Modular Phosphate-Aminophosphate Ligands Based on Chiral 1,2,3,4-Tetrahydro-1-naphthylamine Backbone: A New Class of Practical Ligands for Enantioselective Hydrogenations

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Abstract: A series of new chiral phosphate-aminophosphate ligands [(R)-HW-Phos] has been prepared from (R)-1,2,3,4-tetrahydro-1-naphthylamine through a two-step procedure, and successfully applied in the rhodium-catalyzed asymmetric hydrogenation of various functionalized olefins such as \( \alpha \)-enol ester phosphonates, \( \alpha \)-enamido phosphonates, (Z)-\( \beta \)-(acylamino)acrylates and so on. Excellent enantioselectivities have been achieved in the hydrogenation of most substrates tested, demonstrating the high potential of these newly developed phosphate-aminophosphate ligands in asymmetric catalysis. The present research also discloses that these newly developed phosphate-aminophosphate ligands are more efficient than that derived from (S)-1-phenylethylamine, suggesting that the increased rigidity conferred by a cyclohexyl fragment in these phosphate-aminophosphate ligands has a positive effect in the asymmetric induction.

Keywords: asymmetric catalysis; hydrogenation; phosphate-aminophosphate ligands; rhodium; 1,2,3,4-tetrahydro-1-naphthylamine

Catalytic asymmetric hydrogenation is one of the most powerful and practical tools to access optically active compounds in contemporary synthetic organic chemistry, in which the development of new chiral phosphorus-containing ligands has played a significant role. Although many excellent phosphorus-containing ligands have been reported for highly enantioselective hydrogenations in the past decades, the quest for new efficient ligands remains a major challenge. A recent strategy in this area relies upon the use of unsymmetrical hybrid bidentate phosphorus ligands. Because of holding two chemically distinct phosphorus binding sites, these ligands can offer the unique electronic environment around the metal centre, different from that provided by the ubiquitous \( C_2 \)-symmetrical ligands. Among the various unsymmetrical hybrid bidentate phosphorus ligands, a combination of phosphate and aminophosphate fragments was found to be an effective arrangement for the construction of new unsymmetrical hybrid bidentate phosphorus ligands. The first successful phosphate-aminophosphate ligand was known as BoPhoz, reported by Boaz et al in 2002, which showed excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of \( \alpha \)-dehydroamino acid derivatives, itaconate derivatives and \( \alpha \)-keto esters. However, the results in the Rh-catalyzed asymmetric hydrogenation of \( \alpha \)-enamides with these BoPhoz ligands were less satisfactory.

By use of the fluorinated BoPhoz-type ligands, Yip and Chan et al. found that the enantioselectivity for the hydrogenation of this substrate class could be dramatically increased. Chen et al. introduced a stereogenic phosphorus atom into Bophoz-type ligands, and the comparative results demonstrate that \( P \)-chirality improves the enantioselectivity when acting cooperatively with the planar chirality and the chirality at the carbon centre. Although significant progress has been made in the past few years, it should be noted that all of these phosphate-aminophosphate ligands are based on a chiral 1-ferrocenylylthylamine backbone, and few other phosphate-aminophosphate skeletons were found to be effective in asymmetric catalysis. Moreover, the substrate scope with these ligands in catalytic hydrogenation is still limited, whereby some of the more...
challenging substrate classes such as \( \beta \)-dehydroamino acid esters could not be hydrogenated in satisfactory enantioselectivities. Therefore, the search for more practical and efficient phosphine-aminophosphine ligands in terms of ease of preparation and wide substrate scope remains an interesting and important goal.

Very recently, we have developed a readily accessible phosphine-aminophosphine ligand, \((S)-\text{HH-Phos}\), which was prepared through a two-step transformation from inexpensive and commercially available \((S)-1\)-phenylethylamine (Figure 1).[4] Although ee values of 93–97% were achieved in the Rh-catalyzed asymmetric hydrogenation of dimethyl \( \alpha \)-benzoyloxyethenephosphonates and \( N \)-benzyloxycarbonyl \( \alpha \)-enamido phosphonates, the asymmetric induction of this ligand class still needs to be improved. Moreover, \((S)-\text{HH-Phos}\) is less efficient for the hydrogenation of other functionalized olefins, normally giving the hydrogenation products in ee values of <90%. We reasoned that the flexible nature of the chiral phenylethylamine backbone should be responsible for these unsatisfactory results, and ligands with an appropriate rigid structure might have a better asymmetric induction than that derived from \((S)-1\)-phenylethylamine. On the basis of this assumption, we therefore envisioned that chiral 1,2,3,4-tetrahydro-1-naphthylamine-derived phosphine-aminophosphine species might be an excellent ligand class since the increased rigidity conferred by a cyclohexyl fragment may result in high enantioselectivities. Herein we report the synthesis of this new phosphine-aminophosphine ligand class and their applications in highly efficient rhodium-catalyzed asymmetric hydrogenation of \( \alpha \)-enol ester phosphonates, \( \alpha \)-enamido phosphonates, \((Z)\)-\( \beta \)-(acylamino)acrylates and so on.

These new phosphine-aminophosphine ligands can be easily prepared from commercially available, optically active 1,2,3,4-tetrahydro-1-naphthylamine \((R)-\text{THNANH}_2\) through a two-step transformation, which is shown in Scheme 1. The key to the synthesis of these target compounds is the direct \textit{ortho}-functionalization of the \textit{primary} amine, which can be easily carried out by a direct and experimentally convenient one-pot protocol. Thus, \((R)-\text{THNANH}_2\) was treated with \( n \)-BuLi at 0°C, following by slow addition of neat \( \text{ClSiMe}_3 \), \textit{in situ} generated a monosilylated product, \( N \)-(trimethylsilyl)-1,2,3,4-tetrahydro-1-naphthylamine. The latter was further dilithiated by addition of 3 equiv. of \( n \)-BuLi at \(-25^\circ \text{C}\), and then \textit{ortho}-phosphinated with \( \text{ClPPh}_2 \). After work-up and crystallization from \( n \)-hexane, the key intermediate \((R)-\text{THNANH}_2\) was obtained in 52% overall yields. \((R)-\text{THNANH}_2\) was then converted into the corresponding phosphine-aminophosphine ligand \((R)-\text{HW-Phos}\) in high yield by the reaction with \( \text{ClPPh}_2 \) in \( \text{CH}_2\text{Cl}_2 \) at 0°C in the presence of \( \text{Et}_3\text{N} \) as a scavenger.

![Figure 1. Structure of phosphine-aminophosphine ligands](image)

![Scheme 1. Synthesis of \((R)-\text{HW-Phos}\) ligands 1a-d.](image)
Modular Phosphine-Aminophosphine Ligands

Table 1. Rh-catalyzed asymmetric hydrogenation of α-enol ester phosphonates 4\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Conversion [%]</th>
<th>ee [%]</th>
<th>(Configuration)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-HH-Phos</td>
<td>4a: R = H</td>
<td>100</td>
<td>93.1 (S)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>4a: R = H</td>
<td>100</td>
<td>96.5 (R)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>4a: R = H</td>
<td>100</td>
<td>97.7 (R)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>4a: R = H</td>
<td>100</td>
<td>98.7 (R)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>4a: R = H</td>
<td>100</td>
<td>99.4 (R)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>4b: R = Me</td>
<td>100</td>
<td>99.2 (R)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>4c: R = Et</td>
<td>100</td>
<td>99.6 (R)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1d</td>
<td>4d: R = Ph</td>
<td>100</td>
<td>99.2 (R)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1d</td>
<td>4e: R = 4-Cl-C6H4</td>
<td>100</td>
<td>99.0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1d</td>
<td>4f: R = 3-Cl-C6H4</td>
<td>100</td>
<td>99.1</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1d</td>
<td>4g: R = 2-Cl-C6H4</td>
<td>100</td>
<td>98.5</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1d</td>
<td>4h: R = 4-F-C6H4</td>
<td>100</td>
<td>99.8</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1d</td>
<td>4i: R = 4-NO2-C6H4</td>
<td>100</td>
<td>98.7</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1d</td>
<td>4j: R = 4-CH3O-C6H4</td>
<td>100</td>
<td>99.1</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1d</td>
<td>4k: R = 3-CH3OC6H4</td>
<td>100</td>
<td>98.9</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1d</td>
<td>4l: R = O-i-Pr</td>
<td>100</td>
<td>99.7</td>
<td></td>
</tr>
</tbody>
</table>

\[a\] All reactions were performed with 0.25 mmol of substrate at room temperature under an H2 pressure of 10 atm in 2 mL of CH2Cl2 for 24 h. Substrate/[Rh(COD)3]BF4/ligand = 1/0.01/0.011. Full conversions were achieved in all reactions.

\[b\] The ee values were determined by HPLC on a chiral column. The absolute configuration was determined by comparing the optical rotation with the reported data.

For a comparison in the asymmetric induction between (S)-1-phenylethylamine (entry 1, Table 1), significantly higher than that obtained with the phosphine-aminophosphine ligand [(S)-HH-Phos] derived from (S)-1-phenylethylamine (entry 1, Table 1). These results suggested that the increased rigidity in these phosphine-aminophosphine ligands has a positive effect in the asymmetric induction. As it is deduced from the data in Table 1, (R)-HW-Phos 1d, bearing two CF3 groups in the 3,5-positions of the phenyl ring of the aminophosphino moiety, was the most efficient ligand with regard to asymmetric induction and afforded the hydrogenation product with an ee value of 99.4% (entry 5, Table 1). With the optimal ligand 1d, we next examined the enantioselectivity of the hydrogenation of β-alkyl substituted α-benzoyloxyethenephosphonates 4b and c. The results indicated that the β-aryl substituted in the substrate has little effect on the enantioselectivity. Thus, 4b with a methyl group and 4c with an ethyl group were hydrogenated in 99.2% ee and 99.6% ee, respectively (entries 6 and 7, Table 1). To further broaden the synthetic interest of this highly enantioselective procedure, a set of structurally diverse β-aryl substituted substrates 4d-k was submitted to the optimized Rh-catalyzed asymmetric hydrogenation. The catalytic asymmetric hydrogenation of β-aryl substituted α-enol ester phosphonates remains a challenging task.\[5\] It is only very recently that some unsymmetrical hybrid bidentate phosphorus ligands have been found to show good to
excellent enantioselectivities in this transformation.\[^{[6]}\]

Therefore, the search of new chiral ligands with the properties superior to their predecessors for this transformation is still highly desirable. Gratifyingly, we found that all \(\beta\)-aryl substituted substrates \(4d-k\) were hydrogenated in excellent enantioselectivity (98.5–99.8\% \(ee\)) with the present catalytic system, regardless of the substitution pattern and electronic properties of the substituent in the phenyl ring of the substrate (entries 8–15, Table 1). High enantioselectivity was also observed in the hydrogenation of the \(\beta\)-alkoxy-substituted substrate \(4l\), for which 99.7\% \(ee\) was obtained (entry 16, Table 1). These results demonstrate that the present catalytic system is highly enantioselective in the hydrogenation of \(\alpha\)-enol ester phosphonates, comparable to the best results reported so far.\[^{[5,4]}\] However, an attempt to lower the catalyst loadings to 0.1 mol% failed, under the optimized hydrogenation conditions, <50\% conversions were achieved.

To further demonstrate the scope and flexibility of the present catalytic system, we decided to apply the phosphine-aminophosphine ligands \(1\) to the hydrogenation of \(\alpha\)-enamido phosphonates \(6\). Although the catalytic asymmetric hydrogenation of \(\alpha\)-dehydroamino acid derivatives is one of the most studied and widely applied methods for the enantioselective preparation of \(\alpha\)-amino acids, there are only a few catalytic hydrogenation methods available to access optically active \(\alpha\)-aminophosphonic acid derivatives, partly due to the difficult accessibility of a variety of substituted enamido phosphonates.\[^{[3]}\]

Some \(N\)-protected \(\alpha\)-enamido phosphonates \(6a-d\) were prepared in moderate yields by the condensation reaction between acyl phosphonates and amides as described in the literature.\[^{[6]}\] However, the synthesis of other substituted substrates using the same method failed. The subsequent hydrogenation was performed under the optimized conditions (CH\(_2\)Cl\(_2\) as the reaction media, H\(_2\) pressure of 10 atm, and room temperature for 24 h) as employed in the hydrogenation of \(\alpha\)-enol ester phosphonates. The results in Table 2 disclose that these newly developed phosphine-aminophosphine ligands \([(R)]-HW-Phos \(1a-d\)] are also highly efficient for the hydrogenation of dimethyl \(\alpha\)-benzamidocarboxynitrophenyl phosphonate \((6a)\), providing higher enantioselectivities than that obtained with \((S)\)-HH-Phos. Again, \((R)\)-HW-Phos \(1d\), bearing two CF\(_3\) groups in the 3,5-positions of the phenyl ring of the aminophosphino moiety, was found to be the most efficient ligand with regard to asymmetric induction and afforded the hydrogenation product with an \(ee\) value of 99.6\% (entry 5, Table 2). Protective groups on the nitrogen had little impact on the enantioselectivity, normally giving \(ee\) values of over 99\% (entries 5 and 6, Table 2). The \(\beta\)-substituent in the substrates had an significant effect in the enantioselectivity. For the hydrogenation of the substrate \(6c\) with a \(\beta\)-methyl substituent, a low conversion was observed even in an elevated H\(_2\) pressure (entry 7, Table 2). In sharp contrast, the substrate \(6d\) with a \(\beta\)-phenyl substituent was hydrogenated in full conversion and 99.1\% \(ee\) (entry 8, Table 2).

We continued our investigation on the use of these new phosphine-aminophosphine ligands \(1a-d\) in the hydrogenation of \((Z)\)-\(\beta\)-aryl-\(\beta\)-(acylamino)acrylates \(8a-h\). The asymmetric hydrogenation of \(\beta\)-(acylamino)acrylates, in particular those bearing an aryl group

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**Table 2. Rh-catalyzed asymmetric hydrogenation of \(\alpha\)-enamido phosphonates \(6\)[a]**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Conversion [%]</th>
<th>(ee) [%]</th>
<th>(Configuration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-HH-Phos</td>
<td>6a: R(^1) = H, R(^2) = Cbz</td>
<td>100</td>
<td>96.2 (S)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>6a: R(^1) = H, R(^2) = Cbz</td>
<td>100</td>
<td>98.7 (R)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>6a: R(^1) = H, R(^2) = Cbz</td>
<td>100</td>
<td>99.5 (R)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>6a: R(^1) = H, R(^2) = Cbz</td>
<td>100</td>
<td>99.9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>6a: R(^1) = H, R(^2) = Cbz</td>
<td>100</td>
<td>99.6 (R)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>6b: R(^1) = H, R(^2) = Ac</td>
<td>100</td>
<td>99.9</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>6c: R(^1) = Me, R(^2) = Cbz</td>
<td>100</td>
<td>99.1 (R)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1d</td>
<td>6d: R(^1) = Ph, R(^2) = Cbz</td>
<td>100</td>
<td>99.1 (R)</td>
<td></td>
</tr>
</tbody>
</table>

[a] All reactions were performed with 0.25 mmol of substrate at room temperature under an H\(_2\) pressure of 10 atm in 2 mL of CH\(_2\)Cl\(_2\) for 24 h. Substrate/[Rh(COD)\(_2\)]BF\(_4\) /ligand = 1/0.01/0.011. Full conversions were achieved in all reactions.

[b] The \(ee\) values were determined by HPLC on a chiral column. The absolute configuration was determined by comparing the optical rotation with the reported data.

[c] Not determined because of low conversion.
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Table 3. Rh-catalyzed asymmetric hydrogenation of (Z)-β-aryl-β-(acylamino)acrylates 8,[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Conversion [%]</th>
<th>ee [%] (Configuration)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-HH-Phos</td>
<td>8a: Ar = Ph, R = Et</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>8a: Ar = Ph, R = Et</td>
<td>100</td>
<td>93.5 (R)</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>8a: Ar = Ph, R = Et</td>
<td>100</td>
<td>92.1 (R)</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>8a: Ar = Ph, R = Et</td>
<td>100</td>
<td>94.9 (R)</td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>8a: Ar = Ph, R = Et</td>
<td>100</td>
<td>92.1 (R)</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>8b: Ar = 4-Me-C6H4, R = Me</td>
<td>100</td>
<td>95.7</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>8c: Ar = 3-Me-C6H4, R = Me</td>
<td>100</td>
<td>95.0</td>
</tr>
<tr>
<td>8</td>
<td>1c</td>
<td>8d: Ar = 2-Me-C6H4, R = Me</td>
<td>100</td>
<td>96.5</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>8e: Ar = 4-MeO-C6H4, R = Me</td>
<td>100</td>
<td>96.8</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>8f: Ar = 4-MeO-C6H4, R = Et</td>
<td>100</td>
<td>96.3</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>8g: Ar = 4-Me-C6H4, R = Et</td>
<td>100</td>
<td>96.2</td>
</tr>
<tr>
<td>12</td>
<td>1c</td>
<td>8h: Ar = 3-MeO-C6H4, R = Et</td>
<td>100</td>
<td>96.8</td>
</tr>
</tbody>
</table>

[a] All reactions were performed with 0.25 mmol of substrate at room temperature under an H2 pressure of 10 atm in 2 mL of MeOH for 24 h. Substrate/[Rh(COD)2]BF4/ligand = 1/0.01/0.011.

[b] The ee values were determined by GC or HPLC on a chiral column. The absolute configuration was determined by comparing the optical rotation with the reported data.

at β-position, remains much less successful compared to the hydrogenation of their α-analogues. Although some chiral monodentate and bidentate phosphorus-containing ligands have recently been reported to show good to excellent enantioselectivities,[9] phosphine-aminophosphine ligands have proved to be an inferior ligand for this transformation and displayed only low to moderate enantioselectivities.[10] Initially, we examined the influence of the ligand structure on the reactivity and enantioselectivity. Hydrogenation was conducted in MeOH at room temperature under an H2 pressure of 10 bar in the presence of 1.0 mol% catalysts prepared in situ from [Rh(COD)2]BF4 and 1.1 equiv. of chiral ligand. As shown in Table 2, phe-nyl ethylamine-derived phosphine-aminophosphine ligand [(S)-HH-Phos] surprisingly showed no activity in the hydrogenation of (Z)-β-phenyl-β-(acylamino)acrylates 8a (entry 1, Table 3). In sharp contrast, the corresponding (R)-HW-Phos 1a exhibited satisfactory results, providing the hydrogenation product in full conversion with 93.5% ee (entry 2, Table 3). The subsequent experiments disclosed that all of the chiral 1,2,3,4-tetrahydro-1-naphthylamine-derived phosphine-aminophosphine ligands 1a–d were efficient for the hydrogenation of (Z)-β-phenyl-β-(acylamino)acrylates 8a, giving the hydrogenation products in full conversions with good enantioselectivities (92.1–94.9% ee, entries 2–5, Table 3). However, different from that in the hydrogenation of α-enol ester phosphonates, (R)-HW-Phos 1c with a CF3 group in the 4-position of the phenyl ring of the aminophosphino moiety exhibited the highest enantioselectivity (94.9% ee, entry 4, Table 3). With the optimal ligand 1c, a variety of (Z)-β-aryl-β-(acylamino)acrylates 8b–h were hydrogenated in excellent enantioselectivities (95.0–96.8% ee, entries 6–12, Table 3), which represented the best result in the hydrogenation of β-(acylamino)acrylates with phosphine-aminophosphine ligands.

We also investigated the efficiency of these newly developed phosphine-aminophosphine ligands 1 in the hydrogenation of some other functionalized olefins such as α-dehydroamino acid esters, α-enamides and itaconate (Figure 2), and the results are summarized in Table 4. For the hydrogenation α-dehydroamino acid esters 10, (R)-HW-Phos 1d proved to be the best ligand and provided the hydrogenation products in good enantioselectivities (entries 1–4, Table 4). Unexpectedly, this kind of ligands was inefficient in the hydrogenation of dimethyl itaconate 11 in terms of asymmetric induction, in which an ee value of only
Table 4. Rh-catalyzed asymmetric hydrogenation of functionalized olefins and ketones 10-13.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Conversion [%]</th>
<th>ee [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1d</td>
<td>10a: R¹ = H, R² = Me</td>
<td>100</td>
<td>95.2</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>10b: R¹ = H, R² = Et</td>
<td>100</td>
<td>95.4</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>10c: R¹ = OMe, R² = Me</td>
<td>100</td>
<td>95.6</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>10d: R¹ = Cl, R² = Me</td>
<td>100</td>
<td>94.0</td>
</tr>
</tbody>
</table>

[a] All reactions were performed with 0.25 mmol of substrate at room temperature under an H2 pressure of 10 atm in 2 mL of CH2Cl2 for 24 h. Substrate/[Rh(COD)2]BF4/ligand = 1.0/0.01/0.01.
[b] The ee values were determined by GC on a chiral column.
[c] Not determined because of low conversion.

55% ee was achieved (entry 5, Table 4). Different from that in the hydrogenation of α-dehydroamino acid esters, (R)-HW-Phos 1b with two F-atoms in the 3,5-positions of the phenyl ring of the aminophosphino moiety was found to be the most efficient ligand for the hydrogenation of enamides 12. A variety of enamides 12 was hydrogenated in good enantioselectivities, regardless of the electronic properties of the substrates (entries 6-11, Table 4). The hydrogenation of functionalized ketone 13 with Rh and Ru catalysts proved to be inefficient, only low conversions were achieved (entry 12, Table 4).

In summary, we have developed a new class of readily available, air-stable chiral phosphino-amino-phosphine ligands [(R)-HW-Phos 1] and successfully applied them to the enantioselective hydrogenation of various functionalized olefins such as α-enol ester phosphonates, α-enamido phosphonates and (Z)-β-aryl-β-(acylamino)acyrates and so on. Excellent enantioselectivities have been achieved in the hydrogenation of most substrates tested, demonstrating the high potential of these phosphine-amino phosphine ligands in the preparation of optically active α-hydroxyphosphonates, α-amino phosphonates, β-aryl-β-amino acid esters and so on. The present research also indicated that the increased rigidity conferred by a cyclohexyl fragment in these phosphine-amino phosphine ligands has a positive effect in the asymmetric induction. Studies to further investigate the scope of these ligands are currently in progress.

Experimental Section

General Procedure for the Synthesis of Phosphine-Amino-phosphine Derivatives (R)-HW-Phos 1

Chlorodiphenylphosphine (0.2 mL, 1.1 mmol, 1.1 equiv.) was dissolved in 2.0 mL of dried CH2Cl2, which was cooled to 0°C. A solution of amino-phosphine intermediate (R)-THNANH2 3 (331 mg; 1.0 mmol) and Et3N (303 mg, 3.0 mmol) in 2.0 mL of CH2Cl2 was added dropwise to above solution during 30 min. The resulting mixture was left standing at room temperature overnight. The residue was purified by column chromatography, resulting in (R)-HW-Phos 1a as white solid: yield: 440 mg (85%), mp 128-129°C; [α]D:[b] = -118.2 (c 0.504, CHCl3); 1H NMR (400 MHz, CDCl3); δ = 1.54–1.61 (m, 2H), 1.91–1.92 (m, 1H), 2.15–2.18 (m, 1H), 2.29–2.34 (m, 1H), 2.72–2.75 (m, 1H), 2.83–2.87 (m, 1H), 5.05 (m, 1H), 6.81 (m, 1H), 7.05–7.27 (m, 20H), 7.38 (m, 2H); 31P NMR (162 MHz, CDCl3); δ = -16.5, 34.8; 13C NMR (100 MHz, CDCl3); δ = 16.5, 29.5, 30.2, 50.2, 127.4, 127.9, 128.2, 128.3, 128.4, 128.5, 130.7, 131.5, 131.7, 133.0, 133.4, 133.6, 133.8, 134.0, 137.2, 138.7; HR-MS: m/z: 516.1991, calcd. for C35H28NP2 [M+H]+: 516.2010.

(R)-HW-Phos 1b: mp 94–95°C; [α]D:[b] = -94.3 (c 0.582, CHCl3); 1H NMR (400 MHz, CDCl3); δ = 1.65–1.73 (m, 2H), 1.91 (m, 1H), 2.08–2.12 (m, 1H), 2.32–2.37 (m, 1H), 2.79–2.83 (m, 1H), 2.88–2.90 (m, 1H), 4.97–4.98 (m, 1H), 6.83–6.86 (m, 6H), 7.08–7.72 (m, 13H); 31P NMR (162 MHz, CDCl3); δ = -16.2, 34.5; 13C NMR (100 MHz, CDCl3); δ = 16.7, 29.5, 30.2, 50.3, 103.4, 104.2, 104.5, 104.7, 113.4, 113.7, 113.9, 127.8, 128.7, 130.9, 133.0, 133.5, 133.7, 133.8, 134.0, 136.8, 136.9, 137.1, 137.3, 138.0, 138.1, 161.7; HR-MS: m/z: 586.1483, calcd. for C35H28F4NP2 [M+H]+: 586.1477.

(R)-HW-Phos 1c: mp 88–89°C; [α]D:[b] = -90.8 (c 0.526, CHCl3); 1H NMR (400 MHz, CDCl3); δ = 1.63–1.71 (m, 2H), 1.95 (m, 1H), 2.07–2.11 (m, 1H), 2.39–2.44 (m, 1H), 2.78–2.82 (m, 1H), 2.88–2.89 (m, 1H), 4.96–4.97 (m, 1H), 6.76 (m, 1H), 7.00 (m, 2H), 7.09–7.29 (m, 13H), 7.43–8.03 (m, 5H); 31P NMR (162 MHz, CDCl3); δ = -15.8, 34.2; 13C NMR (100 MHz, CDCl3); δ = 16.7, 29.5, 30.4, 52.3, 125.5, 125.6, 127.7, 128.0, 128.6, 128.7, 128.9, 130.9, 132.9, 133.5, 133.7, 133.8, 134.0, 134.5, 134.7, 134.8, 138.2, 143.5; HR-MS: m/z: 650.1626, calcd. for C35H28F3NP2 [M+H]+: 650.1601.

(R)-HW-Phos 1d: mp 164–165°C; [α]D:[b] = -65.7 (c 0.504, CHCl3); 1H NMR (400 MHz, CDCl3); δ = 1.69–1.80 (m, 2H), 2.02–2.05 (m, 2H), 2.53–2.58 (m, 1H), 2.81–2.85 (m, 1H), 2.91–2.93 (m, 1H), 4.92–4.93 (m, 1H), 6.72 (m, 1H), 6.87–6.91 (m, 2H), 7.11–7.31 (m, 10H), 7.77–7.84 (m, 6H); 31P NMR (162 MHz, CDCl3); δ = -15.1, 34.0; 13C NMR (100 MHz, CDCl3); δ = 16.8, 29.5, 30.7, 52.6, 123.0, 123.2, 124.7, 126.1, 128.5, 128.6, 128.7, 128.8, 129.0, 130.8, 131.0, 131.5, 131.7, 132.8, 133.5, 133.7, 133.8, 137.4, 144.8, 146.0, 146.2; HR-MS: m/z: 786.1326, calcd. for C35H28F3NP2 [M+H]+: 786.1349.

General Procedure for Asymmetric Hydrogenation

In a nitrogen-filled glove-box, [Rh(COD)2]BF4 (1.0 mg, 0.0025 mmol) and (R)-1a (1.4 mg, 0.0028 mmol) were dissolved in degassed CH2Cl2 (1 mL) in a 5-mL vial. After stirring at room temperature for 15 min, a solution of dimethyl
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100:1) in 1 mL of degassed CH₂Cl₂ was added. The resulting mixture was transferred to an autoclave, which was then charged with H₂ (10 atm). The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen gas, the reaction mixture was concentrated under reduced pressure. The residue was purified through a plug of silica gel (eluting with a mixture of hexanes/EtOAc, 2/1) to afford 5a. The enantiomeric excess was determined by chiral GC.

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References


