

# Catalytic Asymmetric Ring-Opening of *meso*-Aziridines with Malonates under Heterodinuclear Rare Earth Metal Schiff Base Catalysis

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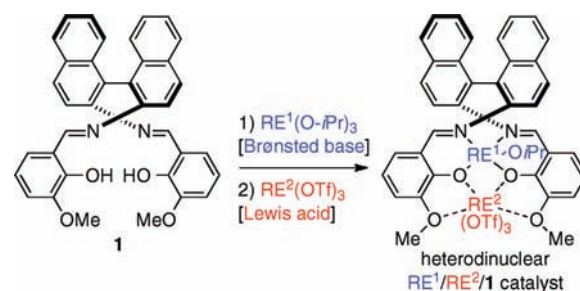
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**S** Supporting Information

**ABSTRACT:** Catalytic asymmetric ring-opening of *meso*-aziridines with malonates is described. The combined use of two rare earth metal sources with different properties promoted the desired ring-opening reaction. A 1:1:1 mixture of a heterobimetallic La(O-*i*Pr)<sub>3</sub>/Yb(OTf)<sub>3</sub>/Schiff base **1a** (0.25–10 mol %) efficiently promoted the reaction of five-, six-, and seven-membered ring cyclic *meso*-aziridines as well as acyclic *meso*-aziridines with dimethyl, diethyl, and dibenzyl malonates, giving chiral cyclic and acyclic  $\gamma$ -amino esters in 99–63% yield and >99.5–97% ee.

$\gamma$ -Amino acids are key structural motifs in many biologically active compounds, such as clinically used neurotransmission modulators.<sup>1</sup> Among unnatural amino acids, cyclic amino acids have recently received much attention in foldamer research due to their interesting folding properties.<sup>2</sup> Few methods exist, however, for catalytic enantioselective synthesis of chiral cyclic  $\gamma$ -amino acids.<sup>3</sup> In 2009, Cobb et al. and Gellman et al. independently reported the first highly enantioselective catalytic asymmetric methods via an intramolecular Michael reaction of nitronates onto conjugated esters<sup>3a</sup> and intermolecular Michael addition of aldehydes onto 1-nitrocyclohexene,<sup>3b,c</sup> giving  $\gamma$ -amino acids with a six-membered ring in excellent enantioselectivity. Further studies toward the synthesis of structurally diverse sets of chiral cyclic  $\gamma$ -amino acids, especially those with different ring size, are highly demanded. Herein, we report an alternative approach to chiral cyclic  $\gamma$ -amino acids via desymmetrization of *meso*-aziridines. Heterobimetallic rare earth metals Schiff base **1** complexes (Figure 1) promoted enantioselective ring-opening of *meso*-aziridines **2** with malonate **3**.

Catalytic enantioselective ring-opening of *meso*-aziridines with malonates provides straightforward access to cyclic  $\gamma$ -amino acids. Although racemic reactions using a stoichiometric amount of base at elevated temperatures have been reported,<sup>4</sup> catalytic asymmetric methods have never been reported, possibly due to the low reactivity of aziridines toward enolates and difficulty in differentiating the enantiotopic center of *meso*-aziridines.<sup>5</sup> Based on previous reports of highly enantioselective ring-opening desymmetrization of *meso*-aziridines<sup>6–9</sup> with cyanide<sup>7</sup> and azide<sup>8</sup> nucleophiles using homodinuclear rare earth metal complexes by our group and RajanBabu/Parquette et al., as well as our ongoing projects on bimetallic Schiff base catalysis,<sup>10–12</sup> we envisioned using a bimetallic rare earth metal



**Figure 1.** Dinucleating Schiff base **1a** and postulated structure of heterodinuclear rare earth (RE) catalyst bearing acid/base moieties.

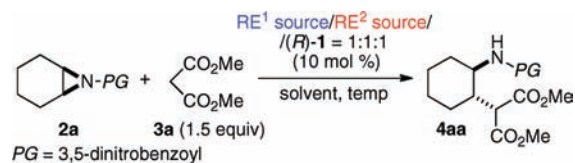
Schiff base complex in the present study. As shown in Figure 1, we planned to combine a Brønsted basic rare earth metal alkoxide [RE<sup>1</sup>(O-*i*Pr)<sub>3</sub>]<sup>10</sup> and a Lewis acidic rare earth metal triflate [RE<sup>2</sup>(OTf)<sub>3</sub>]<sup>11</sup> onto a dinucleating Schiff base **1**. With the suitable metal combination, simultaneous activation of malonates and aziridines with two different metal centers would be possible via a well-organized transition state, giving products in high yield and enantioselectivity.

After screening several Schiff base scaffolds to incorporate two different rare earth metal sources, Schiff base **1** with a binaphthyl backbone afforded promising results.<sup>13</sup> Optimization studies using *meso*-aziridine **2a** and malonate **3a** are summarized in Table 1. Both rare earth metal alkoxide (entries 1–6) and rare earth metal triflate (entries 6–10) had a significant impact on the yield of product **4a**. Among rare earth metal alkoxides screened, the most Brønsted basic La(O-*i*Pr)<sub>3</sub> gave the best results (entry 6, 89% yield and >99.5% ee). As a Lewis acidic counterpart, the most Lewis acidic Yb(OTf)<sub>3</sub> (entry 6) and Y(OTf)<sub>3</sub> (entry 7) gave comparably good results compared with other less Lewis acidic Gd, Sm, and La triflates (entries 8–10).<sup>14</sup> In the present reaction, the combined use of Brønsted basic and Lewis acidic rare earth metals is critically important to promote the desired reaction in good enantioselectivity and reactivity. Negative control experiments are shown in entries 11 and 12. La(O-*i*Pr)<sub>3</sub>/**1a** = 1:1 in the absence of Yb(OTf)<sub>3</sub> resulted in 24% yield and 4% ee (entry 11). Yb(OTf)<sub>3</sub>/**1a** = 1:1 in the absence of La(O-*i*Pr)<sub>3</sub> did not afford the desired product **4aa** (entry 12, 0% yield). Although aziridine **2a** was completely consumed, the rearrangement of aziridine **2a** into 2-aryloxazoline predominantly proceeded under the simply Lewis acidic reaction conditions in entry 12.<sup>15</sup> Thus, both La(O-*i*Pr)<sub>3</sub> and

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Table 1. Optimization Studies



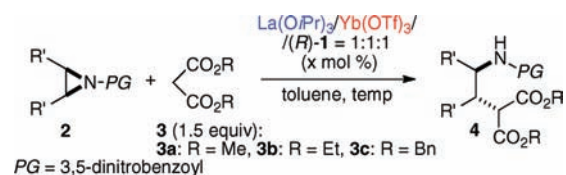
entry	RE <sup>1</sup> source	RE <sup>2</sup> source	solvent	temp (°C)	time (h)	yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1	Sc(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	THF	rt	24	trace	ND
2	Er(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	THF	rt	24	16	>99.5
3	Gd(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	THF	rt	24	24	99
4	Sm(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	THF	rt	24	28	99
5	Nd(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	THF	rt	24	83	99
6	La(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	THF	rt	24	89	>99.5
7	La(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	THF	rt	24	90	>99.5
8	La(OiPr) <sub>3</sub>	Gd(OTf) <sub>3</sub>	THF	rt	24	82	99
9	La(OiPr) <sub>3</sub>	Sm(OTf) <sub>3</sub>	THF	rt	24	21	96
10	La(OiPr) <sub>3</sub>	La(OTf) <sub>3</sub>	THF	rt	24	10	92
11	La(OiPr) <sub>3</sub>	none	THF	rt	24	24	4
12	none	Yb(OTf) <sub>3</sub>	THF	rt	24	0	ND
13	La(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	THF	40	15	92	>99.5
14	La(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	toluene	40	4	99 <sup>c</sup>	>99.5

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the crude mixture. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> Isolated yield of **4** after purification by column chromatography.

Yb(OTf)<sub>3</sub> are essential for the present reaction. After further optimization of the reaction temperature (entry 13, 40 °C) and solvent (entry 14, toluene), **4aa** was obtained in 99% isolated yield and in >99.5% ee after 4 h.

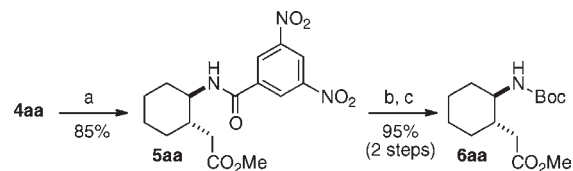
The substrate scope of the reaction as well as trials to reduce catalyst loading are summarized in Table 2. Catalyst loading was successfully reduced to 2.5 mol % and 0.5 mol % without problems (entries 2 and 3). When further reducing the catalyst loading to 0.25 mol %, the addition of a catalytic amount of Et<sub>3</sub>N (0.25 mol %) was effective to improve the catalyst efficiency, and **4aa** was obtained in 94% yield and 99% ee after 30 h (entry 4).<sup>16</sup> Malonates **3b** and **3c** also reacted well with aziridine **2a**, giving products **4ab** and **4ac** in 97–99% yield and 99–99.5% ee (entries 5 and 6). Other six-membered ring *meso*-aziridines **2b** and **2c** also reacted smoothly to give products **4ba** and **4ca** in 99% ee (entries 7 and 8).<sup>17</sup> The present heterobimetallic system was applicable to substrates with different ring sizes, giving products in 98–99% ee (entries 9–11). In entry 11, the yield of desired product **4fa** was moderate (63% yield), because undesired rearrangement of aziridine **2f** to 2-aryloxazoline competed with the desired reaction even in the presence of Et<sub>3</sub>N additive. Acyclic *meso*-aziridines **2g** and **2h** also reacted without problems under the heterobimetallic catalysis, giving products in 91–97% yield and 97–99% ee (entries 12 and 13). The product was readily converted into Boc-protected cyclic  $\gamma$ -amino ester as shown in Scheme 1. Decarboxylation of **4aa** gave **5aa** in 85% yield. Protection of **5aa** with Boc-group, followed by removal of the 3,5-dinitrobenzoyl group with NaOMe at rt, gave **6aa** in 95% yield (2 steps).

In summary, we developed a new heterodinuclear rare earth metal Schiff base catalyst for an enantioselective ring-opening

Table 2. Catalytic Enantioselective Ring-Opening of *meso*-Aziridines with Malonates<sup>a</sup>

entry	aziridine <b>2</b>	cat. (x mol %)	<b>3</b>	<b>4</b>	temp (°C)	time (h)	yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1		10	<b>3a</b>	<b>4aa</b>	40	4	99	>99.5
2		2.5	<b>3a</b>	<b>4aa</b>	40	14	96	>99.5
3		0.5	<b>3a</b>	<b>4aa</b>	40	21	93	>99.5
4 <sup>c</sup>		0.25	<b>3a</b>	<b>4aa</b>	40	30	94	99
5		10	<b>3b</b>	<b>4ab</b>	40	4	99	99
6		10	<b>3c</b>	<b>4ac</b>	40	5	97	>99.5
7		10	<b>3a</b>	<b>4ba</b>	40	24	98	99
8 <sup>c</sup>		10	<b>3a</b>	<b>4ca</b>	60	40	99	99
9 <sup>c</sup>		10	<b>3a</b>	<b>4da</b>	60	48	95	99
10 <sup>c</sup>		10	<b>3a</b>	<b>4ea</b>	80	60	83	98
11 <sup>c</sup>		10	<b>3a</b>	<b>4fa</b>	60	72	63	98
12 <sup>c</sup>		10	<b>3a</b>	<b>4ga</b>	40	21	97	99
13 <sup>c</sup>		10	<b>3a</b>	<b>4ha</b>	60	46	91	97

<sup>a</sup> Isolated yield of **4** after purification by column chromatography. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> Reaction was run in the presence of catalytic amount of Et<sub>3</sub>N (0.25 mol % in entry 4 and 10 mol % in entries 8–13).

Scheme 1. Transformation of Ring-opening Adduct<sup>a</sup>

<sup>a</sup> Reagents and reaction conditions: (a) LiCl, H<sub>2</sub>O, DMSO, 130 °C, 5 h, 85% yield; (b) Boc<sub>2</sub>O, Et<sub>3</sub>N, cat. DMAP, THF, rt, 24 h; (c) NaOMe, MeOH, rt, 1 h, 95% yield (2 steps).

desymmetrization of cyclic and acyclic *meso*-aziridines with dimethyl, diethyl, and dibenzyl malonates. The combined use of two rare earth metal sources with different properties, Brønsted basic rare earth metal alkoxide and Lewis acidic rare earth metal triflate, was important to promote the desired ring-opening reaction. The La(O-*i*Pr)<sub>3</sub>/Yb(OTf)<sub>3</sub>/Schiff base **1a** complex gave chiral cyclic and acyclic  $\gamma$ -amino esters in 99–63% yield and >99.5–97% ee. Further applications of

the heterodinuclear rare earth metal Schiff base catalysts are ongoing.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Experimental procedures, determination of relative and absolute configuration by X-ray crystallographic analysis (CIF), and spectral data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) The reactions were run using 10 mol % catalyst loading in entries 7–13, because the reactivity of aziridines **2b–2h** was lower than that of aziridine **2a**.