Catalytic Asymmetric Synthesis of Nitrogen-Containing *gem*-Bisphosphonates Using a Dinuclear Ni_2–Schiff Base Complex

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Received 30 January 2009

Abstract: A catalytic asymmetric synthesis of nitrogen-containing *gem*-bisphoshonates is described. A Lewis acid–Brønsted base bifunctional homodinuclear Ni_2–Schiff base complex promoted catalytic enantioselective conjugate addition of nitroacetates to ethylidenebisphosphonates, giving products in up to 93% ee and 94% yield. Transformation of the product into a chiral α-amino ester with a *gem*-bisphosphonate moiety is also described.

Key words: asymmetric catalysis, asymmetric synthesis, bisphosphonates, Michael addition

gem-Bisphosphonates (BP) have high affinity for hydroxyapatite bone mineral surfaces and constitute an important class of biologically active compounds.[1] Some BP are used clinically for the prevention and treatment of several bone disorders, such as Paget's disease, osteoporosis, bone metastasis, myeloma, and rheumatoid arthritis.[2] The use of BP as carriers for bone-specific therapeutic agents has also been intensively studied.[1] In addition, BP are effective growth inhibitors of several protozoan parasites that cause African sleeping sickness, malaria, and others.[3] Because of these important pharmacologic activities, synthetic methods for various BP have been intensively investigated over the last two decades. Catalytic asymmetric approaches for the synthesis of optically active BP are, however, quite limited.[4] Highly enantioselective organocatalytic 1,4-additions[5] of aldehydes,[4a] β-keto esters,[4b] and ketones[4c] to ethylidenebisphosphonates have been reported, but there are no reports of a catalytic asymmetric synthesis of nitrogen-containing BP. Because nitrogen-containing BP are often biologically much more active than BP without an amino functional group,[6] the development of a new method for chiral nitrogen-containing BP is in high demand. Herein, we report catalytic asymmetric 1,4-addition of nitroacetates to ethylidenebisphosphonates. A Lewis acid–Brønsted base bifunctional homodinuclear Ni_2–Schiff base **1** complex (Figure 1) promoted the reaction, giving products in up to 93% ee and 94% yield.

Initially, we screened catalysts for the reaction of ethylidenebisphosphonate **2a** with nitroacetate **3a**. Among various Lewis acid/Brønsted base cooperative catalysts,[7–9] dinuclear Schiff base complexes[10,11] showed promising results for the present reaction. The optimization studies are summarized in Table 1 and Table 2. With a homodinuclear Ni_2–Schiff base **1** complex,[10c,e] which was originally developed for a Mannich-type reaction of nitroacetates, the reaction of **2a** with **3a** proceeded at 0 °C in THF, and product **4aa** was obtained in quantitative conversion and 38% ee (Table 1, entry 1). With other homodinuclear complexes, such as a Co_2-**1** complex,[10f] the reactivity was good, but the enantioselectivity was worse than that in entry 1 (entries 2–4: 21–0% ee). The heterodinuclear transition metal/rare earth metal Schiff base complexes are effective in other reactions.[10a,b,d] Therefore, we also examined heterodinuclear Ni/rare earth metal complexes (entries 5–7), but the results were much less satisfactory. The reaction conditions were further optimized using the Ni_2-**1** complex (Table 2). By changing the ester moiety of the nitroacetate to a bulkier *tert*-butyl group, enantioselectivity improved to 58% ee (entry 2, **3b**). Solvent affected the enantioselectivity, and toluene in entry 5 was the best, giving **4ab** in 75% ee. The addition of 5 Å MS further improved the enantioselectivity to 83% ee (entry 6). Catalyst loading was successfully reduced to 3 mol% in entry 7, while maintaining good conversion and enantioselectivity.

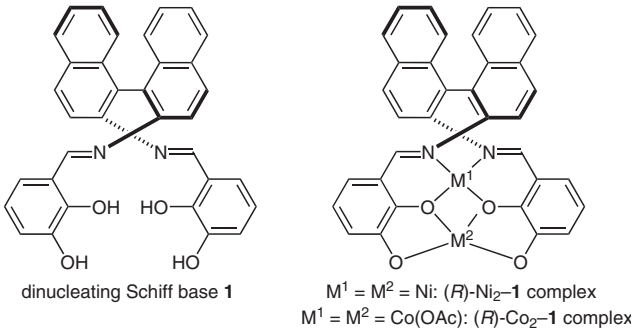
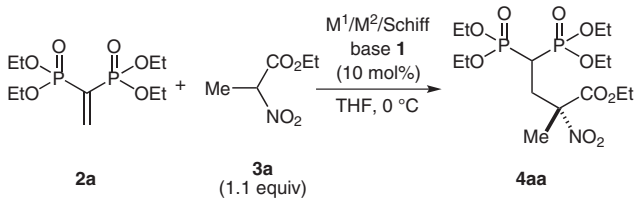


Figure 1 Structures of dinucleaing Schiff base **1** and homodinuclear Schiff base complexes

Because the Ni_2–**1** complex is bench-stable and storable, the substrate scope of the reaction (Table 3) was investigated using a catalyst stored for more than 3 months.[12] Various α-substituted nitroacetates were applicable under the optimized reaction conditions in toluene with the 5 Å MS additive. In addition to methyl-substituted nitroacetate **3b** (entry 1), ethyl, *n*-propyl, and benzyl-substituted nitroacetates **3c**–**e** gave products in good isolated yields and 84–82% ee (entries 2–4). It is noteworthy that the reaction proceeded nicely using functionalized nitro-

SYNLETT 2009, No. 10, pp 1635–1638
Advanced online publication: 02.06.2009
DOI: 10.1055/s-0029-1217192; Art ID: Y00609ST

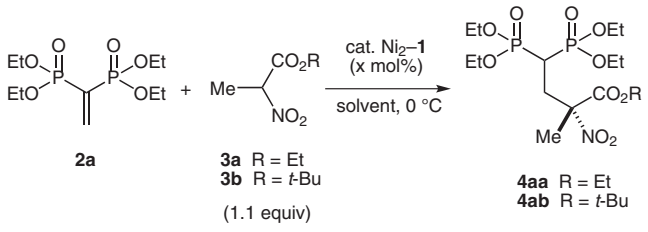
Table 1 Catalyst Screening for the Reaction of Ethylidenebisphosphonate **2a** with Nitroacetate **3a**



Entry	M^1	M^2	Time (h)	Conv. (%)[a]	ee (%)
1	Ni	Ni	41	>95	38
2	$Co^{III}OAc$	$Co^{III}OAc$	41	>95	21
3	Cu	Cu	83	>95	0
4	Pd	Pd	83	>95	0
5	Ni	La(O*i*-Pr)	41	>95	3
6	Ni	Sm(O*i*-Pr)	41	>95	5
7	Ni	Gd(O*i*-Pr)	41	>95	7

[a] Conversion yield determined by ^{1}H NMR analysis of crude reaction mixture.

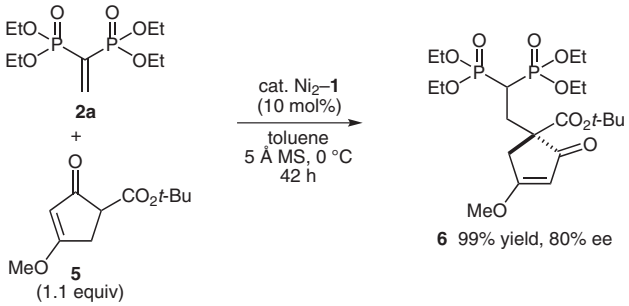
Table 2 Optimization of Reaction Conditions



Entry	Nitroacetate	Solvent	Additive	Catalyst (x mol%)	Time (h)	Conv. (%)[a]	ee (%)
1	**3a**	THF	none	10	41	>95	38
2	**3b**	THF	none	10	45	>95	58
3	**3b**	EtOH	none	10	45	>95	3
4	**3b**	CH_2Cl_2	none	10	45	>95	20
5	**3b**	toluene	none	10	45	>95	75
6	**3b**	toluene	5 Å MS	10	45	>95	83
7	**3b**	toluene	5 Å MS	3	48	95	84

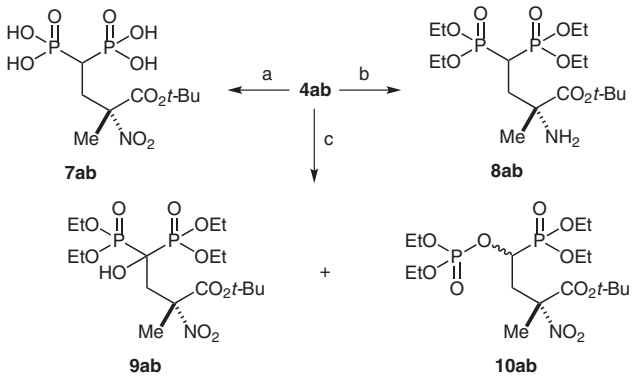
[a] Conversion yield determined by ^{1}H NMR analysis of crude reaction mixture.

acetate **3f** with a phthalimide moiety. Product **4af** was obtained in 81% yield and 93% ee (entry 5). Benzyl and allyl groups were also applicable as protecting groups of bisphosphonic acid (entries 6 and 7), although the reactivity was somewhat decreased, possibly due to steric hindrance. As a donor, not only nitroacetates, but also β-keto ester **5** was applicable, giving product **6** in 80% ee (Scheme 1).[13] Although the precise reaction mechanism is not yet clear, we speculate that a Lewis acid/Brønsted base cooperative mechanism might be involved, as in other reactions promoted by dinuclear Schiff base complexes.[10] A Ni-aryloxide moiety would function as a Brønsted base to deprotonate the α-proton of nitroacetate **3** or β-keto ester **5** to generate a Ni-enolate. The other Ni Lewis acidic metal center would interact with ethylidenebisphosphonate **2**. Mechanistic studies are required to determine the origin of the stereoselectivity.



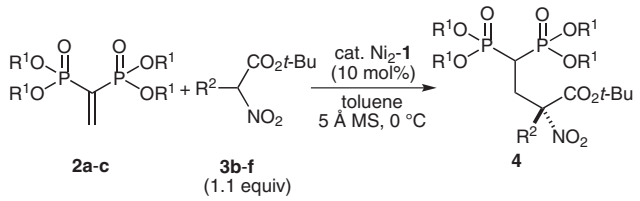
Scheme 1 Catalytic asymmetric 1,4-addition of β-keto ester **5** to vinylidenebisphosphonate **2a**

To demonstrate the utility of the present reaction, transformations of the Michael adduct **4ab** were investigated (Scheme 2). Conversion of the bisphosphonate moiety into a biologically active bisphosphonic acid was successfully performed with TMSBr at 50 °C. The *tert*-butyl ester moiety remained unchanged when the reaction was performed in the presence of *N*,*O*-bis(trimethylsilyl)acetamide,[4b] and bisphosphonic acid **7ab** was obtained in quantitative yield. The nitro group in **4ab** was reduced using $NiCl_2$ and $NaBH_4$ to afford bisphosphonate **8ab** with an α-amino ester group in 92% yield. Because BP with both α-hydroxy and γ-amino moieties have higher biological activities,[6,14] we investigated the introduction of α-hydroxy group to **4ab**. By treatment of **4ab** with KO*t*-Bu and dimethyldioxirane at –78 °C for 10 minutes, desired **9ab** was obtained in 48% isolated yield. The isolated yield

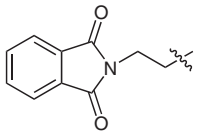


Scheme 2 Transformation of product **4ab**. *Reagents and conditions*: a) TMSBr, *N*,*O*-bis(trimethylsilyl)acetamide, 50 °C, 14 h; then MeOH, r.t., 2 h, quant.; b) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, 0 °C to r.t., 12 h, 92% yield; c) KO*t*-Bu, dimethyldioxirane, THF–acetone, –78 °C, 10 min, 48% (**9ab**), 26% (**10ab**).

Table 3 Catalytic Asymmetric 1,4-Addition of Nitroacetates **3b–f** to Vinylidenebisphosphonate **2a–c**



2a-c **3b-f** (1.1 equiv) **4**

Entry	Bisphosphonate **2**, R^1	Nitroacetate **3**, R^2	**4**	Time (h)	Yield (%)[a]	ee (%)[b]
1	**2a**, Et	**3b**, Me	**4ab**	24	83	82
2	**2a**, Et	**3c**, Et	**4ac**	24	94	82
3	**2a**, Et	**3d**, *n*-Pr	**4ad**	24	81	84
4	**2a**, Et	**3e**, Bn	**4ae**	24	88	82
5	**2a**, Et	 **3f**	**4af**	24	81	93
6	**2b**, Bn	**3b**, Me	**4bb**	24	69	81
7	**2c**, allyl	**3b**, Me	**4cb**	24	65	76

[a] Isolated yield of analytically pure compound after silica gel column chromatography.
[b] Determined by chiral HPLC analysis using DAICEL CHIRALPAK AD-H (entries 1, 3–7) or CHIRALCEL OD-H (entry 2).

of **9ab** was moderate due to the formation of byproducts, such as rearranged adduct **10ab**.[14b,c]

In summary, we developed catalytic asymmetric access to optically active nitrogen-containing bisphosphonates. A homodinuclear Ni_2–Schiff base **1** complex promoted catalytic asymmetric 1,4-additions of α-substituted nitroacetates **3** to ethylidenebisphosphonates **2**, giving products in up to 94% yield and 93% ee.[15]

Acknowledgment

This work was partially supported by Grant-in-Aid for Scientific Research (*S*) (for MS), and Grant-in-Aid for Young Scientists (A) (for SM) from JSPS and MEXT.

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(12) To demonstrate the stability of the Ni_2–Schiff base **1** complex, the catalyst stored for 3 months was used in this study. Freshly prepared Ni_2–Schiff base **1** complex showed comparable reactivity and enantioselectivity. For more detailed information of the Ni_2–Schiff base **1** complex, see ref. 10c.

(13) The absolute configuration of **6** was determined by comparing the sign of optical rotation with the literature data in ref. 4b. The enantiofacial selectivity of β-keto ester was same as that observed in the asymmetric Mannich-type reaction of β-keto ester using the Ni_2–Schiff base **1** complex. The absolute configurations of **4** were tentatively assigned in analogy based on the enantiofacial selectivity of nitroacetate **3b** in the asymmetric Mannich-type reactions.

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(15) **General Procedure**
5 Å MS (Fluka, powder, 20 mg) in a test tube was flame-dried prior to use under vacuum for 5 min. After cooling down to r.t., argon gas was refilled, and the Ni_2–Schiff base **1** catalyst (6.4 mg, 0.01 mmol) and toluene (333 μL) were added. The mixture was cooled down to 0 °C, and nitroacetate **3b** (15.9 μL, 0.11 mmol) was added to the mixture. After stirring for 15 min at 0 °C, ethylidenebisphosphonate **2a** (27.5 μL, 0.1 mmol) was added. The reaction mixture was stirred for 24 h at 0 °C. The mixture was filtered through a short pad of SiO_2 (eluent: hexane–acetone = 1:3). The combined filtrate was concentrated under reduced pressure, and the residue was purified by SiO_2 column chromatography (hexane–acetone = 4:1 to 2:1) to afford **4ab** (39.7 mg, 0.083 mmol, 83% yield) as a colorless oil.
Compound **4ab**: colorless oil. IR(neat): ν = 3473, 2982, 1746, 1555, 1251, 1023 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.29–1.40 (m, 12 H), 1.46 (s, 9 H), 1.76 (s, 3 H), 2.36–2.50 (m, 1 H), 2.77–3.01 (m, 2 H), 4.06–4.26 (m, 8 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ =14.8, 16.1–16.4 (m), 19.0, 29.4, 30.3 (t, *J* = 154.0 Hz), 62.9–63.1 (m), 82.8, 90.6, 164.2. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 20.4, 21.4. ESI-MS: *m/z* = 498 $[M + Na]^+$. HRMS: *m/z* calcd for $C_{17}H_{36}NO_{10}P_2$ $[M + H]^+$: 475.1814; found: 476.1811; $[\alpha]_D^{22.5}$ –19.8 (*c* 0.80, $CHCl_3$). HPLC [DAICEL CHIRALPAK AD-H, hexane–2-PrOH (95:5), flow 1 mL/min, detection at 210 nm]: t_R = 21.8 min (major)and 20.2 min (minor).