Rhodium/phosphoramidite-catalyzed asymmetric arylation of aldehydes with aryloboronic acids†

Richard B. C. Jagt,*a Patrick Y. Toullec,*a Johannes G. de Vries, h Ben L. Feringa*aa and Adriaan J. Minnaard*aa

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Phosphoramidites are effective chiral ligands in the rhodium catalyzed addition of aryloboronic acids to aldehydes providing up to 75% enantioselectivity and up to 96% isolated yield.

Enantiopure diarylmethanols are key structural elements in a number of pharmacologically active compounds and therefore represent important synthetic targets. An attractive route to chiral enantiopure diarylmethanols is the catalytic asymmetric addition of arylorganometallic reagents to aldehydes. Diphenylzinc has been used as a phenyl transfer reagent, but its background reaction with aldehydes makes it difficult to achieve high stereoselectivity. This undesired activity could be moderated by the simultaneous use of diethylzinc. Recently, Bolm et al. reported an excellent method in which the aryl transfer reagent was generated by mixing aryloboronic acids with an excess of diethylzinc. Aryloboronic acids have received increasing attention as arylating reagents because they are shelf stable, readily available, and compatible with a large variety of functional groups. From a practical point of view, the development of an efficient protocol for their direct addition to aldehydes would be highly desirable.

The addition of aryloboronic acids to aromatic aldehydes was initially reported by Miyaura in 1998 employing rhodium catalysts. With MeO–MOP as the chiral ligand, 41% ee was obtained for the addition of phenyloboronic acid to 1-naphthaldehyde. Subsequent attempts to improve the enantioselectivity of this reaction remained unsuccessful. The development of suitable chiral ligands for this transformation is still a major goal.

Recently we have demonstrated that rhodium-catalyzed conjugate additions of aryloboronic acids to enones can be achieved with high efficiency and excellent enantioselectivities by employing the monodentate phosphoramidite L1 (Fig. 1). Phosphoramidites comprise a low-cost class of ligands that are easily tunable and therefore highly suitable for a combinatorial approach in the development of asymmetric catalysts. Herein we report the efficient rhodium-catalyzed addition of aryloboronic acids to aldehydes with enantioselectivities up to 75% using bidentate phosphoramidite L2 (Fig. 1).

Preliminary studies were carried out with p-chlorobenzaldehyde (1a), 3 equiv. of phenyloboronic acid (2a), and a catalyst prepared in situ from 3 mol% Rh(acac)(eth)2 and 7.5 mol% phosphoramidite L1. Although a promising 41% enantioselectivity was obtained, conversion was incomplete under the aqueous conditions commonly used for the rhodium-catalyzed conjugate addition of aryloboronic acid (dioxane : H2O = 10 : 1, Table 1, entry 1).

Interestingly, it was observed that the reaction also proceeded in non-protic media without water as a co-solvent (entries 2, 4, and 6). In conjugate addition processes of aryloboronic acids, water or alcohol additives have been proven essential to protonate the rhodium oxa-π-allyl intermediate and thus achieve catalytic activity. If work-up with 12.5% aqueous ammonia was omitted, a mixture of product 3a and a considerable amount of a product related compound was found. This intermediate was identified as borate ester 4 (see proposed catalytic cycle in Scheme 1).

The presence of 4 suggests that under these conditions the alcoholate functionality of species D is able to induce the transmetallation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dioxane/H2O (10 : 1)</td>
<td>79</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Dry dioxane</td>
<td>87</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>Toluene/H2O (10 : 1)</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>Dry toluene</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Tetrahydrofuran/H2O (10 : 1)</td>
<td>24</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>Dry tetrahydrofuran</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>1,2-Dimethoxyethane/H2O (10 : 1)</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>2-Propanol</td>
<td>&gt;99</td>
<td>52</td>
</tr>
</tbody>
</table>

† Electronic supplementary information (ESI) available: Experimental procedures and 1H NMR and 13C NMR spectral data and analytical data for products 3a–i. See DOI: 10.1039/b518311a

*Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands. E-mail: r.b.c.jagt@rug.nl, b.l.feringa@rug.nl
†DSM Research, Life Sciences-Advanced Synthesis & Catalysis, P.O. Box 18, 6160 MD, Geleen, The Netherlands
‡ Electronic supplementary information (ESI) available: Experimental procedures and 1H NMR and 13C NMR spectral data and analytical data for products 3a–i. See DOI: 10.1039/b518311a

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Table 2  Scope of the rhodium-catalyzed asymmetric addition of arylboronic acids to aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar1 (1)</th>
<th>Ar2 (2)</th>
<th>Product</th>
<th>Yield (%)b</th>
<th>ee (%)c,d</th>
</tr>
</thead>
</table>
| 1     | p-ClC6H4      | Ph            | 3a      | 91         | 60        | (R)  
| 2     | p-CF3C6H4     | Ph            | 3b      | 94         | 51        | (R)  
| 3     | p-PtBuC6H4    | Ph            | 3c      | 93         | 59        | (R)  
| 4     | p-MeC6H4      | Ph            | 3d      | 80         | 60        | (R)  
| 5     | p-MeOC6H4     | Ph            | 3e      | 61         | 60        | (R)  
| 6     | Ph            | p-MeC6H4      | 3f      | 93         | 47        | (S)  
| 7     | Ph            | 2-Naphthyl    | 3i      | 92         | 53        | (S)  
| 8     | m-MeOC6H4     | Ph            | 3f      | 96         | 61        | (R)  
| 9     | o-MeOC6H4     | Ph            | 3g      | 89         | 50        | (R)  
| 10    | 1-Naphthyl    | Ph            | 3h      | 67         | 52        | (R)  
| 11    | 2-Naphthyl    | Ph            | 3i      | 92         | 75        | (R)  

* Reactions were carried out on 0.2 mmol scale in 2 mL of 2-propanol at reflux for 4 h with 3 equiv of boronic acid 2 in the presence of a catalyst generated from 3 mol% Rh(acac)(eth)2 and 3.5 mol% of bidentate phosphoramidite (S,S)-L2. b Isolated yields after column chromatography on silica gel (heptane:EtOAc = 15 : 1). c Determined by chiral HPLC. d The absolute configuration of 3a–i was established by comparison of the optical rotation with literature values or deduced by analogy (see electronic supplementary information (ESI)†).

Scheme 1  Proposed mechanism.

step between arylboronic acids and the rhodium center. Due to the equilibrium between phenylboronic acid and its boroxine trimer, the water content can not be defined. Although formation of 4 from the product and boronic acid during the reaction can not be excluded, the 3a : 4 ratio increased during the course of the reaction, pointing to slow hydrolysis of borate ester 4.

A study of various solvents showed that 2-propanol is the most suitable solvent for this reaction (compare entries 1–8), increasing both reactivity and enantioselectivity. Full conversion is obtained within 4 h resulting in 52% ee. Because of the protic nature of 2-propanol, quenching with aqueous ammonia is not required. Using these optimized conditions, the parallel synthesis and in situ screening of a diverse library of phosphoramidites indicated that bidentate ligand L2 will provide the highest enantioselectivity in this reaction. Full conversion was reached within 4 h and product 3a was obtained in 91% isolated yield with 60% ee (Table 2, entry 1).

The rhodium-catalyzed arylation of aldehydes is compatible with a wide range of functional groups (Table 2). As already observed by Miyaura and Frost, the reaction is rather sensitive to electronic effects both in aldehyde and arylboronic acid. Phenylation of aldehydes with electron-withdrawing chloro- and trifluoromethyl-substituents at the para position gave the corresponding alcohols 3a and 3b in high yields with 60% and 51% enantioselectivity, respectively (entries 1 and 2). In the case of a para-phenyl group, the product could be isolated in 93% yield with 59% ee (entry 3). Substrates with electron-donating methoxy- and methyl-substituents at the para position both provided 60% ee, but did not proceed to full conversion in 4 h (entries 4 and 5). The alternative reaction of benzaldehyde with substituted arylboronic acids did give high yields but showed decreased enantioselectivities (entries 6 and 7). A slightly lower ee and reactivity is also observed for sterically hindered substrates like ortho-methoxy benzaldehyde (entry 9) and 1-naphthyl carboxaldehyde (entry 10). On the contrary, 2-naphthyl carboxaldehyde could be phenylated in 92% isolated yield with an ee of 75% (entry 11).

In summary, catalytic asymmetric synthesis of diarylmethanols has been realized with good enantioselectivities (up to 75%) and high isolated yields (up to 96%) employing a rhodium/phosphoramidite catalyst system.

Acknowledgements

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References


14. Borate ester 4 has a characteristic benzhydryl proton signal in 1H-NMR at 6.21 ppm and was further identified by negative ion ESI-MS, which gave a specific isotopic pattern for C$_13$H$_{11}$ClBO$_3$\(\cdot\)NH$_3$ (M$-$NH$_4^+$): \(m/z\) 277.1 (15%, $^{10}$B, $^{35}$Cl), 278.1 (100%, $^{11}$B, $^{35}$Cl), 279.0 (25%, $^{10}$B, $^{37}$Cl), 280.0 (25%, $^{11}$B, $^{37}$Cl).