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A Heterobimetallic Ga/Yb-Schiff Base Complex for Catalytic Asymmetric α-Addition of Isocyanides to Aldehydes

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α-Additions of isocyanides with both electrophiles and nucleophiles have been utilized for the synthesis of polyfunctional molecules[1] since the early studies on Passerini[2] and Ugi reactions.[3] Although various diastereoselective α-additions of isocyanides using chiral substrates and/or chiral auxiliaries have been reported,[1−3] the number of catalytic asymmetric methods is limited.[4,5] To further improve catalytic activity and selectivity as well as substrate scope, the development of a new catalyst for asymmetric α-additions of isocyanides is highly desirable. Herein, we report a new heterodinuclear Ga/Yb-Schiff base complex for catalytic asymmetric α-additions of α-isocyanoacetamides to aldehydes, giving products in up to 98% ee.

Among previous reports on catalytic asymmetric α-additions of isocyanides,[4,5] Zhu, Wang and co-workers reported salen-Al-catalyzed α-additions of α-isocyanoacetamides to aldehydes.[5a] Although the reaction produced unique building blocks, 2-(1-hydroxyalkyl)-5-aminooxazoles, in one step, the enantioselectivity of the reaction remained less satisfactory (50−80% ee). We recently disclosed the utility of bimetallic Schiff base **1** complexes (Figure 1),[6,7] whose catalytic properties are different from those of monometallic chiral salen complexes. Therefore, we selected the α-addition of α-isocyanoacetamide as a model reaction to apply bimetallic Schiff base catalysts to isocyanide α-additions. The working hypothesis for bimetallic Schiff base catalysis is shown in Figure 2. We assumed that the bimetallic Schiff base complex would not only activate the aldehyde with one metal but might also interact with the α-isocyanoacetamide through the other metal to effectively control the orientation of the two substrates in the enantio-discriminating step (Figure 2, (A)).

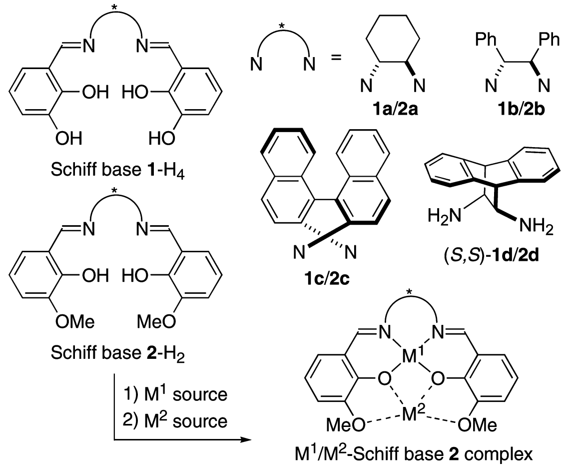

Figure 1. Structures of dinucleating Schiff base **1**-H_4, Schiff bases **2**-H_2, and postulated structure of bimetallic Schiff base **2** complex.

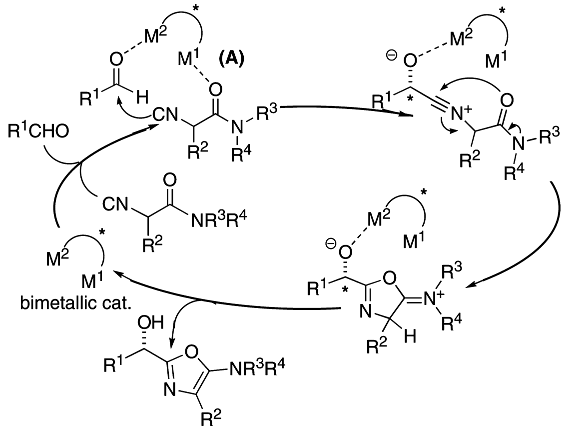

Figure 2. Working hypothesis of bimetallic Schiff base catalysis on α-additions of α-isocyanoacetamides to aldehydes.

Based on this hypothesis, we first examined several previously reported bimetallic catalysts prepared from dinucleating Schiff bases **1a** and **1c**,[6] transition metals, and/or rare earth metal alkoxides for the reaction of α-isocyanoacetamide **3a** to aldehyde **4a**, but the reactivity was poor. We speculated that the Lewis acidity of the catalysts prepared from **1** and rare earth metal alkoxides was not sufficient to promote the present reaction. To incorporate a cationic rare earth metal into the outer cavity of a dinucleating Schiff base, we utilized Schiff base **2** derived from *o*-vanillin.[8] After screening suitable metal combinations for Schiff base **2**, $Ga(O\text{-}i Pr)_3/Yb(OTf)_3$ afforded promising results. The chiral diamine backbone affected both the reactivity and enantioselectivity (entries 1−4). Schiff base **2a** and **2b** gave unsatisfactory results, but **2c** with a binaphthyl diamine unit gave 78% ee (entry 3). The best reactivity and selectivity were achieved using Schiff base **2d** with an anthracene-derived diamine unit (entry 4, 67% yield, 94% ee). After optimization of the solvent (CH_2Cl_2) and Ga/Yb ratio (1:0.95), product **5aa** was obtained in >95% conversion and 96% ee after 24 h (entry 5). To confirm the utility of the $Ga(O\text{-}i Pr)_3/Yb(OTf)_3$ combination, several control experiments with the best ligand **2d** were performed (entries 6−15). Neither Ga-**2d** nor Yb-**2d** alone efficiently promoted the reaction (entries 6−9). With $Ga(O\text{-}i Pr)_3$ and other rare earth metal triflates, the reactivity decreased in correlation with the Lewis acidity of the rare earth metals (Yb > Gd > Nd > La),[9] while good to excellent enantioselectivity was maintained in entries 10−12 (89−96% ee). We investigated Et_2AlCl, $Al(O\text{-}i Pr)_3$, and $In(O\text{-}i Pr)_3$ as other group 13 metals for the inner cavity (entries 13−15), but the results were less satisfactory than that in entry 5. In entry 16, Schiff base **1d** was utilized instead of Schiff base **2d**, but no reaction occurred. These results in entries 6−16 indicated that the $Ga(O\text{-}i Pr)_3/Yb(OTf)_3$ combination as well as Schiff base **2d** were essential to obtain high reactivity and enantioselectivity in the present reaction.

The substrate scope of the reaction under optimized reaction conditions (Table 1, entry 5) is summarized in Table 2. Aryl, heteroaryl, and alkenyl aldehydes reacted well with isocyanide **4a**

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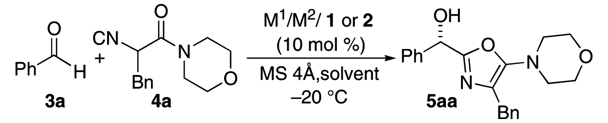
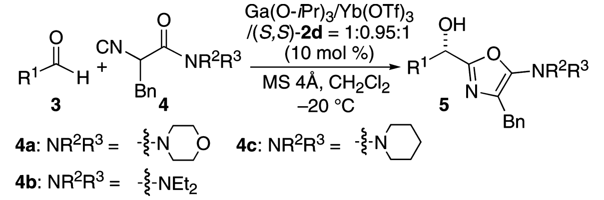
Table 1. Screening of Bimetallic M^1/M^2/Schiff Base Complexes for α-Addition of Isocyanide **4a** to Aldehyde **3a**[a]

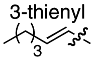


entry	M^1 source	M^2 source (*x* mol %)	ligand	time (h)	% yield[b]	% ee
1	Ga(O-*i*Pr)$_3$	Yb(OTf)$_3$ (10)	**2a**	74	55	29
2	Ga(O-*i*Pr)$_3$	Yb(OTf)$_3$ (10)	**2b**	74	18	11
3	Ga(O-*i*Pr)$_3$	Yb(OTf)$_3$ (10)	**2c**	71	27	78
4	Ga(O-*i*Pr)$_3$	Yb(OTf)$_3$ (10)	**2d**	74	67	94
5	Ga(O-*i*Pr)$_3$	Yb(OTf)$_3$ (9.5)	**2d**	24	>95	96
6	Ga(O-*i*Pr)$_3$	none	**2d**	24	trace	—
7	Ga(O-*i*Pr)$_3$	Ga(O-*i*Pr)$_3$ (10)	**2d**	24	6	—
8	none	Yb(OTf)$_3$ (10)	**2d**	24	trace	—
9	Yb(OTf)$_3$	Yb(OTf)$_3$ (10)	**2d**	24	4	—
10	Ga(O-*i*Pr)$_3$	Gd(OTf)$_3$ (9.5)	**2d**	24	62	96
11	Ga(O-*i*Pr)$_3$	Nd(OTf)$_3$ (9.5)	**2d**	24	33	95
12	Ga(O-*i*Pr)$_3$	La(OTf)$_3$ (9.5)	**2d**	24	11	89
13	Et$_2$AlCl	Yb(OTf)$_3$ (9.5)	**2d**	48	68	37
14	Al(O-*i*Pr)$_3$	Yb(OTf)$_3$ (9.5)	**2d**	24	>95	79
15	In(O-*i*Pr)$_3$	Yb(OTf)$_3$ (9.5)	**2d**	24	55	80
16	Ga(O-*i*Pr)$_3$	Yb(OTf)$_3$ (9.5)	**1d**	24	trace	—

[a] Reactions were performed in dry CH_2Cl_2/toluene = 1:1 (entries 1−4) or in dry CH_2Cl_2 (entries 5−16). [b] Yield was determined by ^1H NMR analysis of crude mixture.

Table 2. Catalytic Asymmetric α-Addition of Isocyanides **4** to Aldehydes **3** Using Ga/Yb/Schiff Base (*S*,*S*)-**2d** Complex[a]



entry	3	R^1	4	time (h)	5	% yield[b]	% ee
1	**3a**	Ph	**4a**	24	**5aa**	91	96
2	**3b**	4-Cl-C_6H_4	**4a**	24	**5ba**	83	97
3	**3c**	4-MeO-C_6H_4	**4a**	24	**5ca**	82	97
4	**3d**	2-MeO-C_6H_4	**4a**	24	**5da**	93	96
5	**3e**	3-furyl	**4a**	24	**5ea**	89	98
6	**3f**	3-thienyl	**4a**	24	**5fa**	80	98
7	**3g**		**4a**	48	**5ga**	70	95
8	**3h**	(*E*)-PhCH=CH	**4a**	24	**5ha**	95	98
9	**3i**	PhCH$_2$CH$_2$	**4a**	24	**5ia**	82	88
10	**3b**	4-Cl-C_6H_4	**4b**	24	**5bb**	83	98
11	**3b**	4-Cl-C_6H_4	**4c**	24	**5bc**	80	97

[a] Reactions were performed in dry CH_2Cl_2 at −20 °C with 1.5 equiv of **4** using 10 mol % of Ga(O-*i*Pr)$_3$/(*S*,*S*)-**2d** and 9.5 mol % of Yb(OTf)$_3$ mixture. [b] Isolated yield after purification by column chromatography.

(entries 1−8). Aromatic aldehydes with either an electron-withdrawing group (entry 2) or an electron-donating group (entries 3−4) gave products in good yield and high enantioselectivity (96−97% ee). Heteroaryl aldehydes **3e**−**3f** (entries 5−6) as well as alkenyl aldehydes **3g**−**3h** (entries 7−8) also gave products in high enantioselectivity (95−98% ee). The reaction of aliphatic aldehyde **3i** proceeded smoothly in the present system, but the enantioselectivity was somewhat lower (entry 9, 88% ee). Further optimization studies for aliphatic aldehydes are ongoing. Isocyanides **4b**−**4c** with different substituents were applicable as well, giving products in 97−98% ee (entries 10−11).

In summary, we have developed a new heterobimetallic Ga(O-*i*Pr)$_3$/Yb(OTf)$_3$/Schiff base **2d** complex for catalytic asymmetric α-additions of α-isocyanoacetamides to aryl, heteroaryl, alkenyl, and alkyl aldehydes (88−98% ee). Schiff base **2d** derived from *o*-vanillin was suitable to utilize cationic rare earth metal triflates with good Lewis acidity in bimetallic Schiff base catalysis. Mechanistic studies to elucidate the precise roles of the two metals as well as trials to expand the substrate scope are ongoing.

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Supporting Information Available: Experimental procedures, spectral data of new compounds, and determination of absolute configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

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