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

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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 Et3N, 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. 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 α,β-unsaturated carbonyl compounds (Scheme 1). Among the various phosphoramidite ligands extensively studied by Feringa and co-workers, 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 Et3N in striking contrast to the reaction occurring at 90 °C in the absence of a base.

The effects of representative phosphoramidite ligands (4) and enones are summarized in Table 1. The catalyst was prepared in situ by mixing Rh(acac)(C2H4)2 (3 mol%) and two equivalents of 4 at room temperature for 1 h. Rh(acac)(coe)2, [RhCl(C2H4)2]2 and [Rh(OH)(cod)]2 also gave analogous yields and enantioselectivities to those of Rh(acac)(C2H4)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 Et3N 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.

Table 1

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, $[\alpha]_{D}^{20} +21.4$ (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)**

<table>
<thead>
<tr>
<th>entry</th>
<th>enone</th>
<th>ArB(OH)(_2)</th>
<th>ligand</th>
<th>yield/%</th>
<th>ee%</th>
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<td>24 (R)</td>
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<td>4d</td>
<td>67</td>
<td>51 (R)</td>
</tr>
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<td>7</td>
<td><img src="image" alt="enone" /></td>
<td>2a</td>
<td>4e</td>
<td>68</td>
<td>89 (R)</td>
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<td>14(^d)</td>
<td><img src="image" alt="enone" /></td>
<td>2a</td>
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<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.
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\[
\begin{align*}
\text{Rh catalyst, KOH (1 eq)} & \quad \text{dioxane-H}_2\text{O (6/1), 50 °C, 6 h} \\
\text{ArB(OH)₂} & \quad \text{up to 99%ee for 2-cyclohexenone}
\end{align*}
\]

Rh catalyst = [Rh(acac)(C₂H₄)₂]

\[
\begin{align*}
\text{R¹} & \text{R²} & \text{R³} \\
\text{ArB(OH)₂} & \text{Ar} & \text{R¹} & \text{R²} & \text{R³} \\
\text{Rh catalyst, KOH (1 eq)} & \text{dioxane-H}_2\text{O (6/1), 50 °C, 6 h} & \text{up to 99%ee for 2-cyclohexenone}
\end{align*}
\]
Table 1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones (Scheme 1)\textsuperscript{a}

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<th>entry</th>
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<td>14\textsuperscript{d}</td>
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\textsuperscript{a}A mixture of enone (1 mmol), ArB(OH)\textsubscript{2} (1.5 mmol), Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} (0.03 mmol), ligand (0.06 mmol) and KOH (1 mmol) in dioxane-H\textsubscript{2}O (6/1, 3 ml) was stirred for 6 h at 50 °C, unless otherwise noted.\textsuperscript{b}The reaction was conducted in the absence of KOH. \textsuperscript{c}Et\textsubscript{3}N (1 mmol) was used in place of KOH. \textsuperscript{d}at 90 °C for 6 h in the absence of KOH.
Scheme 1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones

$$
\text{ArB(OH)}_2 (2) \quad \text{Rh(I)/4 catalyst} \\
\text{KOH (1 eq)} \\
dioxane-H_2O (6/1) \\
50 ^\circ C
$$