Synthesis of Novel $C_2$-Symmetrical Bidentate Phosphoramidite Ligands for Rh-catalyzed Asymmetric Hydrogenation of $\beta$-(Acylamino)acrylates

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Abstract: Two new $C_2$-symmetrical bidentate phosphoramidite ligands were synthesized and employed in the Rh-catalyzed asymmetric hydrogenation of $\beta$-(acylamino)acrylates, up to 89% ee with full conversions was obtained.

Keywords: $\beta$-Aminoacid, phosphoramidite, 1,2-diphenylethylenediamine, Rh-catalyzed asymmetric hydrogenation, $\beta$-(acylamino)acrylates.

Enantiomerically pure $\beta$-amino acids and their derivatives are especially attractive due to their vital importance for biochemical and medicinal applications$^1$. One of the most convenient paths to $\beta$-amino acids involves the asymmetric hydrogenation of the corresponding prochiral substrates such as $\beta$-(acylamino)acrylates. Although this approach has been widely used for the preparation of $\alpha$-amino acids, the synthesis of $\beta$-amino acids by the catalyzed asymmetric hydrogenation has turned out to be more problematic$^{2-4}$. Therefore, the development of novel catalyst system with properties superior to their predecessors is still needed. Recently, monophosphoramidites have been found to show excellent enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of $\beta$-(acylamino)acrylates$^{5,6}$. To the best of our knowledge, however, no bidentate phosphoramidite ligands have been described for this catalytic reaction. With this context, we now report the use of two new $C_2$-symmetrical bidentate phosphoramidite ligands 1 derived from 1, 2-diphenylethylenediamine and 1, 1'-bi-2-naphthol in

![Ph](image)

$\text{(S}_1, \text{S}_2, \text{S}_3, \text{S}_4)\text{-1a}$

$\text{(S}_1, \text{S}_2, \text{S}_3, \text{S}_4)\text{-1b}$

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Scheme 1 Synthesis of bidentate phosphoramidite ligands (Sc′, Sc′, Sa′, Sa′)-1a and (Sc′, Sc′, Ra′, Ra′)-1b

Reagent and conditions: (a) HCO₂Et, 50 °C; (b) LiAlH₄, THF, 0 °C; (c) (R)- or (S)-4-chloro-3, 5-dioxa-4-phosphacyclohepta[2, 1-α; 3, 4-α′]dinaphthalene, toluene, 0 °C to rt

Starting from (S, S)-1, 2-diphenylethylenediamine 2, the target ligands were synthesized through a three-step procedure as outlined in Scheme 1. Initially, the formylation of (S, S)-1, 2-diphenylethylenediamine 2 was performed by the treatment of 2 with HCO₂Et at reflux temperature in quantitative yields. The subsequent reduction of 3 with LiAlH₄ in THF at 0 °C gave the corresponding N,N'-dimethyl-1,2-diphenylethylenediamine 4 in 78.1% yields. (S, S)-4 was then treated with (S)- or (R)-1, 1'-bi-2-naphthol-derived chlorophosphites in toluene at 0 °C to give the target ligands (Sc′, Sc′, Sa′, Sa′)-1a or (Sc′, Sc′, Ra′, Ra′)-1b in nearly quantitative yields.

With these new bidentate phosphoramidite ligands in hand, we then examined their efficiency in the Rh-catalyzed asymmetric hydrogenation of β-(acetylamino)acrylates (Scheme 2). The reaction was performed in CH₂Cl₂ at room temperature under a H₂ pressure of 10 bar in the presence of 1 mol% catalysts prepared in situ from Rh(COD)₂BF₄ and 1.1 equiv. of chiral ligand, and the results are summarized in Table 1.

Table 1  Rh-catalyzed asymmetric hydrogenation of β-(acetylamino)acrylates 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Conv. (%)</th>
<th>Ee (%)b</th>
<th>Config.c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S,S,S,S)-1a</td>
<td>(E)-5a: R¹= Me, R² = Et</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>(S,S,R,R)-1b</td>
<td>(E)-5a: R¹= Me, R² = Et</td>
<td>86</td>
<td>89</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>(S,S,R,R)-1b</td>
<td>(Z)-5a: R¹= Me, R² = Et</td>
<td>45</td>
<td>76</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>(S,S,R,R)-1b</td>
<td>(E)-5b: R¹= Et, R² = Me</td>
<td>93</td>
<td>86</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>(S,S,R,R)-1b</td>
<td>(Z)-5b: R¹= Et, R² = Me</td>
<td>98</td>
<td>79</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>(S,S,R,R)-1b</td>
<td>(E)-5c: R¹= i-Pr, R² = Me</td>
<td>100</td>
<td>89</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>(S,S,R,R)-1b</td>
<td>(Z)-5c: R¹= i-Pr, R² = Me</td>
<td>100</td>
<td>70</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>(S,S,R,R)-1b</td>
<td>(Z)-5d: R¹= Ph, R² = Et</td>
<td>100</td>
<td>75</td>
<td>S</td>
</tr>
</tbody>
</table>

a Substrate/Rh/L* = 1/0.01/0.011, H₂ (10 bar), solvent = CH₂Cl₂, room temperature.

b Conversion and enantiomeric excesses were determined by GC using a CP-Chiralsil-L-Val capillary (0.25 mm x 30 m) column.

c The absolute configuration was determined by comparing the GC retention times with GC data in the literature.
Initially, ligand (\(S_c, S_c, S_a, S_a\))-1a was used in the Rh-catalyzed asymmetric hydrogenation of (E)-5a, however, no hydrogenation product was detected even after 24 hours (entry 1). When its diastereoisomer (\(S_c, S_c, S_a, S_a\))-1b was employed in this reaction, an ee-value of up to 89% with 86% yield was obtained (entry 2). We then selected the ligand (\(S_c, S_c, S_a, S_a\))-1b for further study of this reaction. A variety of \(\beta\)-alkyl-\(\beta\)-(acetylamino)acrylates were undertaken to examine the efficiency of this catalyst system. All substrates were hydrogenated in moderate to good enantioselectivity. In most cases, the hydrogenation of (E)-\(\beta\)-(acetylamino)acrylates exhibited higher enantioselectivity than the corresponding (Z)-isomers. The highest enantioselectivity of 89% ee with full conversions was obtained in the hydrogenation of (E)-5d (entries 2, 4, 6 vs entries 3, 5, 7). Ligand (\(S_c, S_c, S_a, S_a\))-1b also showed high catalytic activity in the hydrogenation of \(\beta\)-phenyl-\(\beta\)-(acetylamino)acrylates 5e, however, the enantioselectivity was moderate (75% ee) (entry 8).

In conclusion, we have prepared two new bidentate phosphoramidite ligands. They showed good enantioselectivity (89% ee) was obtained in the Rh-catalyzed asymmetric hydrogenation of \(\beta\)-(acetylamino)acrylates. Further modification and application of these ligands are still in progress.

Acknowledgments
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References and Notes
9. Selected data for compound (\(S_c, S_c, S_a, S_a\)) \(\beta\)-1a: \([\alpha]_D^{25} +161\) (c 0.3, CHCl3); \(^1\)H NMR (CDCl3, \(\delta\) ppm): 1.63 (d, 3 H), 2.34 (d, 3 H), 3.73-3.80 (m, 2 H), 6.58-7.89 (m, 34 H); \(^{31}\)P NMR (CDCl3, \(\delta\) ppm): 144.9. Selected data for compound (\(S_c, S_c, S_a, S_a\)) \(\beta\)-1b: \([\alpha]_D^{25} -101\) (c 0.3, CHCl3); \(^1\)H NMR (CDCl3, \(\delta\) ppm): 1.91 (s, 3 H), 1.94 (s, 3 H), 3.67-3.74 (m, 2 H), 6.56-7.93 (m, 34 H); \(^{31}\)P NMR (CDCl3, \(\delta\) ppm): 145.5.

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