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# Chiral *N,N′*-dioxide-Yb(III) complexes catalyzed enantioselective hydrophosphonylation of aldehydes

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ABSTRACT

Chiral *N,N′*-dioxide-Ytterbium(III) complexes promoted the asymmetric addition of diethyl phosphate to aldehydes, giving the corresponding products with good yields and enantioselectivities. The addition of pyridine favored both reactivity and enantioselectivity. A possible catalytic cycle was proposed to explain the mechanism of the asymmetric hydrophosphonylation of aldehydes.



## 1. Introduction

The catalytic asymmetric hydrophosphonylation of aldehydes is one of the most powerful strategies for the synthesis of α-hydroxy phosphonates, whose structure–activity relationship demonstrates wide applications in modern pharmaceutical chemistry such as antibiotics, antiviral, HIV protease, and anticancer.[1,2] Since the pioneering study of Wynberg on enantioselective hydrophosphonylation of aldehydes with the use of cinchona alkaloids,[3] various catalytic systems, including organic molecules[4] and chiral metal complexes[5], have been developed. Shibasaki group reported the first highly enantioselective hydrophosphonylation of aldehydes using heterobimetallic complexes as the catalysts.[5d,f] Subsequently, excellent results were also observed by Katsuki,[5j–l] Yamamoto[5o], and our group[5n] using chiral aluminum complexes, respectively. Very recently, titanium-BINOL-cinchonidine complex was also employed to the reaction with excellent results.[5r] However, chiral Ytterbium complexes have not been utilized for this reaction so far. On the other hand, chiral *N*-oxides and their metal complexes have been shown to be highly efficient in many asymmetric reactions.[6] Herein, we wish to present chiral *N,N′*-dioxide **L2**-Ytterbium(III) complex-catalyzed asymmetric hydrophosphonylation of various aldehydes, giving the desired products in good to excellent yields (up to 99%) with good enantioselectivities (up to 82% ee). Based on the previous reports and our experiments, the mechanism of the reaction was carefully discussed.

Initially, benzaldehyde **1a** and diethyl phosphate **2** were chosen as model reaction to optimize the reaction conditions. A series of *N,N′*-dioxide **L2**-metal complexes were examined. However, only poor enantioselectivities were obtained in the presence of $Sc(OTf)_3$, $Y(OTf)_3$, $La(OTf)_3$, and $Sm(OTf)_3$ (Table 1, entries 1–4). Fortunately, **L2**-$Yb(OTf)_3$ showed great potential in this reaction, giving the product **3a** in 53% yield with 60% ee (Table 1, entry 5). Interestingly, the opposite configuration was also obtained with 47% ee, when $Fe(BF_4)_2{\cdot}6H_2O$ was chosen as a central metal (Table 1, entry 6). Considering both the yield and the enantioselectivity, $Yb(OTf)_3$ was chosen for the next investigation.

Then, several *N,N′*-dioxide ligands (Fig. 1, **L1**–**L9**) were complexed in situ with $Yb(OTf)_3$ to catalyze the asymmetric hydrophosphonylation of benzaldehyde **1a**. As shown in Table 2, the chiral backbone and the steric hindrance of R group of amide moiety exhibited their importance in the enantioselectivities. (*S*)-pipecolic acid-oriented *N,N′*-dioxide **L2** was superior to L-ramipril acid-derived and L-proline-based ones (Table 2, entry 2 vs entries 1 and 9). On the other hand, bulkier amine-substituted amide provided better result (Table 2, entry 2 vs entries 3–8). Accordingly, **L2**-$Yb(OTf)_3$ complex has the highest capability.

To further improve the enantioselectivity, the reaction temperature was lowered to 0 °C; the enantioselectivity increased to 68% ee, but the yield was dramatically decreased (Table 2, entry 10). When 4 Å molecular sieves was added to the reaction system,[7] the yield was greatly improved without any loss in enantioselectivity (Table 2, entry 11). Inspired by previous reports, different bases were tested.[5l] $Na_2CO_3$, $K_2CO_3$, $iPr_2NEt$, and $Et_3N$ have little influence on the enantioselectivity, while pyridine improved the

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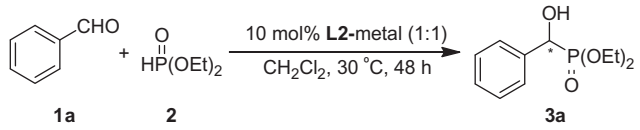
**Table 1**
Central metal effects on the hydrophosphonylation of aldehydes[a]




1a 2 3a

| Entry | Metal | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | $Sc(OTf)_3$ | 53 | 22(*R*) |
| 2 | $La(OTf)_3$ | 58 | 7(*R*) |
| 3 | $Y(OTf)_3$ | 43 | 27(*R*) |
| 4 | $Sm(OTf)_3$ | 50 | 3(*R*) |
| 5 | $Yb(OTf)_3$ | 53 | 60(*R*) |
| 6 | $Fe(BF_4)_2{\cdot}6H_2O$ | 54 | 47(*S*) |

[a] All reactions were carried out under nitrogen, benzaldehyde (0.1 mmol), diethyl phosphite (0.15 mmol), 10 mol % **L2**, and 10 mol % metal in 0.5 mL $CH_2Cl_2$ at 30 °C for 48 h.
[b] Isolated yield.
[c] Determined by HPLC analysis, the absolute configurations of **3a** was determined by comparing specific rotation.[5a,c,n]

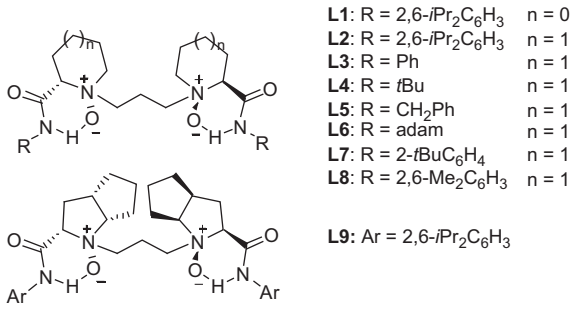


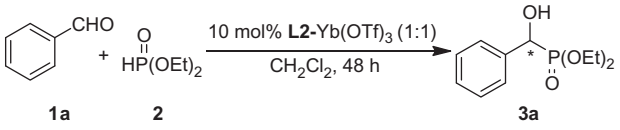

**Figure 1.** Structure of ligands.

enantioselectivity slightly (Table 2, entry 12). Fortunately, when the temperature was further decreased to −20 °C, an obvious increase in the enantiomeric excess, from 71% to 78%, was achieved, but the yield sharply decreased (Table 2, entry 13). When 16 μL of pyridine was added, the yield was improved up to 90% without reduction in enantioselectivity (Table 2, entry 14). Therefore, the optimal reaction conditions were identified as follows: 0.1 mmol benzaldehyde, 1.5 equiv diethyl phosphate, 20 mg 4 Å molecular sieves, 10 mol % **L2**, 10 mol % $Yb(OTf)_3$, 16 μL pyridine as additive in $CH_2Cl_2$ (0.5 mL) at −20 °C.

Under the optimized conditions, a range of aldehydes were investigated,[8] giving the corresponding products in high yields and good ee values. Aldehydes bearing electron-donating groups gave slightly higher enantioselectivities and reactivities than the electron-withdrawing ones (Table 3, entries 2–9 vs 10–13). Furaldehyde was also found to be suitable in the reaction, and good result was obtained (Table 3, entry 14). The α,β-unsaturated aldehyde worked well with diethyl phosphate, giving the desired product in 99% yield and 70% ee (Table 3, entry 15). The condensed-ring aldehydes (1-naphthyl, 2-naphthyl) were also tested, delivering the corresponding products with good yields and enantioselectivities (Table 3, entries 16 and 17).

To clarify the mechanism of the reaction, some control experiments were carried out. When pyridine was used in the absence of **L2**-Yb(III) complex, the reaction did not occur, which implied that the weak base pyridine could not catalyze the reaction independently.[4,9] **L2**-Ytterbium(III) complex promoted the reaction smoothly at 0 °C, and the addition of pyridine favored the yield, while the catalyst did not catalyze the reaction without pyridine at −20 °C.[10] On the other hand, **L2**-Yb(III) complex could efficiently

**Table 2**
Ligand effects on the hydrophosphonylation of aldehydes[a]

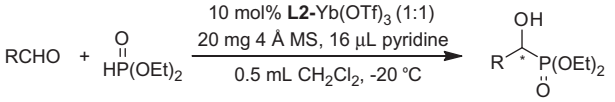



1a 2 3a

| Entry | Ligand | Temp (°C) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **L1** | 30 | 70 | 20 |
| 2 | **L2** | 30 | 53 | 60 |
| 3 | **L3** | 30 | 83 | 11 |
| 4 | **L4** | 30 | 45 | 55 |
| 5 | **L5** | 30 | 61 | 2 |
| 6 | **L6** | 30 | 80 | 30 |
| 7 | **L7** | 30 | 70 | 41 |
| 8 | **L8** | 30 | 53 | 29 |
| 9 | **L9** | 30 | 70 | 21 |
| 10 | **L2** | 0 | 34 | 68 |
| 11[d] | **L2** | 0 | 90 | 68 |
| 12[d,e] | **L2** | 0 | 99 | 71 |
| 13[d,e] | **L2** | −20 | 10 | 78 |
| 14[d,f] | **L2** | −20 | 90 | 78 |

[a] All reactions were carried out under nitrogen, benzaldehyde (0.1 mmol), diethyl phosphite (0.15 mmol), 10 mol % ligand, and 10 mol % $Yb(OTf)_3$ in 0.5 mL $CH_2Cl_2$ for 48 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Molecular sieves (20 mg 4 Å) were added.
[e] Pyridine (0.8 μL) was added.
[f] Pyridine (16 μL) was added.

**Table 3**
Substrate scope for the catalytic asymmetric hydrophosphonylation of aldehydes[a]

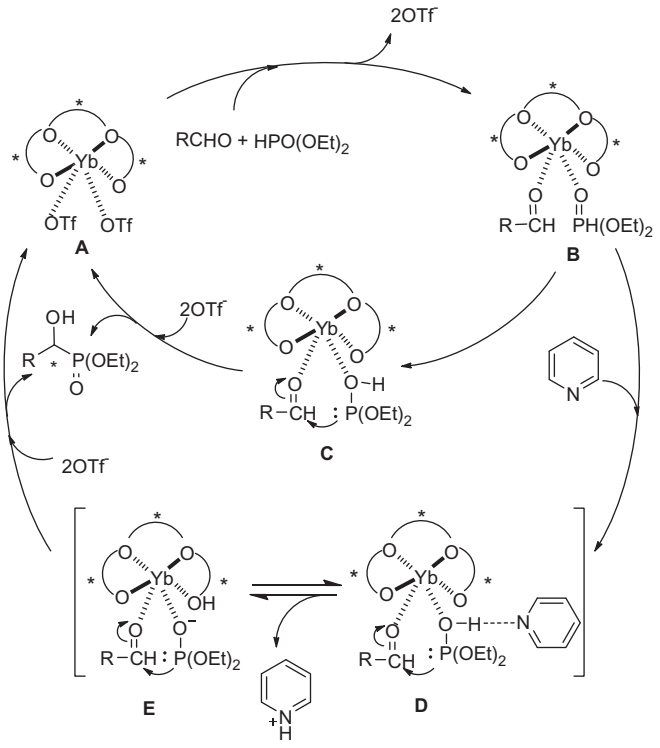



1 2 3

| Entry | R | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | Ph | **3a** | 90 | 78(*R*) |
| 2 | 2-$MeC_6H_4$ | **3b** | 99 | 76 |
| 3 | 3-$MeC_6H_4$ | **3c** | 99 | 80(*R*) |
| 4 | 4-$MeC_6H_4$ | **3d** | 89 | 80 |
| 5 | 2-$MeOC_6H_4$ | **3e** | 97 | 80 |
| 6 | 3-$MeOC_6H_4$ | **3f** | 92 | 71 |
| 7 | 4-$MeOC_6H_4$ | **3g** | 94 | 82(*R*) |
| 8 | 3-$PhOC_6H_4$ | **3h** | 85 | 73 |
| 9 | 4-$PhC_6H_4$ | **3i** | 84 | 74 |
| 10 | 4-$FC_6H_4$ | **3j** | 94 | 71 |
| 11 | 3-$ClC_6H_4$ | **3k** | 72 | 71 |
| 12 | 4-$ClC_6H_4$ | **3l** | 85 | 71(*R*) |
| 13 | 4-$BrC_6H_4$ | **3m** | 79 | 71 |
| 14 | 2-Furyl | **3n** | 87 | 80(*R*) |
| 15 | (*E*)PhCH=CH | **3o** | 68 | 70 |
| 16 | 1-Naphthyl | **3p** | 84 | 74 |
| 17 | 2-Naphthyl | **3q** | 91 | 73 |

[a] All reactions were carried out under nitrogen, aldehyde (0.1 mmol), diethyl phosphite (0.15 mmol), 10 mol % **L2**, 10 mol % $Yb(OTf)_3$, 20 mg 4 Å MS, and 16 μL pyridine in 0.5 mL $CH_2Cl_2$ at −20 °C for 48 h.
[b] Isolated yield.
[c] Determined by HPLC analysis and the absolute configurations were assigned by comparing with reported results of the optical rotation.[5a,c,n]

catalyze the reaction using pyridine as an additive at −20 °C.[11] Based on these facts, a possible mechanism of chiral *N*,*N*′-dioxide **L2**-Ytterbium(III) complex-catalyzed asymmetric hydrophosphonylation was proposed in Scheme 1. As rare metals, Sc(III) and Yb(III) have numerous similar properties, including high oxophilicity and Lewis acidity.[12] We suspected that *N*,*N*′-dioxide-Yb(III)




**Scheme 1.** Proposed mechanism of the hydrophosphonylatin of aldehydes.

generated a transition state similar to *N*,*N*′-dioxide-Sc(III), and all the oxygens of *N*-oxides coordinated with Yb(III).[13]

As a high oxophilic Lewis acid, the **L2**-Ytterbium(III) complex could coordinate with aldehyde and diethyl phosphate efficiently. In addition, Lewis acid favored the conversion of the phosphonate tautomer into the phosphite tautomer (active). After a tautomeric arrangement, the phosphite moiety of intermediate **C** showed enough nucleophilicity to undergo the hydrophosphonylation successfully at 0 °C. However, the reactivity of **C** sharply decreased, when the temperature was lowered to −20 °C. It is supposed that pyridine could enhance the nucleophilicity of the phosphorus atom by trapping the proton of phosphite tautomer,[14] and higher reactive intermediate **D**, **E** could form, in which C–P bond formation could process smoothly at −20 °C. Accordingly, the reaction could proceed in the route of **A**–**B**–**C** at 0 °C without pyridine,[15] while the reaction could proceed in the route of **A**–**B**–**D**–**E** in the presence of pyridine.

In conclusion, we have developed an asymmetric hydrophosphonylation of aldehydes using *N*,*N*′-dioxide **L2**-Ytterbium(III) complex as a catalyst with pyridine as an additive. The reaction underwent smoothly to give the corresponding adducts in good to excellent yields (up to 99%) with good enantioselectivities (up to 82% ee). In addition, a proposed catalyst cycle was depicted. This, along with the expansion of *N*,*N*′-dioxides to other classes of nucleophiles and electrophiles, constitutes the subject of our sustained efforts.

## 2. General procedure

*Typical procedure for the enantioselective hydrophosphonylation of aldehydes.* The mixture of $Yb(OTf)_3$ (6.2 mg), 4 Å molecular sieves (20 mg), **L2** (6.5 mg), and $CH_2Cl_2$ (0.5 mL) was stirred in a test tube under nitrogen atmosphere at room temperature for 30 min. Then aldehyde **1a** (0.1 mmol) was added and stirred for 20 min. The diethyl phosphate (0.15 mmol) and pyridine (16 μL) were added at −20 °C, and the reaction mixture was stirred for 48 h. The pure α-hydroxy phosphonate **3a** was afforded by column chromatography on silica gel (ethyl acetate/petroleum ether 1:1 ~ 5:1) in 90% yield with 78% ee. The ee was determined by HPLC analysis using a Chiral AS-H column (hexane/2-propanol 80:20, 1.0 mL/min, UV = 210 nm; $t_{major}$ = 7.13 min, $t_{minor}$ = 8.92 min). White solid, $[\alpha]_D^{20}$ = +27.4 (*c* 0.175, $CHCl_3$).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.137.

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7. Molecular sieves were added to remove the water that decreased reaction yield, see 5(h).
8. Aliphatic aldehydes were also tested in the reaction, but only poor results were obtained.
9. Benzaldehyde and phenylglyoxal did not react with diethyl phosphate in the presence of 16 μL pyridine, 20 mg 4 Å MS at −20 °C.
10. The catalyst promoted the reaction smoothly in 90% yield with 68% ee in the presence of 10 mol % **L2**-Yb(III) complex, 20 mg 4 Å MS at 0 °C. When 0.8 μL pyridine was added, the yield increased to 99%, but no product was detected at all in the absence of pyridine at −20 °C.
11. The reaction underwent smoothly, giving product in 90% yield with 78% ee in the presence of 10 mol % **L2**-Yb(III) complex, 20 mg 4 Å MS, 16 μL pyridine at −20 °C.
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