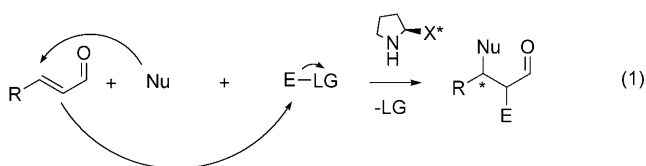


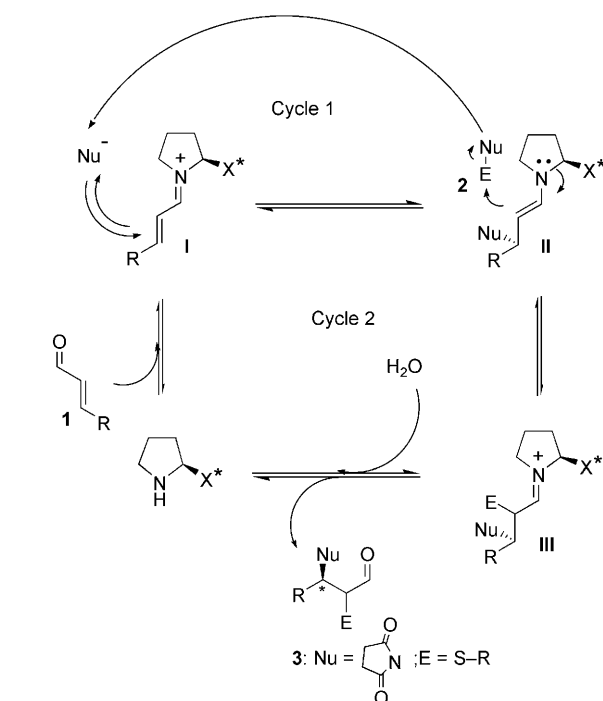
Organocatalytic Enantioselective Aminosulfenylation of α,β -Unsaturated Aldehydes**

Gui-Ling Zhao, Ramon Rios, Jan Vesely, Lars Eriksson, and Armando Córdoba*

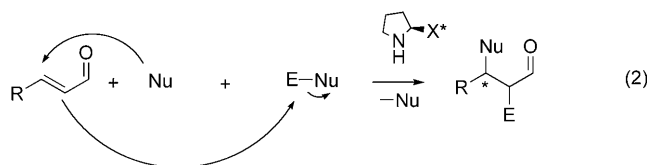
Domino, tandem, or cascade reactions, that involve the formation of multiple carbon–carbon or carbon–heteroatom bonds and stereocenters in one-pot reactions, are a rapidly growing research field within the synthesis of small molecules with complex molecular scaffolds.^[1] The advantages of domino reactions include “green chemistry” factors, such as atom economy,^[2] reduction in the number of synthetic steps, and minimization of solvents and waste.^[3] Thus, asymmetric domino reactions using chiral precursors for stereocontrol have been developed.^[1] A more challenging task is to develop catalytic asymmetric domino reactions. In this context, the development of organocatalytic, asymmetric, one-pot domino reactions is a rapidly growing research area.^[4–5] In particular, versions involving a subsequent intramolecular reaction step that forms cyclic products are economical, since the donor species includes both nucleophilic and electrophilic reactivities. However, in intermolecular domino reactions that form acyclic products, the nucleophilic and the electrophilic substrates are added sequentially in one pot [Eq. (1); Nu = nucleophile, E = electrophile, LG = leaving group].



Based on our research interest in organocatalysis,^[6] we became intrigued as to whether it would be possible to efficiently incorporate all components of the reacting substrates in a catalytic domino process encompassing entirely intermolecular reaction steps using a small organic catalyst [Eq. (2), Scheme 1], thus reducing the generation of side products and waste.



Scheme 1. Proposed reaction pathway. Nu = nucleophile; E = electrophile.



According to this scenario, all components of electrophile **2** (Nu–E), which includes a masked nucleophilic component, are incorporated into the electrophilic enal **1** by the merging of the two catalytic cycles shown in Scheme 1, affording the aldehyde product **3**. Herein, we demonstrate for the first time that it is possible to efficiently apply this strategy in intermolecular organocatalytic domino reactions and to the novel highly enantioselective aminosulfenylation of α,β -unsaturated aldehydes (93–>99% *ee*).

The β -amino- α -mercapto carbonyl motif displays potent biological activity, for example, in potent inhibitors of aminopeptidase A,^[7] tetanus neurotoxin,^[8] botulinum neurotoxin type B,^[9] and cholesterol absorption.^[10,11] As a result of the important biological activity associated with this motif, we decided to investigate the catalytic domino approach depicted in Scheme 1 for the aminosulfenylation of α,β -unsaturated

[*] Dr. G.-L. Zhao, Dr. R. Rios, Dr. J. Vesely, Prof. Dr. A. Córdoba
Department of Organic Chemistry
The Arrhenius Laboratory, Stockholm University
10691 Stockholm (Sweden)
Fax: (+46) 8-154-908
E-mail: acordova@organ.su.se

Prof. Dr. L. Eriksson
Department of Structural Chemistry, Stockholm University

[**] We gratefully acknowledge the Swedish National Research Council and Carl Trygger Foundation for financial support.

Supporting Information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200802335>.

aldehydes. In addition, α -sulfenylation reagents looked promising since they usually contain a weakly basic heterocyclic nitrogen-centered nucleofuge.^[12] However, the conjugate transformations between the nucleofuges of *N*-(alkylthio)succinimides or *N*-(alkylthio)phthalimides (succinimide and phthalimide, respectively) and cinnamic aldehyde derivatives **1** are not productive [Eq. (3)].^[13]

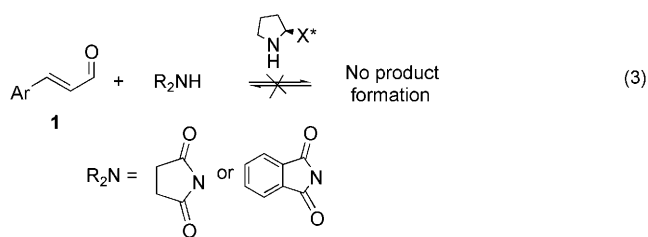
Moreover, the use of *N*-(alkylthio)succinimides **2** in amine-catalyzed α -sulfenylation reactions of aldehydes proceeds with only sluggish conversion and, in the past, 1-benzylsulfanyl-1,2,4-triazole has been used instead.^[12] Nevertheless, we began the asymmetric aminosulfenylation reaction between cinnamic aldehyde **1a** and *N*-(benzylthio)succinimide **2a**, as a successful merging of the two catalytic cycles in the domino process has the potential to push the equilibrium towards product formation (Table 1).

A small amount of succinimide (10 mol %) was also added in order to initiate cycle 1 in Scheme 1. After screening various chiral amines as catalysts and different suitable conditions for the aminosulfenylation of **1a**, we found that amines **5–9** catalyzed the asymmetric domino reaction (Table 1). The protected chiral diarylprolinols **7**

Table 1: Catalyst screen for the reaction between **1a** and **2a**.^[a]

Entry	Catalyst	Solvent	<i>t</i> [h]	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	4	CHCl ₃	16	0	—	—
2	5	CHCl ₃	16	36	47:53	56, 56
3	6	CHCl ₃	16	traces	n.d.	n.d.
4	7	CHCl ₃	16	33	66:34	85, 86
5	8	CHCl ₃	16	83	52:48	96, > 99
6	9	CHCl ₃	16	traces	n.d.	n.d.
7	8	Toluene	16	49	54:46	95, > 99
8	8	CH ₃ CN	16	traces	n.d.	n.d.
9	8	CHCl ₃	16 ^[e,h]	51	33:67	94, 97
10	8	CHCl ₃	16 ^[f,h]	80	49:51	94, 97
11	8	CHCl ₃	72 ^[g]	73	50:50	96, > 99
12	8	CHCl ₃	48 ^[h,k]	78	53:47	96, 99
13	8	CHCl ₃	16 ^[j]	81	55:45	96, 99
14	8	CHCl ₃	40 ^[i,l]	55	48:58	93, 99

[a] Experimental conditions unless otherwise stated: A mixture of **1a** (0.25 mmol), **2a** (0.30 mmol), catalyst (20 mol %, TMS = trimethylsilyl), and succinimide (0.025 mmol) in solvent (0.5 mL) was stirred at room temperature and reaction times given. [b] Yield of **3a** and **3a'** isolated by silica-gel column chromatography. [c] Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. [d] *Syn, anti*; determined by chiral-phase HPLC analysis. [e] Reaction performed at 40 °C. [f] Benzoic acid (20 mol %) was added. [g] Reaction run at 4 °C. [h] Reaction run without succinimide. [i] 4 mol % succinimide was used. [j] 10 mol % of catalyst **8** was used. [k] 10 mol % of α -sulfenylated cinnamic aldehyde^[15] was also formed. [l] 5 mol % of α -sulfenylated cinnamic aldehyde was also formed.



and **8**^[12,14] exhibited the highest reactivity and catalyzed the formation of the corresponding β -amino- α -mercaptoaldehydes **3a** and **3a'** in 33% and 83% combined yields, respectively (Table 1, entries 4 and 5). The highest enantioselectivity was achieved in chloroform solution when chiral amine **8** was the catalyst. The two diastereoisomers **3a** and **3a'** were readily separated and isolated by silica-gel column chromatography with 96% and > 99% *ee*, respectively (Table 1, entry 5). Excellent enantioselectivity was also achieved

in toluene (Table 1, entry 7). The reaction was also productive without the initial addition of a small amount of succinimide (Table 1, entries 9 and 12). However, the reaction rate slightly decreased. The rate loss could be avoided if a small amount of organic acid (20 mol %) was added (Table 1, entry 10). Running the reaction at a lower temperature also decreased the reaction rate (Table 1, entry 11). The amount of initiating succinimide could be decreased to 4 mol % without affecting the efficiency and enantioselectivity of the transformation (Table 1, entry 13). The domino reaction also worked at lower catalyst loadings without significantly affecting the enantioselectivity, however a slight decrease in efficiency was detected (Table 1, entry 14). Based on these results, we decide to investigate the amine **8**-catalyzed enantioselective aminosulfenylation of enals **1** in CHCl₃ with 10 mol % of succinimide as an additive (Table 2).

The organocatalytic asymmetric domino reactions gave the corresponding *syn*- and *anti*- β -amino- α -mercaptoaldehydes **3a–3i** and **3a'–3i'**, respectively, in high yields (60–83%)

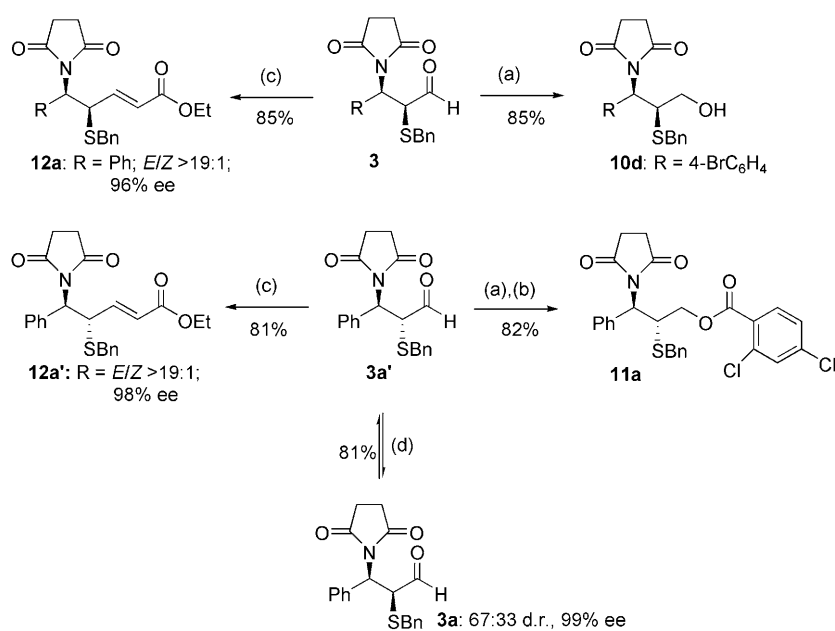
and diastereomeric ratios varying from 52:48 to 77:23. The enantioselectivity of the reaction was high in all cases (93–>99% *ee*). In general, the *syn*- and *anti*-diastereoisomers can be separated from each other by silica-gel column chromatography. Notably, no conjugate addition product was formed if first succinimide (1.2 equiv) was added to the 3-aryl-substituted enals **1a–h** and catalyst **8** under our reaction conditions. Hence, the equilibrium of the first conjugate addition is not towards product formation. However, when aliphatic enal **1i** was used as the substrate, the conjugate addition gave the corresponding Michael product after 16 h, before the electrophile **2a** was added (Table 2, entry 10). This procedure gave nearly identical results as to when electrophile **2a** was directly added to the aliphatic enal (Table 2, entry 9). However, the reaction time was increased. The reaction also worked with other thiosuccinimides **2**. For example, the reaction between 4-cyanocinnamic aldehyde and *N*-(4-chlorophenylthio)succinimide **2b** gave the corresponding mercaptoaldehydes **3j** and **3j'** in 55% yield with 62:38 diastereomeric ratio and 90% *ee* (see Supporting Information). The β -amino- α -mercaptoaldehydes **3** can be readily converted into other useful compounds, such as both diastereoisomers of β -mercapto- γ -amino alcohols **10**, esters **11**, and α,β -unsaturated esters **12**, which can be further rearranged to unsaturated α -amino acid derivatives (Scheme 2).^[15] The reduction and Wittig transformations can also be performed as one-pot operations. The absolute configuration of β -amino- α -mercaptoaldehydes **3** at C3 was *R* as established by X-ray analysis of **3a** (Figure 1).^[16] The absolute configuration of the *anti*-diastereomers **3a'–3i'** was determined by epimerization of pure *anti*-**3a'** to *syn*-**3a** with imidazole (Scheme 2). Chiral-phase HPLC analysis of the isolated *syn*-isomer revealed that the epimerization gave **3a** (*R* configuration at C3), indicating that the absolute configuration at C3 of aminoaldehydes **3a'–3i'** was also *R*.

Thus, efficient shielding of the *Re*-face (*R* = Ar) of the chiral iminium intermedi-

Table 2: Catalytic asymmetric aminosulfenylation of enals **1**.^[a]

Entry	R ¹	Product	Yield [%] ^[b]	d.r. ^[c]	<i>ee</i> [%] ^[d]
1		3a/3a'	83	52:48	96, >99
2		3b/3b'	73	55:45	94, 99
3		3c/3c'	60	63:37	94, 98
4		3d/3d'	65	57:43	98, 99
5		3e/3e'	67	49:51	95, 95
6		3f/3f'	79	55:45	93, 99
7		3g/3g'	78	56:44	95, 95
8		3h/3h'	67	71:29	95, 95
9		3i/3i'	67	71:29	95, n.d.
10		3i/3i'	74 ^[e]	77:23	97, n.d.

[a] Experimental conditions: A mixture of enal **1** (0.25 mmol), **2a** (0.30 mmol), catalyst (20 mol%), and succinimide (0.025 mmol) in solvent (0.5 mL) was stirred at room temperature for 16 h. [b] Yield of **3** and **3'** isolated by silica-gel column chromatography. [c] Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. [d] *Syn*, *anti*; determined by chiral-phase HPLC analysis. [e] Succinimide (1.2 equiv) was first added to the enal in the presence of catalyst **8** at 4 °C. After 16 h **2a** was added and the reaction was stirred for an additional 4 h. The formation of the Michael intermediate was monitored by NMR spectroscopic analysis.



Scheme 2. a) NaBH₄, MeOH, 0 °C; b) 2,4-Cl₂C₆H₃COCl, triethylamine, CH₂Cl₂; c) Ph₃P=CHCO₂Et, CHCl₃; d) Imidazole, CH₂Cl₂.

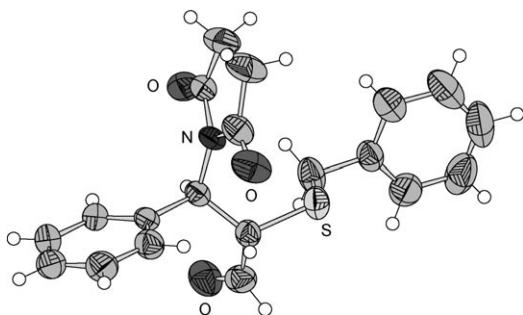


Figure 1. ORTEP representation of β -amino- α -sulphenyl aldehyde **2a**. Thermal ellipsoids set at 50% probability level

ate **I** by the bulky aryl groups of **8** leads to stereoselective *Si*-facial nucleophilic conjugate attack on the β -carbon by the succinimide (Scheme 1). Next, the resultant chiral enamine intermediate **II** attacks the electrophilic **2a** in a S_N2 -type mechanism, releasing succinimide (Nu^- in cycle 1). Hydrolysis of iminium intermediate **III** gives the aldehyde product **3** and regenerates the catalyst (cycle 2). The formation of both diastereoisomers, as a result of epimerization of the α -carbon of aminoaldehydes **3** by the chiral amine catalyst, was established by mixing pure **3a** with amine **8**, which led to the formation of *anti*-**3a'** and α -sulphenylated cinnamic aldehyde^[15] by epimerization and elimination of **3a**, respectively.

In summary, we have demonstrated that it is possible to efficiently employ all components of an electrophile, which includes a nucleofuge, in organocatalytic domino reactions of enals. This concept^[17] was employed in the highly enantioselective aminosulphenylation of α,β -unsaturated aldehydes that gives access to valuable β -amino- α -mercaptoaldehydes and derivatives thereof in high yields with 93–>99% *ee*.

Received: May 19, 2008

Revised: June 19, 2008

Published online: September 26, 2008

Keywords: aldehydes · asymmetric catalysis · domino reactions · nucleophilic substitution · organocatalysis

- [1] For reviews, 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.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, 45, 7134; d) H. Guo, J. Ma, *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem. Int. Ed.* **2006**, 45, 354; e) H. Pellissier, *Tetrahedron* **2006**, 62, 2143; f) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, 44, 1602.
- [2] a) B. M. Trost, *Science* **1991**, 254, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 259–281.
- [3] 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.
- [4] For an excellent review on organocatalytic domino reactions see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, 46, 1570.
- [5] For selected examples of organocatalytic asymmetric domino reactions see: a) N. Halland, P. S. Aburell, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292; *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.* **2003**, *115*, 4365; *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. Ibrahim, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955; *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. Ibrahim, 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) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354; m) R. Rios, H. Sundén, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2006**, 47, 8547; n) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, 17, 1763; o) H. Sundén, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, 13, 574; p) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, 46, 1101; q) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471; *Angew. Chem. Int. Ed.* **2007**, 46, 467; r) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, 350, 267; s) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 9362; *Angew. Chem. Int. Ed.* **2007**, 46, 9202; t) H. Sundén, R. Rios, Y. Xu, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, 349, 2549.
- [6] a) I. Ibrahim, A. Córdova, *Angew. Chem.* **2006**, *118*, 1986; *Angew. Chem. Int. Ed.* **2006**, 45, 1952; b) G.-L. Zhao, J. Vesely, R. Rios, I. Ibrahim, H. Sundén, A. Córdova, *Adv. Synth. Catal.* **2008**, 350, 237; c) J. Vesely, I. Ibrahim, G. L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792; *Angew. Chem. Int. Ed.* **2007**, 46, 778; d) H. Sundén, R. Rios, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, 349, 827; e) J. Vesely, R. Rios, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2008**, 14, 2693.
- [7] C. David, L. Bischoff, H. Meudal, A. Mothé, N. De Mota, S. DaNascimento, C. Llorens-Cortes, M.-C. Fournié-Zaluski, B. P. Roques, *J. Med. Chem.* **1999**, 42, 5197.
- [8] L. Martin, F. Cornille, S. Turcaud, H. Meudal, B. P. Roques, M.-C. Fournié-Zaluski, *J. Med. Chem.* **1999**, 42, 515.
- [9] a) C. Anne, S. Turcaud, J. Quancard, F. Teffo, H. Meudal, M.-C. Fournié-Zaluski, B. P. Roques, *J. Med. Chem.* **2003**, 46, 4648; b) C. Anne, A. Blommaert, S. Turcaud, A. S. Martin, H. Meudal, B. P. Roques, *Bioorg. Med. Chem.* **2003**, 11, 4655; c) C. Anne, S. Turcaud, A. G. S. Blommaert, F. Darchen, E. A. Johnson, and B. P. Roques, *ChemBioChem* **2005**, 6, 1375.
- [10] B. A. McKittrick, K. Ma, K. Huie, N. Yumibe, H. Davis, Jr., J. W. Clader, M. Czarniecki, *J. Med. Chem.* **1998**, 41, 752.
- [11] For examples of diastereoselective synthesis of β -amino- α -mercapto carbonyl compounds see: Refs. [7–10] and a) J. I. Candela-Lena, S. G. Davies, P. M. Roberts, B. Roux, A. J. Russel, W. M. Sánchez-Fernández, A. D. Smith, *Tetrahedron: Asymmetry* **2006**, 17, 1135; b) N. Shibata, J. E. Baldwin, A. Jacobs, M. E. Wood, *Synlett* **1996**, 519; c) N. Shibata, J. E. Baldwin, A. Jacobs, M. E. Wood, *Tetrahedron* **1996**, 52, 128.
- [12] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, 44, 794.

- [13] a) J. Vesely, I. Ibrahim, R. Rios, G.-L. Zhao, Y. Xu, A. Córdova, *Tetrahedron Lett.* **2007**, 48, 2193; b) H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.* **2007**, 13, 9068.
- [14] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, 117, 4284; *Angew. Chem. Int. Ed.* **2005**, 44, 4212.
- [15] A. Armstrong, L. Challinor, J. H. Moir, *Angew. Chem.* **2007**, 119, 5465; *Angew. Chem. Int. Ed.* **2007**, 46, 5369.
- [16] CCDC 682103 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.
- [17] In preliminary experiments, we also found that chiral amines can catalyze the aminoselenylation of enals based on this strategy (See Supporting Information).
-