Asymmetric Catalysis

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# Highly Enantioselective Synthesis of α-Hydroxy Phosphonic Acid Derivatives by Rh-Catalyzed Asymmetric Hydrogenation with Phosphine–Phosphoramidite Ligands**

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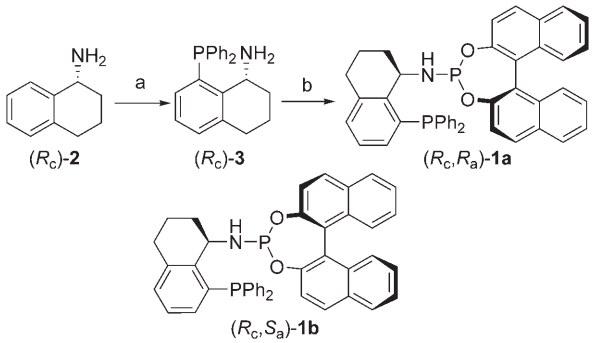
Optically active α-hydroxy phosphonic acid derivatives are widely used as enzyme inhibitors, antibacterial agents, antiviral agents, antibiotics, anticancer agents, and pesticides, as well as useful building blocks for the synthesis of many other important α-functionalized optically active phosphonates.[1] Therefore, an enantioselective synthesis of these compounds is highly desirable. Asymmetric catalysis has provided several novel solutions for the synthesis of chiral α-hydroxy phosphonic acid derivatives, including asymmetric reduction of ketophosphonates[2] and phosphonylation of carbonyl compounds.[3]

For its inherent efficiency and atom economy, much effort in the past few years has been directed toward the development of an asymmetric hydrogenation of α-enol esters of phosphonate substrates.[4] By this means, β-alkyl-substituted α-acyloxy phosphonates were hydrogenated with good enantioselectivities by using Rh catalysts bearing DuPHOS (1,2-bis((2*R*,5*R*)-2,5-dialkylphospholano)benzene), BisP* ((*S*,*S*)-1,2-bis(alkylmethylphosphino)ethane), MiniPHOS (*R*,*R*-bis(alkylmethylphosphino)methane),and phosphine–phosphite ligands. However, catalyst performance for β-aryl- and β-alkoxy-substituted substrates was less than satisfactory, as moderate enantioselectivities or low conversions were observed in most cases.

Recently, Pizzano and co-workers[4d,f] reported that the use of a phosphine–phosphite/Rh catalyst could give rise to an *ee* value of up to 92% in the asymmetric hydrogenation of β-aryl-substituted substrates, although only the β-phenyl-substituted substrate afforded an *ee* value over 90% under full conversion. As for the hydrogenation of β-alkoxy-substituted substrates, there is only one report on the asymmetric hydrogenation of this class of substrates, in which 87% *ee* was obtained.[4c] Therefore, the highly enantioselective synthesis of α-hydroxy phosphonate derivatives by asymmetric hydrogenation of α-enol ester phosphonates, especially those bearing β-aryl or β-alkoxy substituents, is still a significant challenge for organic chemists. Herein, we report a new chiral phosphine–phosphoramidite ligand derived from ($R_c$)-1,2,3,4-tetrahydro-1-naphthylamine ($R_c$ = central chirality), which promoted unprecedented enantioselectivities (up to 99.9% *ee*) in Rh-catalyzed asymmetric hydrogenation across a broad range of substrates bearing β-aryl, β-alkoxy, and β-alkyl substituents.

Ligand design has played a pivotal role in the development of efficient metal-catalyzed asymmetric reactions. Although a large number of bidentate phosphorus ligands with $C_2$ symmetry or two closely related binding sites have been prepared and examined for asymmetric hydrogenation, significantly fewer unsymmetrical hybrid bidentate phosphorus ligands were disclosed.[5] We[6] and others[7] have recently revealed that chiral phosphine–phosphoramidite ligands are highly efficient for the asymmetric hydrogenation of various functionalized olefins, including α- and β-dehydroamino acid esters, itaconate, and enamides. In our ongoing efforts toward the development of new and practical chiral ligands for use in the hydrogenation of challenging substrates, we designed a class of rigid chiral phosphine–phosphoramidite ligands with a 1,2,3,4-tetrahydronaphthalene backbone.

The phosphine–phosphoramidite ligands **1** can be readily prepared from optically pure ($R_c$)-1,2,3,4-tetrahydro-1-naphthylamine (($R_c$)-**2**) through a concise synthetic procedure (Scheme 1). The initial step involves functionalization of




***Scheme 1.*** Synthesis of phosphine–phosphoramidite ligands ($R_c$,$R_a$)-**1a** and ($R_c$,$S_a$)-**1b**: a) 1. *n*BuLi, $ClSiMe_3$, $Et_2O$, 0°C; 2. *n*BuLi, $ClPPh_2$, $Et_2O$, −30°C→RT, 52%; b) ($R_a$)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-α′;3,4-α′]dinaphthalene, $Et_3N$, $CH_2Cl_2$, 0°C–RT, 89%.

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position 8 of ($R_c$)-**2** by a directed metalation reaction to form the key aminophosphine intermediate ($R_c$)-**3**.[8] This compound is then converted into the corresponding phosphine–phosphoramidite ligand ($R_c$,$R_a$)-**1a** ($R_a$ = axial chirality) in high yields by reaction with ($R_a$)-binol-derived chlorophosphite (binol = 1,1′-binaphthalene-2,2′-diol) in $CH_2Cl_2$ at 0 °C in the presence of $Et_3N$. By a similar procedure, diastereomeric ligand ($R_c$,$S_a$)-**1b** was also prepared in good yields. Besides their ready availability, another salient and practical feature of these phosphine–phosphoramidite ligands is their excellent air and moisture stability, which makes the synthesis, use, and storage of these ligands very convenient.

To establish the conformational orientation of the chiral phosphine–phosphoramidite ligand in its coordinated forms, a crystal of the complex [Rh(cod){($R_c$,$R_a$)-**1a**}]$BF_4$ (cod = cycloocta-1,5-diene) prepared from $[Rh(cod)_2]BF_4$ and ($R_c$,$R_a$)-**1a** in $CH_2Cl_2$ was grown and subjected to X-ray diffraction analysis.[9] As shown in Figure 1, a seven-membered heterometallacyclic ring was formed by the chelate coordination of the phosphine and phosphoramidite P atoms of ($R_c$,$R_a$)-**1a** to rhodium, with a P-Rh-P bite angle of 89.5°.

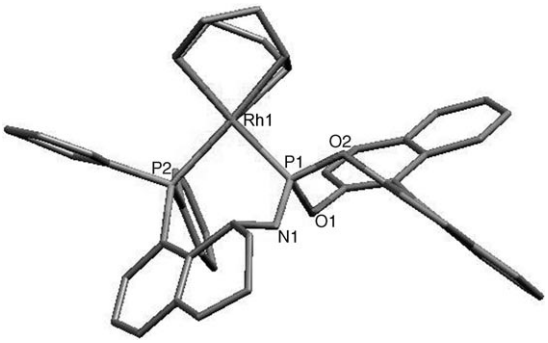
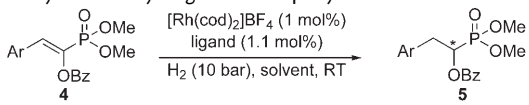



***Figure 1.*** Crystal structure of [Rh(cod)(($R_c$,$R_a$)-**1a**)]$BF_4$. The counter anion ($BF_4^-$), hydrogen atoms, and solvent are omitted for clarity.

These novel phosphine–phosphoramidite ligands were then tested in the Rh-catalyzed asymmetric hydrogenation of enol ester phosphonates. For the initial screening and optimization process, the highly challenging β-phenyl enol ester phosphonate **4a** was selected as substrate, and the results are summarized in Table 1. To our delight, we found that the catalyst generated by mixing $[Rh(cod)_2]BF_4$ (1.0 mol%) with ligand ($R_c$,$R_a$)-**1a** (1.1 mol%) in $CH_2Cl_2$ under a $H_2$ pressure of 10 bar led to full conversion of **4a** into **5a** with an unprecedented *ee* value of 99.4%, which suggests the high potential of this catalytic system in the hydrogenation of enol ester phosphonates (Table 1, entry 1). In contrast, ligand ($R_c$,$S_a$)-**1b** with an ($S_a$)-binaphthyl fragment displayed low enantioselectivity and favored a hydrogenation product with a configuration the same as that obtained with ($R_c$,$R_a$)-**1a** (Table 1, entry 2). These results demonstrate that the central chirality has more influence in determining the absolute configuration of the predominant hydrogenation product, and the matched stereogenic elements are $R_c$ (central chirality) and $R_a$ (axial chirality).

***Table 1:*** Asymmetric hydrogenation of β-aryl substrates **4**.[a]




| Entry | Substrate, Ar | Solvent | *ee* [%] |
|---|---|---|---|
| 1 | **4a**, Ph | $CH_2Cl_2$ | 99.4 |
| 2[b] | **4a**, Ph | $CH_2Cl_2$ | 60.3 |
| 3 | **4a**, Ph | *i*PrOH | 99.5 |
| 4 | **4a**, Ph | toluene | n.d.[c] |
| 5 | **4b**, *p*-$FC_6H_4$ | *i*PrOH | 99.9 |
| 6 | **4c**, *p*-$ClC_6H_4$ | *i*PrOH | 99.9 |
| 7 | **4d**, *p*-$BrC_6H_4$ | *i*PrOH | 99.6 |
| 8 | **4e**, *p*-$NO_2C_6H_4$ | *i*PrOH | 99.2 |
| 9 | **4f**, *p*-$MeOC_6H_4$ | *i*PrOH | 99.9 |
| 10 | **4g**, *m*-$MeOC_6H_4$ | *i*PrOH | 99.8 |
| 11 | **4h**, *m*-$ClC_6H_4$ | *i*PrOH | 99.3 |
| 12 | **4i**, *o*-$ClC_6H_4$ | *i*PrOH | 99.9 |
| 13 | **4j**, 1-naphthyl | *i*PrOH | 99.2 |
| 14 | **4k**, 2-thienyl | $CH_2Cl_2$ | 99.3 |
| 15[d] | **4a**, Ph | $CH_2Cl_2$ | 99.4 |

[a] All reactions were carried out with 0.25 mmol of substrate in 2 mL of the indicated solvent for 12 h under the conditions given in the equation and with 100% conversion, unless otherwise specified. Degrees of conversion were determined by $^1H$ NMR spectroscopy. The *ee* values were determined by HPLC on a chiral column (Chiralpak AD, Chiralcel OD-H, or Chiralcel OJ-H). [b] ($R_c$,$S_a$)-**1b** was used instead of ($R_c$,$R_a$)-**1a** [c] Conversion and *ee* value were not determined because of low conversion. [d] Substrate/$[Rh(cod)_2]BF_4$ = 1000:1, $H_2$ (20 bar).

Subsequent solvent-screening experiments revealed that the nature of the solvent had a profound effect on the catalytic reaction. The hydrogenation reactions performed in $CH_2Cl_2$ and *i*PrOH gave comparable results (Table 1, entries 1 and 3). However, very low conversion was observed when the reaction was carried out in toluene, probably because of the low solubility of the ligand and the resulting catalyst in toluene (Table 1, entry 4). With these encouraging results, we proceeded to investigate the scope of this challenging reaction on various β-aryl enol ester phosphonates, with *i*PrOH as the standard solvent. As the β-2-thienyl substrate has a low solubility in *i*PrOH, in this case $CH_2Cl_2$ was selected as the reaction medium.

As shown in Table 1, a wide range of substituted β-phenyl enol ester phosphonates were hydrogenated to provide the corresponding β-aryl-α-hydroxy phosphonic acid derivatives at high conversions and extremely high enantioselectivities (*ee* values of over 99.0% for all substrates tested) under mild conditions (10 bar $H_2$, room temperature; Table 1, entries 5–12). These results indicate that the reaction system has a high tolerance to the substitution pattern and electronic properties of the substrates.

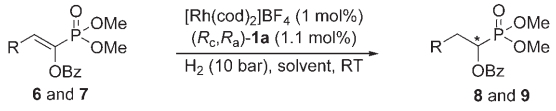
The best enantioselectivities were obtained in the hydrogenation of **4b**, **4c**, **4f**, and **4i**, which afforded the corresponding hydrogenation product with 99.9% *ee* (Table 1, entries 5, 6, 9, and 12). The β-1-naphthyl-substituted substrate led to the corresponding hydrogenation product with 99.2% *ee* (Table 1, entry 13). An outstanding enantioselectivity of 99.3% *ee* was also observed in the hydrogenation of the substrate containing a thienyl group (Table 1, entry 14). To further demonstrate the efficiency of the present catalytic

system, the hydrogenation of **4a** was also performed with reduced catalyst loadings (0.1 mol%); in this reaction, the excellent enantioselectivity remained (Table 1, entry 15). To the best of our knowledge, these results represent the highest catalytic activities and enantioselectivities in the asymmetric hydrogenation of enol ester phosphonates reported so far.

Having established a highly enantioselective hydrogenation of β-aryl enol ester phosphonates **4**, we decided to apply this efficient methodology to the hydrogenation of β-alkoxy enol ester phosphonates **6** (Table 2). The hydrogenation of

***Table 2:*** Asymmetric hydrogenation of β-alkoxy and β-alkyl substrates **6** and **7**.[a]




| Entry | Substrate, R | Solvent | *ee* [%] |
|---|---|---|---|
| 1 | **6a**, OMe | $CH_2Cl_2$ | 99.7 |
| 2 | **6b**, OEt | $CH_2Cl_2$ | 99.9 |
| 3 | **6c**, O*i*Pr | $CH_2Cl_2$ | 98.9 |
| 4 | **7a**, H | *i*PrOH | 99.5 |
| 5 | **7b**, Me | *i*PrOH | 99.8 |
| 6 | **7c**, Et | *i*PrOH | 99.9 |
| 7[b] | **7a**, H | $CH_2Cl_2$ | 99.7 |
| 8[c] | **7a**, H | $CH_2Cl_2$ | 99.1 |

[a] All reactions were carried out with 0.25 mmol of substrate in 2 mL of the indicated solvent for 12 h under the conditions given in the equation, unless otherwise specified. Full conversions were achieved in all reactions. The *ee* values were determined by HPLC on a chiral column (Chiralpak AD or Chiralcel OD-H). [b] Substrate/catalyst = 1000:1. [c] Substrate/catalyst = 2000:1, $H_2$ (20 bar).

these substrates has rarely been investigated, and the highest enantioselectivity of 87% *ee* was reported by Imamoto and co-workers in the hydrogenation of β-methoxy enol ester phosphonate **6a**.[4c] Gratifyingly, the hydrogenation of these substrates proceeded with similar enantiocontrol and conversion as that in the hydrogenation of β-aryl enol ester phosphonates **4**. All β-alkoxy-substituted substrates were hydrogenated with full conversion and excellent enantioselectivities, and the best result of 99.9% *ee* was obtained in the hydrogenation of β-ethoxy enol ester phosphonate **6b** (Table 2, entries 1–3). The enantioselectivity decreased slightly in the hydrogenation of the phosphonate with a branched substituent, as is demonstrated in the result obtained with **6b** (R = EtO, 99.9% *ee*) compared to that with **6c** (R = *i*PrO, 98.9% *ee*; Table 2, entries 2 and 3).

To further demonstrate the scope and flexibility of this methodology, the hydrogenation of two β-alkyl-substituted substrates was also studied with the ligand ($R_c$,$R_a$)-**1a** under the optimized conditions as employed in the hydrogenation of β-aryl enol ester phosphonates. As expected, outstanding enantioselectivity was achieved (Table 2, entries 5 and 6). The outstanding catalytic activity was also demonstrated by the use of low catalyst loadings. The reduction of the catalyst loadings to 0.1 mol% did not affect the conversion and enantioselectivity of the β-unsubtituted derivative **7a** (compare Table 2, entries 4 and 7), although a higher $H_2$ pressure (20 bar) was needed to complete the reaction at lower catalyst loadings of 0.05 mol% (Table 2, entry 8), which is the lowest amount of catalyst used to date. As reported by Burk et al.,[4a] the α-benzoyloxy phosphonates can be simply deprotected by $K_2CO_3$ in methanol at room temperature to afford the corresponding α-hydroxy phosphonates with no apparent loss of optical purity.

In conclusion, new unsymmetrical hybrid phosphine–phosphoramidite ligands have been developed and applied to the enantioselective hydrogenation of various enol ester phosphonates, including β-aryl-, β-alkoxy-, and β-alkyl-substituted substrates. Unprecedented enantioselectivities (up to 99.9% *ee*) have been observed in the hydrogenation of all classes of substrates tested, which represents the best results obtained in the asymmetric hydrogenation of enol ester phosphonates reported so far. Optimization and application of these phosphine–phosphoramidite ligands will be reported in due course.

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[9] CCDC-652171 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

  