Y. Shi, S. H. Gellman, *Org. Lett.* **2005**, 4253.

[17] The protected diarylprolinol catalyzed reactions between 2′-aminoacetophenone and enals gave the corresponding optically active Michael adducts under the investigated reaction conditions.

[18] The enal products can enolize upon isolation by silica gel chromatography, which can lead to a decrease in diastereomeric ratio.

