Asymmetric Synthesis

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Stereodivergent Direct Catalytic Asymmetric Mannich-Type Reactions of α-Isothiocyanato Ester with Ketimines**

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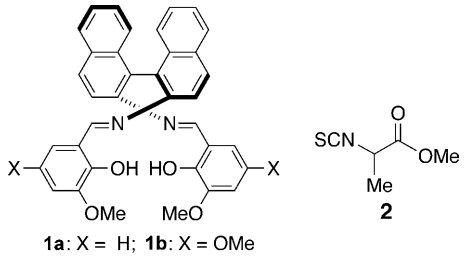
Chiral α,β-diamino acids are key structural motifs in many biologically active compounds.[1] Catalytic asymmetric direct Mannich-type reactions of aldimines and nucleophiles, which contain an α-amino equivalent unit, provide straightforward access to chiral α,β-diamino acids.[2] Unnatural amino acids that contain tetrasubstituted carbon centers are useful chiral building blocks for the synthesis of pharmaceuticals, and artificial peptides with distinctive chemical and biological properties.[3] Several research groups including ours, have reported Mannich-type reactions of aldimines with α-substituted donors, such as an alanine methyl ester Schiff base,[4] α-substituted nitroacetates,[5] and α-substituted oxazolones,[6] for the synthesis of α,β-diamino acid surrogates bearing an α-tetrasubstituted carbon center.[7] In contrast, there are no reports of the catalytic asymmetric synthesis of β-tetrasubstituted chiral α,β-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 α,β-tetrasubstituted α,β-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 α-methyl-α-isothiocyanato ester **2** with ketimines **3** (see Table 1), thus providing stereodivergent access to α,β-diamino esters with vicinal tetrasubstituted carbon stereocenters.

We have previously reported the direct asymmetric aldol reaction of α-methyl-α-isothiocyanato ester **2** with ketones, catalyzed by Bu_2Mg/Schiff base **1a**.[8] Therefore, we initially utilized Bu_2Mg/**1a** for the reaction of **2** with ketimines.[9]



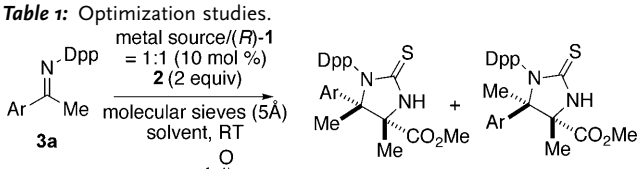
1a: X = H; **1b**: X = OMe

2

Figure 1. Structures of Schiff bases **1a** and **1b** and α-methyl-α-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 Bu_2Mg/**1a** (10 mol%) promoted the 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, $CHCl_3$ 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-

Table 1: Optimization studies.



syn-**4a** *anti*-**4a**

Entry	Metal source	(*R*)-**1**	Solvent	*t* [h]	Yield[a]	d.r. *syn*/*anti*	*ee* [%][b] (*syn*)
1	Bu_2Mg	**1a**	THF	47	>95	68:32	44
2	Bu_2Mg	**1b**	THF	28	>95	71:29	67
3	Bu_2Mg	**1b**	$CHCl_3$	20	>95	86:14	80
4[c]	Bu_2Mg	**1b**	$CHCl_3$	48	87[d]	91:9	84
5	$Ca(O\text{-}iPr)_2$	**1b**	$CHCl_3$	48	trace	n.d.	n.d.
6	$Sr(O\text{-}iPr)_2$	**1b**	$CHCl_3$	48	86[d]	6:94	92[e]
7	$Ba(O\text{-}iPr)_2$	**1b**	$CHCl_3$	48	trace	n.d.	n.d.

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction was run at −10°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.

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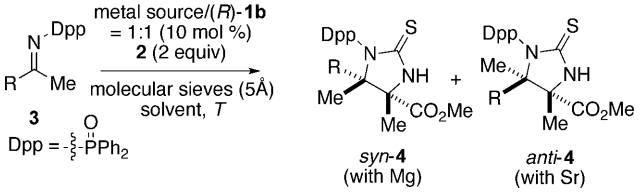
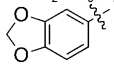
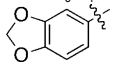
tivity (*syn*/*anti* = 91:9) and enantioselectivity (84% *ee*) were obtained at −10°C (Table 1, entry 4). In entries 5–7, other group 2 metals were utilized.[10,11] Although $Ca(O\text{-}iPr)_2$ and $Ba(O\text{-}iPr)_2$ gave poor results, $Sr(O\text{-}iPr)_2$ gave **4a** in an 86% yield (Table 1, entry 6). In addition, the use of $Sr(O\text{-}iPr)_2$/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).[12] The enantiofacial selectivity of the reaction of the ketimines (**3**) catalyzed by Sr/**1b** was opposite to that of the reaction catalyzed by Mg/**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°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 Sr/**1b** and Mg/**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 α-ethyl-α-isothiocyanato ester also showed much lower reactivity and stereoselectivity than the α-methyl-α-isothiocyanato ester **2**; this result is possibly due to the severe steric hindrance in the construction of vicinal tetrasubstituted carbon stereocenters.[13] Further optimization studies, such as ligand modifications to overcome the severe steric hindrance, and expansion of the scope of the ketimines as well as α-isothiocyanato esters, are ongoing.

Investigations to obtain a preliminary insight into the structural differences of the two catalysts by using ^{1}H NMR spectroscopy failed. The ^{1}H NMR spectra of the Bu_2Mg/**1b** (1:1) complex and the $Sr(O\text{-}iPr)_2$/**1b** (1:1) complex were complicated, which is possibly due to the oligomeric structures of the catalysts.[14] Circular dichroism (CD) spectra of the Bu_2Mg/**1b** (1:1) complex and the $Sr(O\text{-}iPr)_2$/**1b** (1:1) complex provided an insight into the differences between the aggregates of the two catalysts (Figure 2).[15] The CD spectrum of Schiff base **1b** was clearly different from those of Mg/**1b** and Sr/**1b**, thus suggesting that a chiroptically different aggregate was formed in each metal/**1b** solution. In addition, clear differences between Mg/**1b** and Sr/**1b** in the 210–250 nm region can be ascribed to the difference in the dihedral angle of the binaphthyl unit in Mg/**1b** and Sr/

Table 2: Stereodivergent direct catalytic asymmetric Mannich-type reaction of α-methyl-α-isothiocyanato ester **2** to ketimines **3**.[a]



Entry	Cat.	R	3	*T* [°C]	*t* [h]	Yield[e] [%]	d.r.[f] *syn*/*anti*	4	*ee*[g] [%]
1[b]	Sr	4-BrC_6H_4	**3a**	RT	48	86	6:94	*anti*-**4a**	92
2[b]	Sr	4-ClC_6H_4	**3b**	RT	48	82	10:90	*anti*-**4b**	87
3[b]	Sr	4-FC_6H_4	**3c**	RT	48	71	6:94	*anti*-**4c**	90
4[b]	Sr	4-$CF_3C_6H_4$	**3d**	RT	48	85	11:89	*anti*-**4d**	92
5[c]	Sr	4-MeC_6H_4	**3e**	RT	20	97	6:94	*anti*-**4e**	95
6[c]	Sr	3-MeC_6H_4	**3f**	RT	24	99	8:92	*anti*-**4f**	93
7[c]	Sr	4-$MeOC_6H_4$	**3g**	RT	24	91	4:96	*anti*-**4g**	97
8[c]	Sr	4-$Me_2NC_6H_4$	**3h**	RT	69	45	4:96	*anti*-**4h**	97
9[c]	Sr		**3i**	−5	47	76	6:94	*anti*-**4i**	95
10[c]	Sr	2-thienyl	**3j**	0	48	70	13:87	*anti*-**4j**	90
11[c]	Sr	3-thienyl	**3k**	−5	48	74	12:88	*anti*-**4k**	92
12[c]	Sr	2-furyl	**3l**	−10	48	84	17:83	*anti*-**4l**	84
13[b]	Mg	4-BrC_6H_4	**3a**	−10	48	87	91:9	*syn*-**4a**	84
14[b]	Mg	4-ClC_6H_4	**3b**	−10	48	90	92:8	*syn*-**4b**	85
15[b]	Mg	4-FC_6H_4	**3c**	0	44	96	93:7	*syn*-**4c**	84
16[d]	Mg	3-MeC_6H_4	**3f**	−25	48	99	90:10	*syn*-**4f**	82
17[d]	Mg		**3i**	−5	17	96	92:8	*syn*-**4i**	81
18[b]	Mg	2-naphthyl	**3m**	0	48	99	93:7	*syn*-**4m**	95
19[d]	Mg	3-thienyl	**3k**	−25	48	80	93:7	*syn*-**4k**	81
20[b]	Mg	2-furyl	**3l**	−5	48	70	93:7	*syn*-**4l**	80

[a] Reaction conditions: ketimine **3** (1.0 mmol), **2** (2.0 equiv), $Sr(O\text{-}iPr)_2$ (10 mol%; entries 1–12) or Bu_2Mg (10 mol%; entries 13–20), (*R*)-Schiff base **1b** (10 mol%), molecular sieves (5 Å; 200 mg). [b] The reaction was run in $CHCl_3$ (0.2 M). [c] The reaction was run in $CHCl_3$/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}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.

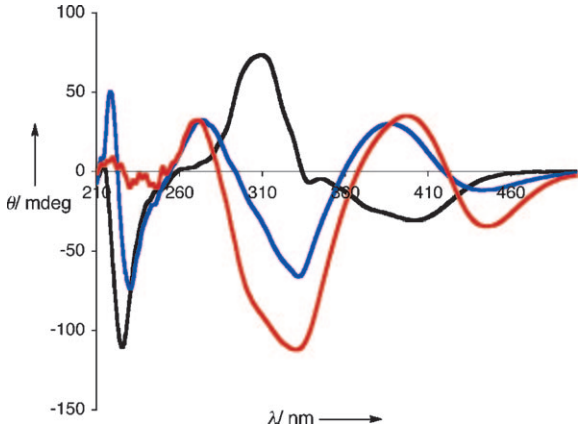
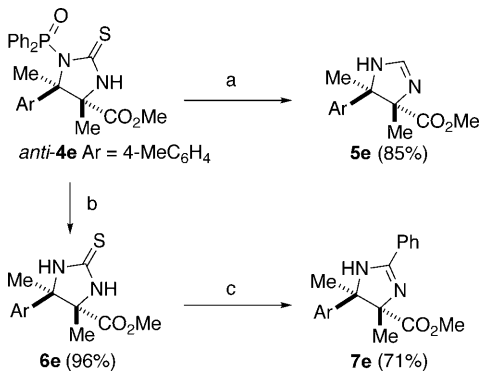


Figure 2. CD spectra of a) Schiff base **1b** (black line), b) Bu_2Mg/**1b** (1:1; blue line), and c) Sr(O-*i*Pr)$_2$/**1b** (1:1 in THF without stabilizer; red line).

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

To demonstrate the synthetic utility of the protected α,β-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,[19] 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 [$Cp_2Zr(H)Cl$] (96% yield), a palladium-catalyzed cross-coupling reaction of **6e** with $PhB(OH)_2$ proceeded in the presence of excess copper(thiophen-2-carboxylate) in DMF under microwave irradiation (130 °C, 1 h)[20] to give the 2-phenyl-imidazoline **7e**, which contains vicinal tetrasubstituted carbon stereocenters, in a 71% yield.



Scheme 1. Transformation of the Mannich adduct into imidazolines: a) Raney Ni, MeOH, H_2 (1 atm), 60 °C, 22 h, 85% yield; b) [$Cp_2Zr(H)Cl$], toluene, RT, 4 h, 96% yield; c) $PhB(OH)_2$, CuTC (3 equiv), [$Pd(PPh_3)_4$] (10 mol%), DMF, microwave, 130 °C, 1 h, 71% yield. Cp = cyclopentadienyl, DMF = *N*,*N*′-dimethylformamide, TC = thiophen-2-carboxylate.

In summary, we developed a stereodivergent direct catalytic asymmetric Mannich-type reaction of the α-methyl-α-isothiocyanato ester **2** with aryl or heteroaryl methyl ketimines, in which access to both diastereomers is achieved by a switch in the metal source. Sr(O-*i*Pr)$_2$/**1b** gave *anti* adducts in 84–97% *ee* and 17:83–4:96 d.r. (*syn*/*anti*), and the Bu_2Mg/**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 α-isothiocyanato esters are ongoing.

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[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.

[13] The reaction of ketimines **3e** with α-ethyl-α-isothiocyanato ester using the Sr/**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 Mg/**1b** and Sr/**1b**.

[15] Because Schiff base **1b** in the absence of a metal source was relatively unstable in $CHCl_3$ and gradually decomposed, THF (without stabilizer) was used for the CD analysis. THF was also used as the solvent, and showed similar diastereoselectivity.

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