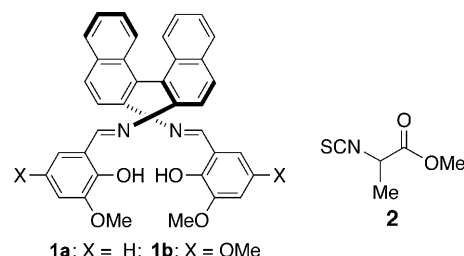


# Stereodivergent Direct Catalytic Asymmetric Mannich-Type Reactions of $\alpha$ -Isothiocyanato Ester with Ketimines\*\*

Gang Lu, Tatsuhiko Yoshino, Hiroyuki Morimoto, Shigeki Matsunaga,\* and Masakatsu Shibasaki\*

Chiral  $\alpha,\beta$ -diamino acids are key structural motifs in many biologically active compounds.<sup>[1]</sup> Catalytic asymmetric direct Mannich-type reactions of aldimines and nucleophiles, which contain an  $\alpha$ -amino equivalent unit, provide straightforward access to chiral  $\alpha,\beta$ -diamino acids.<sup>[2]</sup> Unnatural amino acids that contain tetrasubstituted carbon centers are useful chiral building blocks for the synthesis of pharmaceuticals, and artificial peptides with distinctive chemical and biological properties.<sup>[3]</sup> Several research groups including ours, have reported Mannich-type reactions of aldimines with  $\alpha$ -substituted donors, such as an alanine methyl ester Schiff base,<sup>[4]</sup>  $\alpha$ -substituted nitroacetates,<sup>[5]</sup> and  $\alpha$ -substituted oxazolones,<sup>[6]</sup> for the synthesis of  $\alpha,\beta$ -diamino acid surrogates bearing an  $\alpha$ -tetrasubstituted carbon center.<sup>[7]</sup> In contrast, there are no reports of the catalytic asymmetric synthesis of  $\beta$ -tetrasubstituted chiral  $\alpha,\beta$ -diamino acids, which require the reaction of much less reactive ketimines. Thus, there is a high demand for the development of a new method for the synthesis of  $\alpha,\beta$ -tetrasubstituted  $\alpha,\beta$ -diamino acid surrogates. To address this issue, we herein report the utility of group 2 metal/Schiff base **1** complexes (Figure 1). The Sr/**1** and Mg/**1** catalysts promoted a direct Mannich-type reaction of  $\alpha$ -methyl- $\alpha$ -isothiocyanato ester **2** with ketimines **3** (see Table 1), thus providing stereodivergent access to  $\alpha,\beta$ -diamino esters with vicinal tetrasubstituted carbon stereocenters.

We have previously reported the direct asymmetric aldol reaction of  $\alpha$ -methyl- $\alpha$ -isothiocyanato ester **2** with ketones, catalyzed by  $\text{Bu}_2\text{Mg}$ /Schiff base **1a**.<sup>[8]</sup> Therefore, we initially utilized  $\text{Bu}_2\text{Mg}/\mathbf{1a}$  for the reaction of **2** with ketimines.<sup>[9]</sup>



**Figure 1.** Structures of Schiff bases **1a** and **1b** and  $\alpha$ -methyl- $\alpha$ -isothiocyanato ester **2**.

Among the ketimines screened, diphenylphosphinoyl (Dpp) imine **3a** gave promising results in terms of reactivity and selectivity. Optimization studies using **3a** are summarized in Table 1. A 1:1 ratio of  $\text{Bu}_2\text{Mg}/\mathbf{1a}$  (10 mol %) promoted the

**Table 1:** Optimization studies.

$\text{Ar}-\text{C}(=\text{N}-\text{Dpp})-\text{Me} \xrightarrow[\text{solvent, RT}]{\begin{array}{l} \text{metal source}/(\text{R})-\mathbf{1} \\ = 1:1 \text{ (10 mol \%)} \\ \mathbf{2} \text{ (2 equiv)} \\ \text{molecular sieves (5\AA)} \end{array}} \text{Dpp}-\text{N}(\text{C}(\text{Me})_2)-\text{C}(\text{Me})_2-\text{CO}_2\text{Me} + \text{Dpp}-\text{N}(\text{C}(\text{Me})_2)-\text{C}(\text{Me})_2-\text{CO}_2\text{Me}$							
Ar = 4-BrC <sub>6</sub> H <sub>4</sub> ; Dpp = $-\text{P}(\text{Ph})_2$							
Entry	Metal source	(R)- <b>1</b>	Solvent	t [h]	Yield <sup>[a]</sup>	d.r. syn/anti	ee [%] <sup>[b]</sup> (syn)
1	$\text{Bu}_2\text{Mg}$	<b>1a</b>	THF	47	> 95	68:32	44
2	$\text{Bu}_2\text{Mg}$	<b>1b</b>	THF	28	> 95	71:29	67
3	$\text{Bu}_2\text{Mg}$	<b>1b</b>	$\text{CHCl}_3$	20	> 95	86:14	80
4 <sup>[c]</sup>	$\text{Bu}_2\text{Mg}$	<b>1b</b>	$\text{CHCl}_3$	48	87 <sup>[d]</sup>	91:9	84
5	$\text{Ca}(\text{O}-i\text{Pr})_2$	<b>1b</b>	$\text{CHCl}_3$	48	trace	n.d.	n.d.
6	$\text{Sr}(\text{O}-i\text{Pr})_2$	<b>1b</b>	$\text{CHCl}_3$	48	86 <sup>[d]</sup>	6:94	92 <sup>[e]</sup>
7	$\text{Ba}(\text{O}-i\text{Pr})_2$	<b>1b</b>	$\text{CHCl}_3$	48	trace	n.d.	n.d.

[a] Determined by  $^1\text{H}$  NMR analysis of the crude reaction mixture.

[b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction was run at  $-10^\circ\text{C}$ . [d] Yield of the isolated product after purification by column chromatography on silica gel. [e] Enantiomeric excess of **anti-4a**. n.d. = not determined, THF = tetrahydrofuran.

addition of **2** to **3a** in THF at room temperature, to give **4a** in a greater than 95 % yield, as determined by NMR spectroscopy, albeit with modest diastereo- and enantioselectivity (Table 1, entry 1). By using the Schiff base **1b**, which has additional methoxy substituents relative to **1a**, improved the enantioselectivity to 67 % ee (Table 1, entry 2). Among the solvents screened,  $\text{CHCl}_3$  gave the best selectivity, and **4a** was obtained with 86:14 (syn/anti) diastereoselectivity and 80 % ee at room temperature (Table 1, entry 3). The best syn selec-

[\*] Dr. G. Lu, T. Yoshino, Dr. H. Morimoto, Dr. S. Matsunaga  
Graduate School of Pharmaceutical Sciences  
The University of Tokyo  
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)  
Fax: (+81) 3-5684-5206  
E-mail: smatsuna@mol.f.u-tokyo.ac.jp  
Homepage: [http://www.f.u-tokyo.ac.jp/~kanai/e\\_index.html](http://www.f.u-tokyo.ac.jp/~kanai/e_index.html)  
Prof. Dr. M. Shibasaki  
Institute of Microbial Chemistry, Tokyo  
Kamiosaki 3-14-23, Shinagawa-ku, Tokyo 141-0021 (Japan)  
Fax: (+81) 3-3447-7779  
E-mail: mshibasa@bikaken.or.jp

[\*\*] This work was supported by JSPS (Young Scientists A), the Takeda Science Foundation (S.M.), and the Inoue Science Foundation (S.M.). G.L. and H.M. thank JSPS for fellowships. We thank Prof. Ohwada and Dr. Otani at the University of Tokyo for their generous technical support, and helpful discussions. T.Y. and S.M. thank Prof. Kanai at the University of Tokyo for his generous support, fruitful discussions, and unrestricted access to the analytical facilities.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201101034>.

tivity (*syn/anti* = 91:9) and enantioselectivity (84% *ee*) were obtained at  $-10^{\circ}\text{C}$  (Table 1, entry 4). In entries 5–7, other group 2 metals were utilized.<sup>[10,11]</sup> Although  $\text{Ca}(\text{O-}i\text{Pr})_2$  and  $\text{Ba}(\text{O-}i\text{Pr})_2$  gave poor results,  $\text{Sr}(\text{O-}i\text{Pr})_2$  gave **4a** in an 86% yield (Table 1, entry 6). In addition, the use of  $\text{Sr}(\text{O-}i\text{Pr})_2$ /Schiff base **1b** led to an unexpected reversal of the diastereoselectivity, and the *anti* adduct was obtained in high diastereoselectivity (*syn/anti* = 6:94) and enantioselectivity (92% *ee*, *anti-4a*) at ambient temperature.

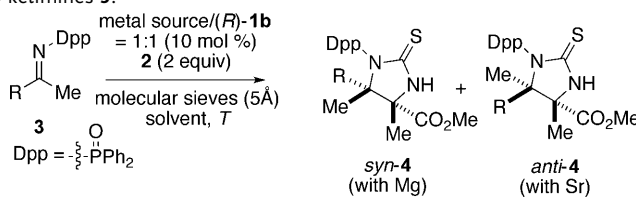
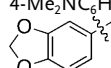
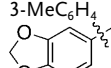
The substrate scope of the strontium- and magnesium-catalyzed reactions is summarized in Table 2. The reaction temperature and solvent were optimized for each ketimine, and the best results are reported. Absolute and relative configurations of the products were unequivocally determined by X-ray crystallographic analysis (see the Supporting Information).<sup>[12]</sup> The enantiofacial selectivity of the reaction of the ketimines (**3**) catalyzed by  $\text{Sr}/\mathbf{1b}$  was opposite to that of the reaction catalyzed by  $\text{Mg}/\mathbf{1b}$ . The results of the strontium-catalyzed *anti*-selective reaction are shown in Table 2, entries 1–12. Aryl ketimines **3a–3i** gave products with high

*anti* selectivity and high enantioselectivity at either room temperature or  $-5^{\circ}\text{C}$  (Table 2, entries 1–9). Good yields were achieved even with ketimines bearing an electron-donating group at the *para* position, such as 4-methyl imine **3e** (Table 2, entry 5) and 4-methoxy imine **3g** (entry 7). However, a strongly electron-donating 4-dimethylamine group had adverse effects on the yield, but high *anti* selectivity and enantioselectivity were maintained (Table 2, entry 8). Heteroaryl ketimines **3j–3l** were also applicable, and the products were obtained in good to high enantioselectivity (Table 2, entries 10–12), although slightly lower *anti* selectivity was observed (entries 10–12). The results of the magnesium-catalyzed *syn*-selective reaction are shown in entries 13–20. Although the enantioselectivity was slightly lower than with the strontium catalyst, except for ketimine **3m** (Table 2, entry 18), high *syn* selectivity was achieved in all cases (Table 2, entries 13–20). Unfortunately, the present  $\text{Sr}/\mathbf{1b}$  and  $\text{Mg}/\mathbf{1b}$  systems were not applicable to other ketimines, such as aryl ethyl ketimines and aliphatic ketimines, because of the lower reactivity of these ketimines. The  $\alpha$ -ethyl- $\alpha$ -isothiocyanato ester also showed

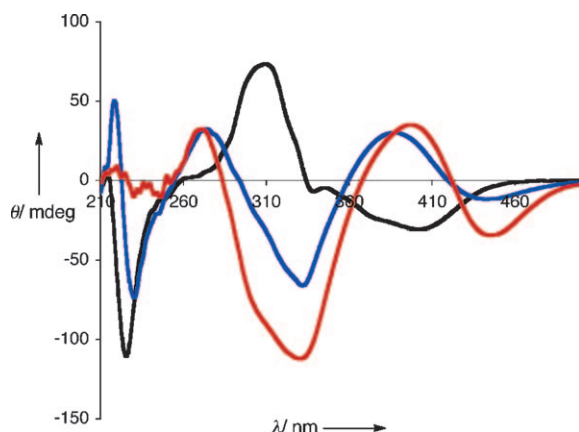
much lower reactivity and stereoselectivity than the  $\alpha$ -methyl- $\alpha$ -isothiocyanato ester **2**; this result is possibly due to the severe steric hindrance in the construction of vicinal tetrasubstituted carbon stereocenters.<sup>[13]</sup> Further optimization studies, such as ligand modifications to overcome the severe steric hindrance, and expansion of the scope of the ketimines as well as  $\alpha$ -isothiocyanato esters, are ongoing.

Investigations to obtain a preliminary insight into the structural differences of the two catalysts by using  $^1\text{H}$  NMR spectroscopy failed. The  $^1\text{H}$  NMR spectra of the  $\text{Bu}_2\text{Mg}/\mathbf{1b}$  (1:1) complex and the  $\text{Sr}(\text{O-}i\text{Pr})_2/\mathbf{1b}$  (1:1) complex were complicated, which is possibly due to the oligomeric structures of the catalysts.<sup>[14]</sup> Circular dichroism (CD) spectra of the  $\text{Bu}_2\text{Mg}/\mathbf{1b}$  (1:1) complex and the  $\text{Sr}(\text{O-}i\text{Pr})_2/\mathbf{1b}$  (1:1) complex provided an insight into the differences between the aggregates of the two catalysts (Figure 2).<sup>[15]</sup> The CD spectrum of Schiff base **1b** was clearly different from those of  $\text{Mg}/\mathbf{1b}$  and  $\text{Sr}/\mathbf{1b}$ , thus suggesting that a chiroptically different aggregate was formed in each metal/**1b** solution. In addition, clear differences between  $\text{Mg}/\mathbf{1b}$  and  $\text{Sr}/\mathbf{1b}$  in the 210–250 nm region can be ascribed to the difference in the dihedral angle of the binaphthyl unit in  $\text{Mg}/\mathbf{1b}$  and  $\text{Sr}/\mathbf{1b}$ .

**Table 2:** Stereodivergent direct catalytic asymmetric Mannich-type reaction of  $\alpha$ -methyl- $\alpha$ -isothiocyanato ester **2** to ketimines **3**.<sup>[a]</sup>

									
Entry	Cat.	R	<b>3</b>	T [ $^{\circ}\text{C}$ ]	t [h]	Yield <sup>[e]</sup> [%]	d.r. <sup>[f]</sup> <i>syn/anti</i>	<b>4</b>	<i>ee</i> <sup>[g]</sup> [%]
1 <sup>[b]</sup>	Sr	4-BrC <sub>6</sub> H <sub>4</sub>	<b>3a</b>	RT	48	86	6:94	<i>anti-4a</i>	92
2 <sup>[b]</sup>	Sr	4-ClC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	RT	48	82	10:90	<i>anti-4b</i>	87
3 <sup>[b]</sup>	Sr	4-FC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	RT	48	71	6:94	<i>anti-4c</i>	90
4 <sup>[b]</sup>	Sr	4-FC <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3d</b>	RT	48	85	11:89	<i>anti-4d</i>	92
5 <sup>[c]</sup>	Sr	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3e</b>	RT	20	97	6:94	<i>anti-4e</i>	95
6 <sup>[c]</sup>	Sr	3-MeC <sub>6</sub> H <sub>4</sub>	<b>3f</b>	RT	24	99	8:92	<i>anti-4f</i>	93
7 <sup>[c]</sup>	Sr	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>3g</b>	RT	24	91	4:96	<i>anti-4g</i>	97
8 <sup>[c]</sup>	Sr	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<b>3h</b>	RT	69	45	4:96	<i>anti-4h</i>	97
9 <sup>[c]</sup>	Sr		<b>3i</b>	$-5^{\circ}\text{C}$	47	76	6:94	<i>anti-4i</i>	95
10 <sup>[c]</sup>	Sr	2-thienyl	<b>3j</b>	0	48	70	13:87	<i>anti-4j</i>	90
11 <sup>[c]</sup>	Sr	3-thienyl	<b>3k</b>	$-5^{\circ}\text{C}$	48	74	12:88	<i>anti-4k</i>	92
12 <sup>[c]</sup>	Sr	2-furyl	<b>3l</b>	$-10^{\circ}\text{C}$	48	84	17:83	<i>anti-4l</i>	84
13 <sup>[b]</sup>	Mg	4-BrC <sub>6</sub> H <sub>4</sub>	<b>3a</b>	$-10^{\circ}\text{C}$	48	87	91:9	<i>syn-4a</i>	84
14 <sup>[b]</sup>	Mg	4-ClC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	$-10^{\circ}\text{C}$	48	90	92:8	<i>syn-4b</i>	85
15 <sup>[b]</sup>	Mg	4-FC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	0	44	96	93:7	<i>syn-4c</i>	84
16 <sup>[d]</sup>	Mg	3-MeC <sub>6</sub> H <sub>4</sub>	<b>3f</b>	$-25^{\circ}\text{C}$	48	99	90:10	<i>syn-4f</i>	82
17 <sup>[d]</sup>	Mg		<b>3i</b>	$-5^{\circ}\text{C}$	17	96	92:8	<i>syn-4i</i>	81
18 <sup>[b]</sup>	Mg	2-naphthyl	<b>3m</b>	0	48	99	93:7	<i>syn-4m</i>	95
19 <sup>[d]</sup>	Mg	3-thienyl	<b>3k</b>	$-25^{\circ}\text{C}$	48	80	93:7	<i>syn-4k</i>	81
20 <sup>[b]</sup>	Mg	2-furyl	<b>3l</b>	$-5^{\circ}\text{C}$	48	70	93:7	<i>syn-4l</i>	80

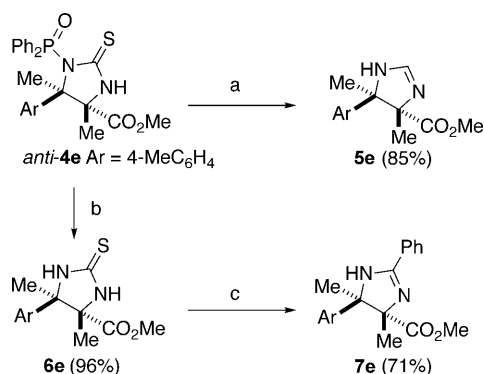
[a] Reaction conditions: ketimine **3** (1.0 mmol), **2** (2.0 equiv),  $\text{Sr}(\text{O-}i\text{Pr})_2$  (10 mol%; entries 1–12) or  $\text{Bu}_2\text{Mg}$  (10 mol%; entries 13–20), (*R*)-Schiff base **1b** (10 mol%), molecular sieves (5 Å; 200 mg). [b] The reaction was run in  $\text{CHCl}_3$  (0.2 M). [c] The reaction was run in  $\text{CHCl}_3/\text{THF}$  (2:1; 0.17 M). [d] The reaction was run in THF (0.2 M). [e] The yield of **4** after isolation and purification by column chromatography on silica gel. The yield of (*syn-4* + *anti-4*) is shown. [f] Determined by  $^1\text{H}$  NMR analysis of the crude mixture. [g] Determined by HPLC analysis on a chiral stationary phase. The enantiomeric excess of *anti-4* is shown in entries 1–12 and that of *syn-4* is shown in entries 13–20.



**Figure 2.** CD spectra of a) Schiff base **1b** (black line), b)  $\text{Bu}_2\text{Mg}/\mathbf{1b}$  (1:1; blue line), and c)  $\text{Sr}(\text{O}-i\text{Pr})_2/\mathbf{1b}$  (1:1 in THF without stabilizer; red line).

**1b**.<sup>[16]</sup> Because the dihedral angle of the binaphthyl unit often plays a key role in the stereodiscriminating step of asymmetric reactions,<sup>[17]</sup> we believe that the difference in the dihedral angles would cause the observed switch in diastereoselectivity.<sup>[18]</sup> Further studies to elucidate the precise structures of the  $\text{Mg}/\mathbf{1b}$  and  $\text{Sr}/\mathbf{1b}$  catalysts are ongoing.

To demonstrate the synthetic utility of the protected  $\alpha,\beta$ -diamino esters **4**, transformations that utilize the unique cyclic thiourea unit were investigated. Treatment of *anti*-**4e** with Raney Ni in MeOH gave the desulfurated adduct **5e** in an 85% yield (Scheme 1). Because the 2-aryl-substituted imidazolines are useful in the field of medicinal chemistry for the design of Nutlin analogues as potent antitumor agents,<sup>[19]</sup> the direct desulfurative cross-coupling reaction of a cyclic thiourea to 2-aryl imidazoline was also investigated. After removal of the diphenylphosphinoyl group in **4e** using  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$  (96% yield), a palladium-catalyzed cross-coupling reaction of **6e** with  $\text{PhB}(\text{OH})_2$  proceeded in the presence of excess copper(thiophen-2-carboxylate) in DMF under microwave irradiation (130°C, 1 h)<sup>[20]</sup> to give the 2-



**Scheme 1.** Transformation of the Mannich adduct into imidazolines:

a) Raney Ni, MeOH,  $\text{H}_2$  (1 atm), 60°C, 22 h, 85% yield; b)  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$ , toluene, RT, 4 h, 96% yield; c)  $\text{PhB}(\text{OH})_2$ , CuTC (3 equiv),  $[\text{Pd}(\text{PPh}_3)_4]$  (10 mol%), DMF, microwave, 130°C, 1 h, 71% yield. Cp = cyclopentadienyl, DMF = *N,N'*-dimethylformamide, TC = thiophen-2-carboxylate.

phenyl-imidazoline **7e**, which contains vicinal tetrasubstituted carbon stereocenters, in a 71% yield.

In summary, we developed a stereodivergent direct catalytic asymmetric Mannich-type reaction of the  $\alpha$ -methyl- $\alpha$ -isothiocyanato ester **2** with aryl or heteroaryl methyl ketimines, in which access to both diastereomers is achieved by a switch in the metal source.  $\text{Sr}(\text{O}-i\text{Pr})_2/\mathbf{1b}$  gave *anti* adducts in 84–97% *ee* and 17:83–4:96 d.r. (*syn/anti*), and the  $\text{Bu}_2\text{Mg}/\mathbf{1b}$  gave *syn* adducts in 80–95% *ee* and 90:10–93:7 d.r. (*syn/anti*). Further studies to expand the range of ketimines and  $\alpha$ -isothiocyanato esters are ongoing.

Received: February 10, 2011

Published online: April 11, 2011

**Keywords:** alkaline earth metals · asymmetric synthesis · homogeneous catalysis · Mannich reaction

- [1] For a general review on synthesis and biological significance of  $\alpha,\beta$ -diamino acids, see: A. Viso, R. Fernández de la Pradilla, A. García, A. Flores, *Chem. Rev.* **2005**, *105*, 3167.
- [2] For a review on Mannich-type reactions for the synthesis of  $\alpha,\beta$ -diamino acids, see: a) R. Gómez Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940; for a general review on the catalytic asymmetric synthesis of  $\beta$ -amino acids, see: b) B. Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656.
- [3] For reviews, see: a) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517; b) Y. Ohfuné, T. Shinada, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115.
- [4] J. Hernández-Toribio, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 16150.
- [5] a) A. Singh, J. N. Johnston, *J. Am. Chem. Soc.* **2008**, *130*, 5866; b) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170; c) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 10878; d) B. Han, Q.-P. Liu, R. Li, X. Tian, X.-F. Xiong, J.-G. Deng, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 8094; e) A. Puglisi, L. Raimondi, M. Benaglia, M. Bonsignore, S. Rossi, *Tetrahedron Lett.* **2009**, *50*, 4340; f) D. Uraguchi, K. Koshimoto, C. Sanada, T. Ooi, *Tetrahedron: Asymmetry* **2010**, *21*, 1189; for the reaction with an  $\alpha$ -imino ester, see: g) K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362.
- [6] a) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088; b) X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 876; for related work, see: c) D. Uraguchi, K. Koshimoto, T. Ooi, *Chem. Commun.* **2010**, *46*, 300.
- [7] For other related works on catalytic asymmetric Mannich-type reactions towards the synthesis of  $\alpha,\beta$ -diamino acids bearing vicinal trisubstituted carbon centers, see the review in Ref. [2a] and references therein.
- [8] T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 17082.
- [9] For related reports on the Mannich-type reaction of aldimines with  $\alpha$ -isothiocyanato imides for the synthesis of  $\alpha,\beta$ -diamino acids bearing vicinal trisubstituted carbon centers, see: a) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632; b) L. Li, M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648; c) Z. Shi, P. Yu, P. J. Chua, G. Zhong, *Adv. Synth. Catal.* **2009**, *351*, 2797; d) X. Chen, S. Dong, Z. Qiao, Y. Zhu, M. Xie, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 2583.
- [10] Magnesium alkoxides resulted in much lower reactivity than  $\text{Bu}_2\text{Mg}$ , possibly because of their poor solubility.

- [11] For the use of  $\text{Sr}(\text{O}i\text{Pr})_2$  in other catalytic asymmetric reactions, see: a) M. Agostinho, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 2430; b) H. Van Nguyen, R. Matsubara, S. Kobayashi, *Angew. Chem.* **2009**, *121*, 6041; *Angew. Chem. Int. Ed.* **2009**, *48*, 5927; c) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 8862.
- [12] CCDC 812101 (*syn*-**6b**) and 812102 (*anti*-**4h**) contain 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](http://www.ccdc.cam.ac.uk/data_request/cif).
- [13] The reaction of ketimines **3e** with  $\alpha$ -ethyl- $\alpha$ -isothiocyanato ester using the  $\text{Sr}/\mathbf{1b}$  catalyst (10 mol %) gave the product in 33 % yield, 15:85 (*syn/anti*), and 57 % *ee* after 24 h at RT.
- [14] ESI-MS analysis also failed to provide useful information on the oligomeric structures of  $\text{Mg}/\mathbf{1b}$  and  $\text{Sr}/\mathbf{1b}$ .
- [15] Because Schiff base **1b** in the absence of a metal source was relatively unstable in  $\text{CHCl}_3$  and gradually decomposed, THF (without stabilizer) was used for the CD analysis. THF was also used as the solvent, and showed similar diastereoselectivity.
- [16] For detailed conformational studies of binaphthyl compounds and the assessment of the dihedral angle in the solution phase using CD analysis, see: a) C. Rosini, S. Superchi, H. W. I. Peerlings, E. W. Meijer, *Eur. J. Org. Chem.* **2000**, 61; b) L. Di Bari, G. Pescitelli, P. Salvadori, *J. Am. Chem. Soc.* **1999**, *121*, 7998; c) S. F. Mason, R. H. Seal, D. R. Roberts, *Tetrahedron* **1974**, *30*, 1671; for the CD analysis of oligonaphthalenes, see: d) K. Takaishi, M. Kawamoto, K. Tsubaki, *Org. Lett.* **2010**, *12*, 1832, and references therein.
- [17] For selected examples of asymmetric reactions catalyzed by metal/biaryl ligand complexes, see: a) K. Mikami, Y. Motoyama, M. Terada, *Inorg. Chim. Acta* **1994**, *222*, 71; b) T. Harada, M. Takeuchi, M. Hatsuda, S. Ueda, A. Oku, *Tetrahedron: Asymmetry* **1996**, *7*, 2479; c) Z. Zhang, H. Qian, J. Longmire, X. Zhang, *J. Org. Chem.* **2000**, *65*, 6223; d) T. T.-L. Au-Yeung, S.-S. Chan, A. S. C. Chan, *Adv. Synth. Catal.* **2003**, *345*, 537; e) Y. Xu, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 3403; *Angew. Chem. Int. Ed.* **2009**, *48*, 3353.
- [18] For a related example of metal dependent diastereo-switching using the same chiral ligand and based on a change in aggregation, see: A. Nojiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 3779.
- [19] For a review, see: a) L. Römer, C. Klein, A. Dehner, H. Kessler, J. Buchner, *Angew. Chem.* **2006**, *118*, 6590; *Angew. Chem. Int. Ed.* **2006**, *45*, 6440; see also: b) L. T. Vassilev, B. T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammlott, C. Lukacs, C. Klein, N. Fotouhi, E. A. Liu, *Science* **2004**, *303*, 844; c) C. Tovar, J. Rosinski, Z. Filipovic, B. Higgins, K. Kolinsky, H. Hilton, X. Zhao, B. T. Vu, W. Qing, K. Packman, O. Myklebost, D. C. Heimbrosk, L. T. Vassilev, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1888.
- [20] a) R. S. Bon, N. E. Sprengels, M. M. Koningstein, R. F. Schmitz, F. J. J. de Kanter, A. Dömling, M. B. Groen, R. V. A. Orru, *Org. Biomol. Chem.* **2008**, *6*, 130; b) C. L. Kusturin, L. S. Liebeskind, W. L. Neumann, *Org. Lett.* **2002**, *4*, 983; c) A. Lengar, C. O. Kappe, *Org. Lett.* **2004**, *6*, 771.