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Construction of Contiguous Tetrasubstituted Chiral Carbon Stereocenters via Direct Catalytic Asymmetric Aldol and Mannich-Type Reactions

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ABSTRACT: Catalytic asymmetric synthesis of unnatural amino acids with vicinal tetrasubstituted chiral carbon stereocenters is described. In the first part, direct catalytic asymmetric aldol reaction of simple non-activated ketone electrophiles with α-substituted α-isothiocyanato ester donors was realized. A Mg/Schiff base catalyst promoted the aldol reaction, and α-amino-β-hydroxy esters were obtained in up to 98% *ee* and 98:2 d.r. In the second part, the Mg/Schiff base catalyst and a Sr/Schiff base catalyst were utilized for stereodivergent direct asymmetric Mannich-type reaction of ketimines. The Mg/Schiff base catalyst gave *syn*-α,β-diamino esters, while the Sr/Schiff base catalyst produced *anti*-α,β-diamino esters in good to high enantioselectivity, up to 97% *ee*. **DOI 10.1002/tcr.201100020**

Keywords: amino acids, aldol reaction, asymmetric synthesis, bifunctional catalysts, Mannich reaction

Introduction

Catalytic asymmetric aldol reaction and Mannich-type reaction are powerful methods for synthesizing chiral β-hydroxy carbonyl compounds and β-amino carbonyl compounds.[1,2] Among them, the "direct" variants provide atom-economical processes over conventional Mukaiyama-type reactions, because the reaction proceeds under simple proton transfer conditions via catalytic in situ enolate formation.[3] Tremendous progress has been achieved in the direct aldol and Mannich-type reactions in the past decade, and many chiral metal catalysts and organocatalysts have been developed for reactions of aldehyde and aldimine electrophiles.[4,5] The authors, in collaboration with Prof. M. Shibasaki, have also reported various bifunctional acid/base asymmetric metal catalysts for those reactions.[6] Representative catalysts developed in our group are shown in Figure 1, namely, a trinulcear Zn/linked-BINOL catalyst,[7] linked-BINOL-catalysts using either In(O-*i*Pr)$_3$, Y{N(SiMe$_3$)$_2$}$_3$, or La(O-*i*Pr)$_3$,[8] a heterobimetallic La/Li/Pybox catalyst,[9] a Ba(O-*i*Pr)$_2$/BINOL catalyst,[10] dinuclear Ni$_2$-Schiff base catalysts,[11] and others. In these bifunctional metal catalyst systems, metal aryloxide moieties function as a Brønsted base to deprotonate the α-proton to generate metal enolate species in situ. Lewis acidic metal center also played key roles for activating electrophiles and controlling their orientation, leading to high enantio- and diastereoselectivity.

Despite intensive investigations on direct aldol and Mannich-type reactions in the past decade, the use of ketone and/or ketimine electrophiles in the direct reactions for constructing tetrasubstituted carbon stereocenters is still limited to either activated ketones, such as α-keto esters, α-keto phosphonates, isatins, and their aza-analogues, or intramolecular direct

aldol reactions with limited examples.[4,5] Intermolecular direct aldol reaction of simple non-activated ketones and Mannich-type reaction of ketimines derived from simple ketones are still formidable tasks.[12] Thus, the development of new catalysts for realizing direct aldol reaction of ketone electrophiles and Mannich-type reaction of ketimine electrophiles is highly desirable. Moreover, catalytic asymmetric construction of vicinal tetrasubstituted chiral carbon stereocenters in carbon-carbon bond-forming reactions is rare,[13] possibly owing to severe steric hindrance. In this account, we describe our efforts to address these issues. Group 2 metal/Schiff base **1** complexes (Figure 2) promoted a direct aldol reaction of simple ketone electrophiles and a Mannich-type reaction of ketimines with α-substituted α-isothiocyanate esters **2**, leading to unnatural amino acids with vicinal tetrasubstituted carbon stereocenters.[14]

Intermolecular Direct Catalytic Asymmetric Aldol Reaction of Ketone Electrophiles

Although catalytic asymmetric intermolecular aldol reactions with simple non-activated ketone electrophiles have been achieved using either preformed silyl enolates[15] or in situ generated enolates with stoichiometric amounts of reducing reagents, i.e. reductive aldol reactions,[16] a direct catalytic asymmetric intermolecular aldol reaction of simple non-activated ketone electrophiles under proton transfer conditions has not been achieved. The direct intermolecular aldol reaction of non-activated ketone electrophiles is difficult due to the small equilibrium constants for ketone electrophiles in comparison with those of aldehyde electrophiles (Scheme 1a vs. Scheme 1b). For example, the equilibrium constant for the aldol reaction of benzaldehyde as an electrophile and acetone as a donor is 11.7 M^{-1}, while that of acetophenone as an electrophile and acetone as a donor is 1.89×10^{-3} M^{-1}.[17] Therefore, rapid retroaldol reaction of tertiary aldols was observed under basic conditions even at −78 °C.[18] To overcome the inherent instability of the tertiary aldols from ketone electrophiles under basic conditions and to obtain products under kinetic control, we hypothesized that irreversibly trapping the unstable tertiary aldols in situ is important to produce more stable adducts. On the basis of pioneering works by Ito and co-workers on direct catalytic asymmetric aldol reaction of aldehydes with

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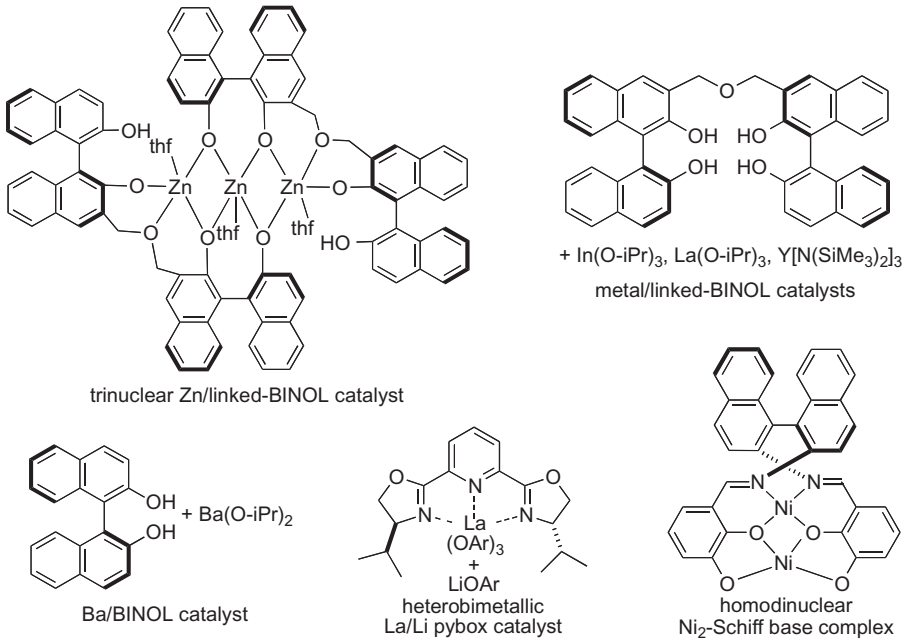


Fig. 1. Representative acid/base bifunctional metal catalysts developed in our group for direct aldol reactions of aldehydes and Mannich-type reactions of aldimines.

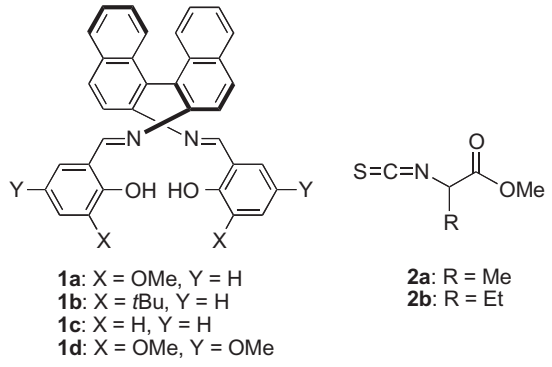
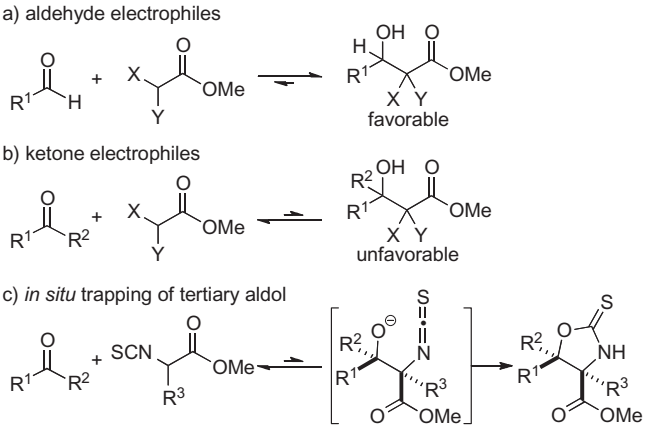


Fig. 2. Structures of Schiff bases **1a**-**1d** and α-substituted α-isothiocyanato esters **2**.

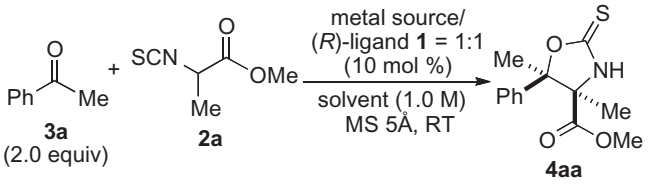


Scheme 1. In situ trapping strategy to obtain aldol-type adducts from ketone electrophiles.

α-isocyano esters[19] and closely related recent works by Willis, Seidel, and Feng using α-isothiocyanato imides and aldehyde electrophiles,[20,21] we selected α-isocyano esters and α-isothiocyanato esters as donors. For the challenging construction of vicinal tetrasubstituted carbon stereocenters, α-methyl substituted donors were used in the initial screening. As shown in Scheme 1c, we anticipated that thermodynamically unfavorable tertiary aldol adduct can be rapidly trapped in intramolecular fashion to afford protected unnatural α-amino-β-hydroxy acids.

Although α-isocyano esters did not afford promising results in terms of both yield and stereoselectivity, α-methyl α-isothiocyanato ester **2a** showed good reactivity towards ketone electrophiles. As a part of our ongoing project on bifunctional Schiff base catalysis,[22–25] we screened various metal/Schiff base complexes. Bimetallic Schiff base catalysts,[23,24] which often showed superior stereoselectivity and reactivity to monometallic Schiff base catalysts, did not afford satisfactory results for the present aldol reaction. Instead, a 1:1 mixture of Bu_2Mg and Schiff base **1a** (Figure 2) derived from vanillin and binaphthyldiamine gave promising reactivity, enantioselectivity, and diastereoselectivity (Table 1, entry 1, >95% yield, 93:7 d.r., and 95% *ee*). In contrast, Schiff base **1b** bearing *tert*-butyl substituents, which is often used as a most effective ligand in

Table 1. Optimization studies of direct aldol reaction of acetophenone and α-isothiocyanato ester.



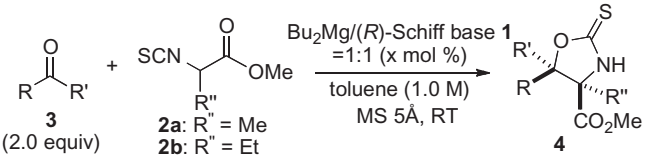
entry	metal source	ligand	solvent	time [h]	% yield[a]	d.r.[a]	% *ee*
1	Bu_2Mg	**1a**	THF	43	>95	93:7	95
2	Bu_2Mg	**1b**	THF	43	13	52:48	0
3	Bu_2Mg	**1c**	THF	43	>95	68:32	10[c]
4	Et_2Zn	**1a**	THF	43	0	—	—
5	$Ba(OiPr)_2$	**1a**	THF	43	>95	38:62	21[c]
6	$La(OiPr)_3$	**1a**	THF	43	90	75:25	14[c]
7	Bu_2Mg	**1a**	toluene	36	97[b]	97:3	97

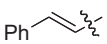
[a]Determined by ^{1}H NMR analysis of the crude mixture. [b]Isolated yield after purification by column chromatography. [c]*ent*-**4aa** was obtained as the major product.

metal/salen chiral catalysts, resulted in poor reactivity and selectivity (entry 2). Schiff base **1c** without a substituent showed good reactivity, but resulted in poor stereoselectivity (entry 3, 10% *ee*). Thus, the methoxy groups in Schiff base **1a** are essential for the present reaction. The ^{1}H NMR spectrum of the Bu_2Mg/Schiff base **1a** was quite complicated, which is possibly due to the oligomeric structure of the catalyst. ESI-MS analysis also supported the oligomeric nature of the Mg catalyst. The chelating *ortho*-methoxy group would play a key role to enhance the oligomeric Mg/Schiff base = *n*:*n* complex formation rather than a standard 1:1 complex. Other metal sources, such as Et_2Zn, $Ba(O\text{-}iPr)_2$, and $La(O\text{-}iPr)_3$ which we previously utilized in direct aldol and Mannich-type reactions,[7–10] also resulted in poor stereoselectivity or reactivity (entries 4–6). Among the solvents screened, the best diastereoselectivity and enantioselectivity were observed in toluene, giving product **4aa** in 97% yield, 97:3 d.r., and 97% *ee* (entry 7).

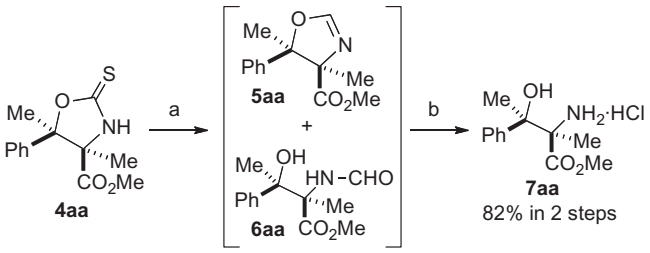
The substrate scope of the reaction is summarized in Table 2. The Bu_2Mg/Schiff base **1a** complex promoted the addition of α-isothiocyanato ester **2a** to aryl and heteroaryl methyl ketones (entries 1–10). The reaction proceeded even with 2.5 mol % catalyst loading, while maintaining high yield, d.r., and enantioselectivity (entry 2). A longer reaction time

Table 2. Bu_2Mg/Schiff base-catalyzed direct asymmetric aldol reaction of ketone eletrophiles with α-substituted α-isothiocyanato esters **2**.



entry	ketone:**3** R	ketone:**3** R′	**2**		ligand **1** [x mol %]	time [h]	**4**	% yield[a]	d.r.[b]	% *ee*
1	Ph	Me	**3a**	**2a**	**1a** (10)	36	**4aa**	97	97:3	97
2[c]	Ph	Me	**3a**	**2a**	**1a** (2.5)	69	**4aa**	95	96:4	97
3	4-Cl-C_6H_4	Me	**3b**	**2a**	**1a** (10)	36	**4ba**	89	97:3	98
4	3-Cl-C_6H_4	Me	**3c**	**2a**	**1a** (10)	48	**4ca**	99	96:4	98
5	4-Me-C_6H_4	Me	**3d**	**2a**	**1a** (10)	48	**4da**	92	95:5	95
6	3-Me-C_6H_4	Me	**3e**	**2a**	**1a** (10)	48	**4ea**	91	95:5	95
7	4-MeO-C_6H_4	Me	**3f**	**2a**	**1a** (10)	48	**4fa**	68	85:15	89
8	2-furyl	Me	**3g**	**2a**	**1a** (10)	48	**4ga**	87	86:14	97
9	3-thienyl	Me	**3h**	**2a**	**1a** (10)	48	**4ha**	93	98:2	98
10	4-pyridyl	Me	**3i**	**2a**	**1a** (10)	48	**4ia**	71	91:9	95
11	$-(CH_2)_4-$	Me	**3j**	**2a**	**1a** (20)	48	**4ja**	75	—	94
12	$PhCH_2CH_2$	Me	**3k**	**2a**	**1d** (20)	48	**4ka**	81	74:26	97
13	cyclopropyl	Me	**3l**	**2a**	**1d** (20)	48	**4la**	79	81:19	93
14		Me	**3m**	**2a**	**1d** (20)	48	**4ma**	96	78:22	96
15		Me	**3a**	**2b**	**1a** (10)	48	**4ab**	94	91:9	82
16	4-Cl-C_6H_4	Me	**3b**	**2b**	**1a** (10)	48	**4bb**	76	95:5	95
17	3-thienyl	Me	**3h**	**2b**	**1a** (10)	48	**4hb**	84	96:4	95

[a]Isolated yield based on the amount of **2** used. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Reaction was performed in toluene (2.0 M).



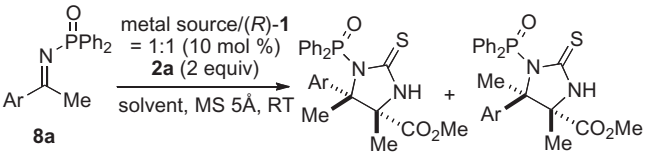
Scheme 2. Transformation of aldol adduct into α-amino-β-hydroxy ester. Reagents and conditions: a) Raney Ni, H_2 (1 atm) MeOH, 50 °C, 14 h; then silica gel column; b) conc. HCl, MeOH, 55 °C, 3 h, 82% yield (from **4aa**).

(69 h), however, was required owing to the modest catalyst turnover frequency even under highly concentrated conditions. Various acetophenone derivatives with either an electron-donating or electron-withdrawing substituent at the *para* or *meta* position of the aromatic ring gave products in good yield, d.r., and high enantioselectivity (entries 3–6, 95–98% *ee*). Compound **3f** with a 4-MeO substituent, however, resulted in a somewhat lower stereoselectivity and yield (entry 7, 89% *ee*). Heteroaryl ketones **3g**-**3i** were also applicable, giving products in 95–98% *ee* (entries 8–10). Ketones **3j**-**3m** showed lower reactivity than aryl methyl ketones, and 20 mol % of catalyst was required to obtain the products in good yield (entries 11–14). Cyclic ketone **3j** gave **4ja** in 75% yield and 94% *ee* (entry 11). For alkyl methyl ketone **3k**, the Bu_2Mg/**1a** complex resulted in poor yield (<30%). Modification of the Schiff base ligand was effective to improve yield, and a Bu_2Mg/**1d** complex gave **4ka** in 81% yield and 97% *ee* (entry 12). Because ligand **1d** with additional MeO substituents showed better reactivity for ketone **3k** than **1a**, we believe that the nucleophilicity of a Mg-enolate generated from the Bu_2Mg/**1** catalysts is important to efficiently promote the present reaction. The Bu_2Mg/**1d** complex was also applicable to ketone **3l** and alkenyl ketone **3m**, giving products in 93–96% *ee* (entries 13–14). The reaction with α-ethyl isothiocyanato ester **2b** proceeded smoothly to afford products in good yield and diastereoselectivity (76–94%, 92:8–96:4 d.r.), but the enantioselectivity somewhat decreased to 82–95% *ee* (entries 15–17). Synthetic utility of the products was demonstrated via transformation of **4aa** into α-amino-β-hydroxy ester (Scheme 2). Treatment of **4aa** with Raney Ni in MeOH gave the desulfurated adducts **5aa** and **6aa**, which were readily hydrolyzed under acidic conditions to give α-amino-β-hydroxy ester•HCl salt **7aa** in 82% yield (two steps).

Direct Catalytic Asymmetric Mannich-Type Reaction of Ketimines

Chiral α,β-diamino acids are important structural motifs found in many biologically active compounds.[26] Direct catalytic asymmetric Mannich-type reactions with donors bearing an α-amino equivalent unit provide straightforward access to chiral α,β-diamino acids.[27] For the synthesis of α,β-diamino acids bearing an α-tetrasubstituted carbon center, several groups including ours have reported Mannich-type reactions of aldimines with α,α-disubstituted donors, such as an alanine methyl ester Schiff base,[28] α-substituted nitroacetates,[11a,29] and α-substituted oxazolones.[30] In contrast, there is no report of the catalytic asymmetric Mannich-type reaction for β-tetrasubstituted α,β-diamino acid synthesis, which require the reaction with much less reactive ketimines. On the basis of successful results in direct aldol reaction of ketone electrophiles described in the previous section, we decided to expand the utility of the Mg/Schiff base **1a** catalyst for the Mannich-type reaction of ketimines.

Table 3. Optimization studies of stereodivergent direct Mannich-type reaction of ketimine and α-isothiocyanato ester.

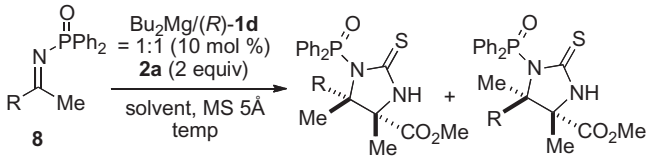


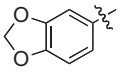
entry	metal source	(*R*)-**1**	solvent	time [h]	% yield[a]	d.r.[a] [*syn*/*anti*]	% *ee* [*syn*]
1	Bu_2Mg	**1a**	THF	47	>95	68:32	44
2	Bu_2Mg	**1d**	THF	28	>95	71:29	67
3	Bu_2Mg	**1d**	$CHCl_3$	20	>95	86:14	80
4[b]	Bu_2Mg	**1d**	$CHCl_3$	48	87[c]	91:9	84
5	$Ca(OiPr)_2$	**1d**	$CHCl_3$	48	trace	ND	ND
6	$Sa(OiPr)_2$	**1d**	$CHCl_3$	48	86[c]	6:94	92[d]
7	$Ba(OiPr)_2$	**1d**	$CHCl_3$	48	trace	ND	ND

[a]Determined by ^1H NMR analysis of the crude mixture. [b]Reaction was run at −10 °C. [c]Isolated yield after column chromatography. [d]Enantiomeric excess of *anti*-**9aa**.

Among ketimines screened, diphenylphosphinoyl (Dpp) ketimines gave promising results in terms of reactivity and selectivity. Optimization studies are summarized in Table 3. A 1:1 ratio of Bu_2Mg/Schiff base **1a** (10 mol %) promoted the addition of α-methyl α-isothiocyanato ester **2a** to ketimines **8a** to give **9aa** in >95% yield in THF at room temperature (entry 1). Diastereoselectivity and enantioselectivity were, however, moderate (*syn*/*anti* = 68:32, 44% *ee*). Schiff base **1d** with additional methoxy substituents improved the enantioselectivity to 67% *ee* (entry 2). Among the solvents screened, $CHCl_3$ gave the best selectivity, and **9aa** was obtained in 86:14 (*syn*/*anti*) diastereoselectivity and 80% *ee* at room temperature (entry 3). The best *syn* selectivity and enantioselectivity were obtained at −10 °C (entry 4, 91:9 and 84% *ee*). In entries 5–7, other Group 2 metals were screened. Although $Ca(O\text{-}iPr)_2$ and $Ba(O\text{-}iPr)_2$ gave poor results, $Sr(O\text{-}iPr)_2$ gave **9aa** in 86%

Table 4. Mg/Schiff base-catalyzed *syn*-selective direct Mannich-type reaction of ketimines.

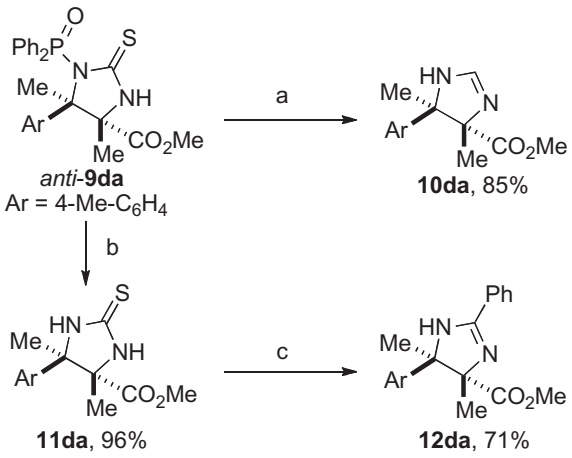


entry	R:ketimine	8	temp [°C]	time [h]	9	% yield[a]	d.r.[b] [*synlanti*]	% *ee* [*syn*]
1[c]	4-Br-C_6H_4	**8a**	−10	48	**9aa**	87	91:9	84
2[c]	4-Cl-C_6H_4	**8b**	−10	48	**9ba**	90	92:8	85
3[c]	4-F-C_6H_4	**8c**	0	44	**9ca**	96	93:7	84
4[d]	4-Me-C_6H_4	**8d**	−25	48	**9da**	94	92:8	79
5[d]	3-Me-C_6H_4	**8e**	−25	48	**9ea**	99	90:10	82
6[d]		**8f**	−5	17	**9fa**	96	92:8	81
7[c]	2-naphthyl	**8g**	0	48	**9ga**	99	93:7	95
8[d]	3-thienyl	**8h**	−25	48	**9ha**	80	93:7	81
9[c]	2-furyl	**8i**	−5	48	**9ia**	70	93:7	80

[a]Isolated yield of **9** after purification by column chromatography. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Reaction was run in $CHCl_3$ (0.2 M). [d]Reaction was run in THF (0.2 M).

isolated yield (entry 6). In addition, the use of Sr(O-*i*Pr)$_2$/Schiff base **1d** = 1:1 mixture led to an unexpected reversal of the diastereoselectivity, and the *anti* adduct was obtained in high diastereoselectivity (6:94 = *syn/anti*) and enantioselectivity (92% *ee*, *anti*-**9aa**) at room temperature.

The substrate scope of the Mg and Sr-catalyzed reaction is summarized in Tables 4 and 5. The reaction temperature and solvent were optimized for each ketimine, and the best results are listed. Various aryl and heteroaryl ketimines were applicable with the Mg/Schiff base **1d**, and products were obtained in good to high yield. Although enantioselectivity was more or less 80% *ee* (79–85% *ee*), except for ketimine **8g** (**9ga**, 95% *ee*, entry 7), high *syn* selectivity (90:10–93:7) was achieved in all cases in Table 4. The results of the Sr/Schiff base-catalyzed *anti*-selective reaction are shown in Table 5. Absolute and relative configurations of the products in Table 4 and Table 5 were unequivocally determined by X-ray crystallographic analysis, and the enantiofacial selectivity of the reaction of ketimines catalyzed by the Sr/Schiff base **1d** was opposite to that of the reaction catalyzed by the Mg/Schiff base **1d**. Aryl ketimines gave Mannich adducts with high *anti* selectivity and enantioselectivity at either room temperature or −5 °C (entries 1–9). Good yields were obtained even with ketimines bearing an electron-donating group at the *para* position, such as 4-Me-C_6H_4 imine **8d** (entry 5) and 4-MeO-C_6H_4 imine **8k** (entry 7). On the other hand, a strongly electron-donating

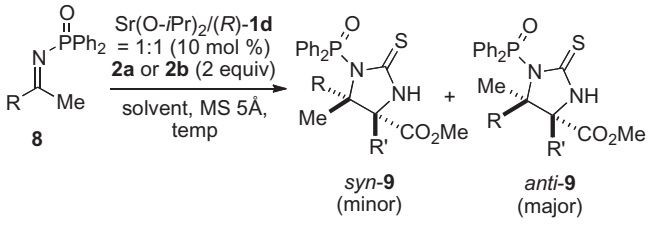


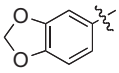
Scheme 3. Transformation of Mannich-adduct into imidazolines. Reagents and reaction conditions: a) Raney Ni, MeOH, H_2 (1 atm), 60 °C, 22 h, 85% yield; b) $Cp_2Zr(H)Cl$, toluene, RT, 4 h, 96% yield; c) $PhB(OH)_2$, CuTC (3 equiv), $Pd(PPh_3)_4$ (10 mol %), DMF, microwave, 130 °C, 1 h, 71% yield.

4-dimethylamino group had adverse effects on the reactivity, while high *anti* selectivity and enantioselectivity were maintained (entry 8, *syn/anti* = 4:96, 97% *ee*). Heteroaryl ketimines were also applicable as shown in entries 10–12. The products were obtained in 84–92% *ee*, but slightly lower *anti* selectivity was observed in comparison with aryl ketimines. Unfortunately, neither Mg nor Sr Schiff base **1d** catalyst was suitable for other types of ketimines, such as aryl ethyl ketimines and aliphatic ketimines, owing to the poor reactivity of these ketimines. The α-ethyl-α-isothiocyanato ester **2b** also showed much lower reactivity and stereoselectivity than α-methyl-α-isothiocyanato ester **2a** (Table 5, entry 5 vs. entry 13). This is possibly due to the severe steric hindrance in the construction of vicinal tetrasubstituted carbon centers from diphenylphosphinoyl ketimines. Further studies are required to overcome the steric hindrance and broaden the substrate scope of ketimines and α-isothiocyanato esters.

To show the synthetic utility of the protected α,β-diamino esters **9**, transformations that utilize the unique cyclic thiourea unit in **9** were demonstrated (Scheme 3). Treatment of *anti*-**9da** with Raney Ni in MeOH gave the desulfurated adduct **10da** in 85% yield. Because the 2-aryl-substituted imidazolines are useful in the field of medicinal chemistry for the design of Nutlin analogues as potent antitumor agents,[31] direct desulfurative cross-coupling reaction of cyclic urea to 2-arylimidazoline was also investigated.[32] After removal of the diphenylphosphinoyl group in **9da** with $Cp_2Zr(H)Cl$ (96% yield), a Pd-catalyzed cross-coupling reaction of **11da** with $PhB(OH)_2$ proceeded in the presence of excess Cu(thiophen-2-carboxylate) (CuTC) in DMF under microwave irradiation (130 °C, 1 h) to give 2-phenyl-imidazoline **12da** with vicinal tetrasubstituted carbon stereocenters in 71% yield.

Table 5. Sr/Schiff base-catalyzed *anti*-selective direct Mannich-type reaction of ketimines.



entry	R:ketimine	8	2	temp [°C]	time [h]	9	% yield[a]	d.r.[b] [*synlanti*]	% *ee* [*anti*]
1[c]	4-Br-C_6H_4	**8a**	**2a**	25	48	**9aa**	86	6:94	92
2[c]	4-Cl-C_6H_4	**8b**	**2a**	25	48	**9ba**	82	10:90	87
3[c]	4-F-C_6H_4	**8c**	**2a**	25	48	**9ca**	71	6:94	90
4[c]	4-CF_3-C_6H_4	**8j**	**2a**	25	48	**9ja**	85	11:89	92
5[d]	4-Me-C_6H_4	**8d**	**2a**	25	20	**9da**	97	6:94	95
6[d]	3-Me-C_6H_4	**8e**	**2a**	25	24	**9ea**	99	8:92	93
7[d]	4-MeO-C_6H_4	**8k**	**2a**	25	24	**9ka**	91	4:96	97
8[d]	4-Me_2N-C_6H_4	**8l**	**2a**	25	69	**9la**	45	4:96	97
9[d]		**8f**	**2a**	−5	47	**9fa**	76	6:94	95
10[d]	2-thienyl	**8m**	**2a**	0	48	**9ma**	70	13:87	90
11[d]	3-thienyl	**8h**	**2a**	−5	48	**9ha**	74	12:88	92
12[d]	2-furyl	**8i**	**2a**	−10	48	**9ia**	84	17:83	84
13[d]	4-Me-C_6H_4	**8d**	**2b**	25	24	**9db**	33	15:85	57

[a]Isolated yield of **9** after purification by column chromatography. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Reaction was run in $CHCl_3$ (0.2 M). [d]Reaction was run in $CHCl_3$/THF = 2:1 (0.17 M).

In Tables 4 and 5, interesting reversal of diastereoselectivity was observed just by changing the Group 2 metal source from Bu_2Mg to Sr(O-*i*Pr)$_2$. Because both the Mg/Schiff base **1d** and Sr/Schiff base **1d** have complicated oligomeric structures, ^{1}H NMR analysis was not useful to gain information on structural differences. Instead, circular dichroism (CD) spectra provided an insight into the differences in aggregation form between the two catalysts.[33] As shown in Figure 3, the CD spectra of Schiff base **1d** alone was clearly different from those of the Mg/Schiff base **1d** and Sr/Schiff base **1d**, suggesting that a chiroptically different aggregate was formed in each metal/Schiff base **1d** = 1:1 solution. Moreover, clear differences between the Mg/Schiff base **1d** and Sr/Schiff base **1d** in the 210–250 nm region were observed, which can be assigned to the difference in the dihedral angle of the binaphthyl unit in the Mg/Schiff base **1d** and Sr/Schiff base **1d**.[34] Because the dihedral angle of the binaphthyl unit often plays a key role in the stereodiscriminating step of asymmetric reactions, we believe that the difference in the dihedral angles caused the observed reversal of diastereoselectivity.

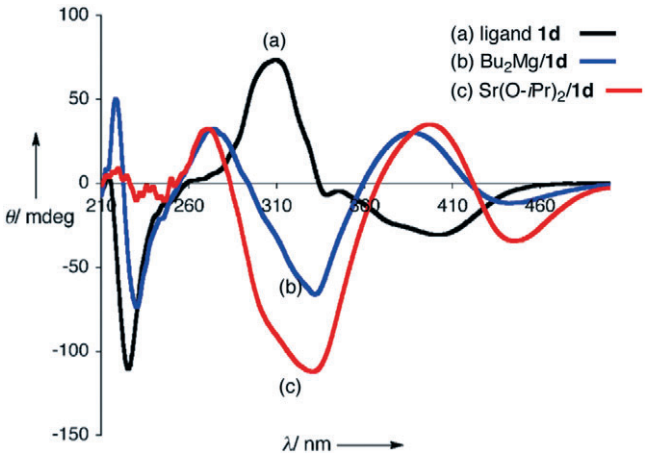


Figure 3. CD spectra of a) Schiff base **1d** (black line), b) the Bu_2Mg/**1d** = 1:1 (blue line), and c) the Sr(O-*i*Pr)$_2$/**1d** = 1:1 (red line).

Conclusion

We have succeeded for the first time in the direct catalytic asymmetric intermolecular aldol reaction of simple non-activated ketone electrophiles and Mannich-type reaction of ketimines derived from non-activated ketones using α-substituted α-isothiocyanato esters as donors. Oligomeric Group 2 metal/Schiff base complexes promoted the reaction under proton transfer conditions, giving products in high diastereoselectivity and enantioselectivity. The methods provided access to unnatural α-amino acids bearing vicinal tetrasubstituted carbon stereocenters, which are not accessible via well-established catalytic asymmetric hydrogenation processes. At the moment, the substrate scope of the reactions is still limited, especially in the case of direct Mannich-type reactions. Further studies to expand the scope by modification of the Group 2 metal/Schiff base catalysts as well as trials to utilize the unique unnatural α-amino acids with vicinal tetrasubstituted carbon stereocenters for designing new biologically active compounds, such as anti-tumor agents, and biological tools are intensively ongoing in our group.

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