## Dinuclear Ni<sub>2</sub>–Schiff base complex-catalyzed asymmetric 1,4-addition of $\beta$ -keto esters to nitroethylene toward $\gamma^{2,2}$ -amino acid synthesis<sup>†</sup>

Harunobu Mitsunuma and Shigeki Matsunaga\*

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A homodinuclear Ni<sub>2</sub>-Schiff base 1 complex (1–10 mol%) promoted the catalytic asymmetric 1,4-addition reactions of  $\beta$ -keto esters and an *N*-Boc oxindole to nitroethylene, giving products in 98–75% ee.

Catalytic asymmetric 1,4-additions of carbon nucleophiles are highly useful synthetic transformations for the construction of quaternary carbon stereocenters.<sup>1,2</sup> Over recent years, there has been tremendous progress in both metal catalysis and organocatalysis for the asymmetric 1,4-additions of β-keto esters and related compounds.<sup>2</sup> β-Substituted nitroalkenes are most often used as acceptors, giving  $\beta$ -substituted  $\gamma$ -nitro esters with  $\alpha$ -quaternary carbon stereocenters.<sup>3</sup> The use of a β-unsubstituted acceptor (nitroethylene), however, is much less common,<sup>4,5</sup> possibly due to potential difficulties of enantiocontrol and competitive polymerization of nitroethylene. Gellman et al. and Wennermers et al. independently reported highly enantioselective organocatalytic asymmetric 1,4-additions of aldehydes to nitroethylene and their applications to  $\gamma^2$ -amino acid synthesis,<sup>4</sup> but  $\alpha, \alpha$ -disubstituted aldehydes were not utilized as donors. Barbas was the first to successfully construct a quaternary carbon stereocenter via catalytic asymmetric 1,4-addition of an N-Boc oxindole to nitroethylene.<sup>5</sup> Because  $\gamma^2$ -amino acids are potentially useful building blocks for folder research and the synthesis of biologically active compounds,<sup>6,7</sup> further studies to expand the scope of donors, especially for the synthesis of adducts with a quaternary stereocenter adjacent to a carbonyl group  $\gamma^{2,2,8,9}$  are highly desirable. To address this issue, we herein report the utility of a homodinuclear Ni2-Schiff base 1 complex (Fig. 1). Ni2-1 (1–10 mol%) promoted the reactions of  $\beta$ -keto esters to nitroethylene, affording products in 98-75% ee.

As part of our ongoing studies of bifunctional Lewis acid/Brønsted base catalysis in collaboration with Shibasaki,<sup>10</sup> one of authors (S.M.) and Shibasaki recently reported the utility of dinuclear Schiff base complexes.<sup>11–15</sup> Among them, homodinuclear Co<sub>2</sub>–1<sup>12a,b</sup> and Mn<sub>2</sub>–1<sup>12c</sup> complexes were suitable for 1,4-additions with  $\beta$ -substituted nitroalkenes. Thus, we first applied Co<sub>2</sub>–1 and Mn<sub>2</sub>–1 complexes for the reaction of  $\beta$ -keto ester **2a** and nitroethylene. Both of these complexes, however, gave an unsatisfactory yield and enantioselectivity (Table 1, entries 1 and 2, less than 30% NMR yield and 67% ee). Among the homodinuclear<sup>12,13</sup> and

Tokyo 113-0033, Japan. E-mail: smatsuna@mol.f.u-tokyo.ac.jp;

Fax: +81-3-5684-5206; Tel: +81-3-5841-4830



Fig. 1 Structures of dinucleating Schiff base 1 and homodinuclear  $M_2$ -Schiff base 1 complexes.

 Table 1
 Optimization of reaction conditions<sup>a</sup>

0 	CO <sub>2</sub> t-Bu	+ //	∕∼ <sub>NO2</sub> – 2 equiv)	( <i>R</i> )-M <sub>2</sub> - <b>1</b> (x mol % solvent/tolue = 10:1	cat. ₀) ene √	O J J J J J J J J J J J J J J J J J J J	.t-Bu `NO₂
Entry	М	x	$Solvent^b$	$Temp/^{\circ}C$	Time/h	% Yield <sup>c</sup>	% ee
1	Co(OAc)	10	THF	0	25	< 30	67
2	Mn(OAc)	10	THF	0	25	< 20	67
3	Ni	10	THF	0	25	75	97
4	Ni	10	Toluene	0	25	94	68
5	Ni	10	$CH_2Cl_2$	0	25	>95	92
6	Ni	10	CHCl <sub>3</sub>	0	25	>95	90
7	Ni	10	CH <sub>3</sub> CN	0	25	78	78
8	Ni	10	AcOEt	0	25	95	98
9	Ni	5	AcOEt	0	23	91	96
10	Ni	2.5	AcOEt	0	48	83	89
11	Ni	2.5	AcOEt	rt	48	87	92
12	Ni	2.5	AcOEt	40	5	>95	93

<sup>*a*</sup> 1.2 equiv. of nitroethylene (in toluene) were used. <sup>*b*</sup> Reactions were run in solvent/toluene = 10: 1, because nitroethylene stored in toluene was used. <sup>*c*</sup> Yield was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

heterodinuclear<sup>14</sup> Schiff base complexes screened, the Ni<sub>2</sub>–1 catalyst<sup>13</sup> afforded promising results. The reaction of  $\beta$ -keto ester **2a** with 1.2 equiv. of nitroethylene in THF at 0 °C gave product **3a** in 75% yield and 97% ee (entry 3). Among the solvents screened (entry 3–8), AcOEt was the best in terms of yield and enantioselectivity (entry 8, 96% yield and 98% ee). We then tried to reduce catalyst loading in entries 9–12. With 2.5 mol% catalyst, reactivity was decreased at 0 °C and the reaction did not complete after 48 h (entry 10). Raising the reaction temperature to 40 °C drastically improved the reactivity and the reaction completed within 5 h with high enantio-selectivity (entry 12, 93% ee).

Graduate School of Pharmaceutical Sciences,

The University of Tokyo, Hongo 7-3-1, Bunkyo-ku,

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The substrate scope and limitations of the reaction are summarized in Table 2.<sup>16</sup> Because the reactivity of  $\beta$ -keto esters **2** depends on the structure, the reaction conditions, such as catalyst loading and reaction time, were optimized for each  $\beta$ -keto ester. The best results for each substrate are

**Table 2** Catalytic asymmetric 1,4-addition of  $\beta$ -keto esters **2** to nitroethylene<sup>*a*</sup>



<sup>*a*</sup> The reactions were run with 1.2 equiv. of nitroethylene (in toluene). <sup>*b*</sup> Isolated yield after purification by silica gel column chromatography. <sup>*c*</sup> Determined by HPLC analysis.

summarized in Table 2. Indanone-derived B-keto esters 2b-2d showed good reactivity, and products 3b-3d were obtained in 92-90% yield and 98-94% ee after 4.5 to 10 h using 2.5 mol% of Ni<sub>2</sub>-1 (entries 2, 4-5). In entry 3, the reaction was performed with 1 mol% Ni<sub>2</sub>-1 catalyst, but both the reactivity and enantioselectivity decreased (18 h, 84%) yield, 87% ee). The reactivity of  $\beta$ -keto esters 2e and 2f with a six-membered ring was lower than that of  $\beta$ -keto ester 2a, and 10 mol% of Ni<sub>2</sub>-1 was required to obtain products 3e and 3f in 98-73% yield and 91-75% ee after 24 h (entries 6 and 7). The reactivity of acyclic  $\beta$ -keto esters 2g and 2h was much lower than that of cyclic  $\beta$ -keto esters, and products 3g and 3h were obtained in only 35-51% yield even using 10 mol% of the catalyst (entries 8-9, 82-85% ee). We are speculating that the modest to poor reactivity in entries 7-10 is due to poor nucleophilicity of Ni-enolates. The Ni<sub>2</sub>-1 catalyst was also applicable to N-Boc oxindole 2i, giving product 3i in 99% vield and 80% ee after 24 h. To demonstrate the synthetic utility of the reaction, transformation of the products was performed (Scheme 1). Reduction of 3c with RANEY<sup>®</sup> Ni under H<sub>2</sub> (1 atm) in the presence of Boc<sub>2</sub>O gave  $\gamma^{2,2}$ -amino ester 4c in 72% yield. Reduction of 3a with Pd/C under H<sub>2</sub> (1 atm) in MeOH gave bicyclic amino ester, which was isolated after Boc-protection in 82% yield (5a, 2 steps).



Scheme 1 Transformation of 1,4-adducts.



Fig. 2 Postulated catalytic cycle of  $Ni_2$ -1-catalyzed 1,4-addition of  $\beta$ -keto esters to nitroethylene.

In the present reaction, we assume that the two Ni centers function cooperatively as observed in other related reactions using Ni<sub>2</sub>–1.<sup>13</sup> The postulated reaction mechanism is summarized in Fig. 2. One of the Ni–O bonds in the outer  $O_2O_2$  cavity is speculated to work as a Brønsted base to generate Ni–enolate *in situ*.<sup>17</sup> The other Ni in the inner N<sub>2</sub>O<sub>2</sub> cavity functions as a Lewis acid to control the position of nitroethylene, similar to conventional metal–salen Lewis acid catalysis. The C–C bond-formation *via* the transition state (TS in Fig. 2), followed by protonation, affords product and regenerates the Ni<sub>2</sub>–1 catalyst.

In summary, we developed a homodinuclear Ni<sub>2</sub>–Schiff base-catalyzed enantioselective 1,4-addition of  $\beta$ -keto esters to nitroethylene. The reaction proceeded with 1–10 mol% catalyst, and products bearing a quaternary carbon stereocenter adjacent to an ester were obtained in 98–75% ee and 99–35% yield (TON = up to 84). Further studies to improve the poor reactivity for acyclic  $\beta$ -keto esters through ligand modification are ongoing.

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- 17 <sup>1</sup>H NMR analysis of the bimetallic Ni<sub>2</sub>–1 complex does not show any peaks, suggesting that at least one of Ni metal centers has non-planar coordination mode. Based on the molecular model, we assume that the outer Ni center has *cis*-β configuration due to strain of the bimetallic complex. In other words, one of the Ni–O bonds of the outer Ni center is speculated to be in apical position. Thus, the weak Ni–O bond would work as a Brønsted baseto deprotonate β-keto esters to give the Ni–enolate intermediate. Detailed mechanistic studies to clarify the role of two Ni metal centers are ongoing. For the utility of *cis*-β metal complexes of salens in asymmetric catalysis, see a review: T. Katsuki, *Chem. Soc. Rev.*, 2004, **33**, 437.