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Asymmetric Conjugate Addition of Arylboronic Acids to Enones Catalyzed by Rhodium-Monodentate Phosphoramidite Complexes in the Presence of Bases

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Abstract: Rhodium(I)-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds was carried out in the presence of a chiral phosphoramidite ligand based on (R)-binol and dialkylamines. The reaction was significantly accelerated in the presence of a base such as KOH and Et$_3$N, allowing the reaction to be completed within 6 h at 50 °C. The addition to 2-cyclohexenone achieved enantioselectivities up to 99%, though they were less effective for 2-cyclopentenone (79% ee), 2-cycloheptenone (77% ee) and acyclic enones (31-43% ee).

Key words: arylboronic acids, rhodium catalyst, phosphoramidite, asymmetric, conjugate addition

The conjugate addition of nucleophiles to activated alkenes such as Michael reaction of enolates or organocopper reagents to enones is a widely used process in organic chemistry. It was recently demonstrated that rhodium(I) complexes are excellent catalysts for such conjugate additions of aryl- and alkenylboronic acids to α,β-unsaturated carbonyl compounds or other Michael acceptors. Since various chiral phosphines are available for rhodium catalysts, the protocol was recently extended to asymmetric versions using chiral P-P ligands such as BINAP and diphosphonites and P-N ligands such as amidomonophosphines. Although BINAP achieved high enantioselectivities practical for the addition to both cyclic and acyclic enones, the reactions often used large excesses of organoboronic acid because of a competitive hydrolytic B-C bond
cleavage of organoboronic acids due to a low catalyst efficiency requiring a temperature of over 100 °C in an aqueous solvent. This problem has recently been solved by the use of RhOH-binap catalyst that completes the reaction at 35 °C.\textsuperscript{6} However, the substrates that can be used have been limited to relatively simple substrates because of the highly rigid coordination space of a BINAP ligand.

In connection with our interest in rhodium-catalyzed reactions of organoboronic acids, we report here the results of a preliminary study on the effects of monodentate phosphoramidite ligands (4) and bases in the 1,4-addition of arylboronic acids to \(\alpha,\beta\)-unsaturated carbonyl compounds (Scheme 1).\textsuperscript{7} Among the various phosphoramidite ligands extensively studied by Feringa and co-workers,\textsuperscript{8} diethylamino derivative (4a) was found to be an excellent catalyst for cyclic enones. Since the enantioselectivity was reduced by raising the reaction temperature, the presence of a base was critical to carry out the reaction under mild conditions and to achieve high enantioselective. The reaction was completed within 6 h at 50 °C in the presence of 1 equivalent of KOH or Et\textsubscript{3}N in striking contrast to the reaction occurring at 90 °C in the absence of a base.

\textit{Scheme 1}

The effects of representative phosphoramidite ligands (4) and enones are summarized in Table 1. The catalyst was prepared \textit{in situ} by mixing Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} (3 mol%) and two equivalents of 4 at room temperature for 1 h. Rh(acac)(coe), [RhCl(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}]\textsubscript{2} and [Rh(OH)(cod)]\textsubscript{2} also gave analogous yields and enantioselectivities to those of Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}. The addition of phenylboronic acid to 2-cyclohexenone at 50 °C for 6 h in aqueous dioxane (6/1) resulted in 19% yield in the absence of a base (entry 1). In contrast, the yields were almost quantitative in the presence of 1 equivalent of Et\textsubscript{3}N or KOH (entries 2 and 3). Phosphoramidites are sensitive to hydrolysis with water, but their rhodium complexes were sufficiently stable to be used in alkaline solution, whereas the yields decreased when a catalyst of less than 1 mol% was used. The enantioselectivities dramatically changed in a series of N,N-dialkylamino derivatives (entries 3-7). Among the ligands studied,
N,N-diethyl derivative (4a) exhibited the best enantioselectivity (98-99% ee, entries 2 and 3). The selectivities were reduced by increasing the bulkiness of amino groups (entries 4-6) except for the morpholine derivative (4e), which exceptionally showed a high selectivity comparable to that of the N,N-diethylamino derivative (entry 7). The phosphoramidites derived from (R)-(+)-binol generally afforded (R)-3-phenylcyclohexanone.

Although hydrolytic B-C bond cleavage is a serious side-reaction at 100 °C, a 50% excess of arylboronic acids was a sufficient amount to complete the reaction at 50 °C. Indeed, both 3-chloro- (2b) and 3-methoxyphenylboronic acid (2c) afforded 75% and 84% yields of products with 98-99% ee (entries 8 and 9). In contrast to the excellent enantioselectivities for 2-cyclohexenone, the ligand was highly sensitive to enones. The selectivities decreased to 79% ee for 2-cyclopentenone and to 77% ee for 2-cycloheptenone (entries 10 and 11). Acyclic enones such as 3-nonen-2-one and 5-methyl-3-hexen-2-one resulted in 1% ee and 11% ee, respectively. Although reoptimization of the ligands for acyclic enones showed that the N,N-diisopropyl derivative (4b) increases the selectivity to 31-43% ee (entries 12 and 13), all attempts at an enantioselective reaction practical for acyclic enones failed. An extension of the protocol to α,β-unsaturated lactones suffered from a slow addition and a high sensitivity to saponification. Finally, an 84% ee was achieved by heating the mixture at 90 °C in the absence of bases (entry 14).

In conclusion, Feringa's phosphoramidites were found to be excellent ligands for the rhodium-catalyzed conjugate addition of arylboronic acids to cyclic enones. High reaction rates and enantioselectivities up to 99% were obtained for 2-cyclohexenone when the reactions were carried out at 50 °C in the presence of a base. Because of the availability of various derivatives by a simple synthetic route, phosphoramidites are practical chiral ligand that are easily variable depending upon the substrates.
Representative procedure (entry 3 in Table 1): A flask charged with Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} (0.03 mmol), 4a (0.06 mmol) and PhB(OH)\textsubscript{2} (1.5 mmol) was flushed with argon. 1,4-Dioxane-H\textsubscript{2}O (6/1, 3 ml) and KOH (10 M in H\textsubscript{2}O, 0.1 ml, 1 mmol) were successively added. After being stirred for 1 h, 2-cyclohexenone (1 mmol) was added. The resulting mixture was then stirred for 6 h at 50 °C. Chromatography over silica gel gave (R)-3-phenylcyclohexanone: 95% yield, 98% ee, [\alpha]\textsuperscript{20}\textsubscript{D} +21.4 (c 0.95, CHCl\textsubscript{3}). The enantiomer excess was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD) with hexane/2-propanol = 98/2.

References and Notes


7. During the course of our study, analogous reaction was carried out at 100 °C in the absence of bases: Boiteau, J-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* 2003, 5, 681.


9. Addition of phenylboronic acid to 3-nonen-2-one (entry 12) showed the enantioselectivities suggesting the superiority of bulky dialkylamino ligands; 4a (1% ee), 4b (43% ee), 4c (7% ee), 4d (26% ee) and 4e (12% ee).
Scheme 1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones
Table 1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones (Scheme 1)\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>enone</th>
<th>ArB(OH)(_2)</th>
<th>ligand</th>
<th>yield/%</th>
<th>ee%</th>
</tr>
</thead>
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<tr>
<td>1(^b)</td>
<td><img src="entry1.png" alt="enone" /></td>
<td>2a</td>
<td>4a</td>
<td>19</td>
<td>-</td>
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<tr>
<td>2(^c)</td>
<td><img src="entry2.png" alt="enone" /></td>
<td>2a</td>
<td>4a</td>
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<td>99 (R)</td>
</tr>
<tr>
<td>3</td>
<td><img src="entry3.png" alt="enone" /></td>
<td>2a</td>
<td>4a</td>
<td>95</td>
<td>98 (R)</td>
</tr>
<tr>
<td>4</td>
<td><img src="entry4.png" alt="enone" /></td>
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<td>4b</td>
<td>38</td>
<td>22 (S)</td>
</tr>
<tr>
<td>5</td>
<td><img src="entry5.png" alt="enone" /></td>
<td>2a</td>
<td>4c</td>
<td>5</td>
<td>24 (R)</td>
</tr>
<tr>
<td>6</td>
<td><img src="entry6.png" alt="enone" /></td>
<td>2a</td>
<td>4d</td>
<td>67</td>
<td>51 (R)</td>
</tr>
<tr>
<td>7</td>
<td><img src="entry7.png" alt="enone" /></td>
<td>2a</td>
<td>4e</td>
<td>68</td>
<td>89 (R)</td>
</tr>
<tr>
<td>8</td>
<td><img src="entry8.png" alt="enone" /></td>
<td>2b</td>
<td>4a</td>
<td>75</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td><img src="entry9.png" alt="enone" /></td>
<td>2c</td>
<td>4a</td>
<td>84</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td><img src="entry10.png" alt="enone" /></td>
<td>2b</td>
<td>4a</td>
<td>97</td>
<td>79</td>
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<tr>
<td>11</td>
<td><img src="entry11.png" alt="enone" /></td>
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<td>4a</td>
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<td>12</td>
<td><img src="entry12.png" alt="enone" /></td>
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<td>4b</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>13</td>
<td><img src="entry13.png" alt="enone" /></td>
<td>2a</td>
<td>4b</td>
<td>39</td>
<td>31</td>
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<td>14(^d)</td>
<td><img src="entry14.png" alt="enone" /></td>
<td>2a</td>
<td>4a</td>
<td>55</td>
<td>84</td>
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\(^a\)A mixture of enone (1 mmol), ArB(OH)\(_2\) (1.5 mmol), Rh(acac)(C\(_2\)H\(_4\))\(_2\) (0.03 mmol), ligand (0.06 mmol) and KOH (1 mmol) in dioxane-H\(_2\)O (6/1, 3 ml) was stirred for 6 h at 50 °C, unless otherwise noted. \(^b\)The reaction was conducted in the absence of KOH. \(^c\)Et\(_3\)N (1 mmol) was used in place of KOH. \(^d\)at 90 °C for 6 h in the absence of KOH.
Graphical abstract

Asymmetric Conjugate Addition of Arylboronic Acids to Enones Catalyzed by Rhodium-Monodentate Phosphoramidite Complexes in the Presence of Bases
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Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

\[
\begin{align*}
\text{R}^1\text{C}=\text{O} & \quad \text{ArB(OH)}_2 \\
\text{Rh catalyst, KOH (1 eq)} & \quad \text{dioxane-H}_2\text{O (6/1), 50 }^\circ\text{C, 6 h} \\
& \quad \text{up to 99%ee for 2-cyclohexenone}
\end{align*}
\]
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<th>ee%</th>
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<td>1(^b)</td>
<td>![enone structure]</td>
<td>2a</td>
<td>4a</td>
<td>19</td>
<td>-</td>
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<td>2a</td>
<td>4c</td>
<td>5</td>
<td>24 (R)</td>
</tr>
<tr>
<td>6</td>
<td>![enone structure]</td>
<td>2a</td>
<td>4d</td>
<td>67</td>
<td>51 (R)</td>
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<td>8</td>
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<td>12</td>
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<td>2a</td>
<td>4b</td>
<td>50</td>
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<td>2a</td>
<td>4b</td>
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<tr>
<td>14(^d)</td>
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