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Enantioselective Synthesis of 2-Aryl-4-piperidones via Rhodium/Phosphoramidite-Catalyzed Conjugate Addition of Arylboroxines

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ABSTRACT

The highly enantioselective synthesis of 2-aryl-4-piperidones by rhodium/phosphoramidite-catalyzed conjugate addition of arylboroxines to 2,3-dihydro-4-pyridones is described. Both enantiomers of a variety of products with sterically and electronically different R substituents were obtained in high isolated yield and with excellent enantioselectivity up to 99%.

The piperidine ring system is a frequently encountered heterocyclic unit in natural compounds and drug candidates. Piperidine alkaloids exhibit a range of biological activities and as such represent important synthetic targets. Piperidines serve an important role as intermediates en route to substituted piperidines and can be found as a part of more complex biologically active compounds. Therefore, the development of short, enantioselective routes to substituted piperidones is a major goal. An attractive catalytic route toward enantipure piperidines is based on the enantioselective conjugate addition to readily accessible N-protected 2,3-dihydro-4-pyridones, which are frequently used in alkaloid synthesis. Until recently, however, no suitable procedures had been developed.

Monodentate phosphoramidite ligands comprise a cheap and easily tunable class of ligands that has already proven to be successful in a variety of reactions, including rhodium-catalyzed asymmetric hydrogenations, rhodium-catalyzed conjugate additions of trifluoroborates and boronic acids, and copper-catalyzed asymmetric conjugate additions of trifluoroborates and boronic acids, and copper-catalyzed asymmetric conjugate additions of


(6) For a review on the asymmetric preparation and synthetic utility of 2,3-dihydro-4-pyridones, see: Comins, D. L. J. Heterocycl. Chem. 1999, 36, 1491–1500.


diorganozinc reagents. Recently, we have reported the synthesis of 2-alkyl-4-piperidines with high enantiomeric excess using the copper/phosphoramide-catalyzed conjugate addition of dialkylzinc reagents to N-protected 2,3-dihydro-4-pyridones. It was noted that this type of substrate is less reactive toward 1,4-addition than cyclic enones, e.g., 2-cyclohexenone.

Although highly enantioselective 1,4-addition of diphenylzinc, using the same catalyst, has been reported for 2-cyclohexenone, the lack of readily available diarylzinc reagents severely limits this method. A more convenient method for the introduction of aryl and alkenyl moieties is the asymmetric rhodium-catalyzed conjugate addition of boronic acids pioneered by Hayashi and Miyaura. Excellent levels of enantioselectivity have been achieved for a broad range of enones using BINAP. Also phosphonites and amidophosphines were successfully applied as chiral ligands. It was shown by our group that phosphoramidites (i.e., L, Figure 1) are exceptionally efficient ligands for this reaction in terms of reaction rate, chemoselectivity, and enantioselectivity.

![Figure 1](image)

**Figure 1.** Phosphoramidite L, a highly efficient ligand in the rhodium-catalyzed conjugate addition of boronic acids.

We envisioned that introduction of aryl groups to 1 (Scheme 1), using the rhodium/phosphoramide-catalyzed conjugate addition of arylboronic acids, could provide a pathway to 2-substituted 4-piperidines that is complementary to our work with dialkylzinc reagents. During our studies, Hayashi et al. reported the enantioselective addition of arylzinc chlorides to 2,3-dihydro-4-pyridones. In that study, it was noted also that this type of substrate is less reactive toward 1,4-addition compared to other enones. The rhodium/BINAP-catalyzed conjugate addition of phenylboronic acid failed to proceed to full conversion, although the enantioselectivity was excellent.

Initial screening of our catalyst system on substrate 1 was performed under standard conditions in a mixture of dioxane/water (10/1) at 100 °C with a catalyst generated from 3 mol % Rh(acac)(C₂H₄)₂ and 7.5 mol % L. As in the report of Hayashi, with 3 equiv of phenylboronic acid, the reaction did not go to completion according to ¹H NMR (entry 1, Table 1). The enantioselectivity was, however, excellent.

![Scheme 1](image)

**Scheme 1**

\[
\text{PhB(OH)_2} \rightarrow \text{PhCO}_2\text{Bn}
\]

**Table 1.** Optimization of the Reaction Conditions for the Rhodium-Catalyzed Conjugate Addition to 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>&quot;PhB&quot; (equiv)</th>
<th>Conditions</th>
<th>Conversion %</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhB(OH)₂ (3.0)</td>
<td>A</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>(PhBO)₂ (1.0)</td>
<td>B</td>
<td>60</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>(PhBO)₂ (3.0)</td>
<td>B</td>
<td>75</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>(PhBO)₂ (1.0)</td>
<td>C</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>(PhBO)₂ (2.0)</td>
<td>C</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>(PhBO)₂ (3.0)</td>
<td>C</td>
<td>100</td>
<td>99</td>
</tr>
</tbody>
</table>

* All reactions were performed on a 0.2 mmol scale with 3 mol % Rh(acac)(C₂H₄)₂ and 7.5 mol % (R)L at 100 °C for 2 h. Conditions: A: 0.55 mL of dioxane/H₂O (10/1). Conditions: B: 0.5 mL of dioxane, 1 equiv of H₂O with respect to boron. Conditions: C: 0.5 mL of dioxane, slow addition of water by syringe pump, 100 °C, 1 h. * Determined by ¹H NMR. * Determined by chiral HPLC.

(96% ee). We then decided to generate phenylboronic acid in situ from phenylboronate ((PhBO)₂) and water (one...
equivalent with respect to boron), providing mild reaction conditions (entries 2-5). The use of this reagent did not improve the conversion but did improve the enantioselectivity to an excellent ee of 99%. Upon slow addition of water, thereby preventing premature hydrolysis of the boroxine, the reaction could be driven to 84% conversion using 1 equiv of boroxine (entry 4) and to full conversion with retention of 99% ee using 3 equiv of the reagent (entry 6).

To show the applicability of this reaction for synthesis on a laboratory scale, it was performed on a 0.5 g (2.2 mmol) scale. After flash chromatography, the product was isolated in 86% yield with 99% ee.

With these optimized conditions in hand, the scope of the asymmetric conjugate addition of arylboroxines to 1 was investigated. High ee values could be obtained with a variety of sterically and electronically diverse arylboroxines (entries 1-8, Table 2). meta- and para-tolyl groups can be introduced with high enantioselectivity and high yield (entries 3 and 4). A dramatic drop in enantioselectivity was observed for the more sterically demanding ortho-tolyl group (entry 2), illustrating a possible limitation of the catalytic method. Products with one or two electron-donating substituents on the aryl were obtained in high yield with high enantioselectivity (entries 5 and 6). However, electron-withdrawing groups such as chloride or fluoride slow the reaction, leading to incomplete conversions (entries 7 and 8). Despite this observation, the enantioselectivity is largely independent of the electronic properties of the substituents, and all para- or meta-substituted products are obtained with excellent ee values between 94 and 98%.

In summary, we have shown that conjugate addition of arylboroxines with a rhodium/phosphoramidite catalyst can be used to prepare 2-aryl-4-piperidones in high isolated yield (82-92%) and with excellent enantioselectivity (up to 99%). We are currently directing our efforts toward enhancing the scope and applications of this method in the synthesis of more complex heterocycles.

**Acknowledgment.** We thank Mrs. T. D. Tiemersma-Wegman for the technical support. Financial support from DSM, the Ministry of Economic Affairs, and NWO/CW, administered through the CW/CombiChem program, is gratefully acknowledged.

**Supporting Information Available:** Experimental details and chromatographic and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Use of arylboroxines was previously reported to have a beneficial effect on both conversion and enantioselectivity in the conjugate addition to highly deactivated 1-alkenylphosphonates; see: Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* 1999, 121, 11591-11592.

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### Table 2. Scope of Arylboroxines in the Rhodium-Catalyzed Asymmetric 1,4-Addition to 1

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph 2a</td>
<td>86</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>o-MeC₆H₄ 2b</td>
<td>82</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>m-MeC₆H₄ 2c</td>
<td>92</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>p-MeC₆H₄ 2d</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>p-MeOC₆H₄ 2e</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>m,p-(MeO)₂C₆H₃ 2f</td>
<td>86</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>p-FC₆H₄ 2g</td>
<td>71</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>p-ClC₆H₄ 2h</td>
<td>55</td>
<td>96</td>
</tr>
</tbody>
</table>

*All reactions were performed in duplicate with both enantiomers of the ligand on a 0.2 mmol scale with 3 mol % Rh(acac)(C₂H₄)₂ and 7.5 mol % L at 100 °C for 2 h. (R)-L gave the (R)-enantiomer of the product in all cases; see Supporting Information.*

*Isolated yield.*

*Determined by chiral HPLC.*

*Thin-layer chromatography shows a spot to spot conversion in 2 h.*