Enantioselective rhodium-catalyzed addition of arylboronic acids to trifluoromethyl ketones†

Sébastien L. X. Martina,* Richard B. C. Jagt,* Johannes G. de Vries,*b Ben L. Feringa* and Adriaan J. Minnaard**

Received (in Cambridge, UK) 4th July 2006, Accepted 8th August 2006
First published as an Advance Article on the web 22nd August 2006
DOI: 10.1039/b609453h

The catalytic asymmetric 1,2-addition of a series of arylboronic acids to 2,2,2-trifluoroacetophenones is described with high isolated yields (up to 96%) and good enantioselectivities (up to 83% ee) using a rhodium(II)phosphoramidite catalyst.

Due to their unique properties and unusual reactivities, fluorinated compounds have found extensive application in the fields of materials, pharmaceuticals, and agrochemistry. As a consequence, the annual number of publications and patents concerning fluorinated products has steadily increased over the last three decades. Fluorinated compounds bearing a trifluoromethyl substituent represent an interesting sub-class of this type of structures, often providing unique biological activities. In this context, numerous methods for the trifluoromethylation of carbonyl compounds have been reported. However, enantioselective trifluoromethylation is difficult to achieve and enantiomeric excesses exceeding 50% are rarely reached, except when the substrate is very hindered.

An alternative strategy for the synthesis of trifluoromethyl substituted tertiary alcohols (Fig. 1) would be the addition of carbon nucleophiles to trifluoromethyl ketones. However, the formation of quaternary carbons via the addition of carbon nucleophiles to ketones still constitutes a major challenge in synthetic chemistry. So far, the use of trifluoromethyl ketones as substrates in enantioselective organometallic addition reactions has been limited. To the best of our knowledge no catalytic enantioselective arylation of fluorinated ketones has been reported so far.

Most of the enantioselective transformations described for the construction of tertiary alcohols from ketones involve the addition of alkyl, alkenyl and arylzinc reagents. The lack of readily available zinc reagents severely limits these methods. We envisioned that, for activated ketones, the introduction of aryl moieties by asymmetric rhodium-catalyzed addition of arylboron reagents would be a more convenient method. Arylboronic acids have received increasing attention as arylation reagents because they are shelf-stable, readily available, and compatible with a large variety of functional groups. Rhodium-catalyzed addition of sp2-hybridized carbon nucleophiles has made considerable progress during the last decade. Our group has demonstrated that phosphoramidites are excellent ligands for the highly enantioselective rhodium-catalyzed conjugate addition of arylboronic acids to enones. Phosphoramidites comprise a low-cost class of ligands that are easily tunable and therefore highly suitable for ligand variation. Recently, a ligand library approach led to the identification of phosphoramidite ligands that provide high enantioselectivity in the rhodium-catalyzed addition of arylboronic acid to imines and good enantioselectivities in their addition to aldehydes. A recent publication of Hayashi describing the asymmetric arylation of isatins with a Rh/MeO-MOP catalyst prompted us to divulge our own results in this area. Herein we report the first rhodium-catalyzed addition of arylboronic acids to 2,2,2-trifluoroacetophenones with enantioselectivities up to 83%.

Initial experiments were performed with 2,2,2-trifluoroacetophenone (1a) and 3 equivalents of para-methoxyphenylboronic acid (2a). Variation of solvents identified methyl tert-butyl ether (MTBE) as the most suitable solvent for this reaction in terms of activity and enantioselectivity, although virtually identical results were obtained in acetone. An array of binol-based phosphoramidite ligands was screened, leading to the identification of phosphoramidite ligand L (Fig. 2) as an efficient ligand for this reaction.

A catalyst was generated in situ from 5 mol% of [(C5H4)2Rh(acac)] and 12.5 mol% of phosphoramidite L. According to 19F NMR, 60% conversion was obtained after 16 h in refluxing MTBE. Column chromatography afforded the pure product 3a in 50% yield with a promising enantioselectivity of 68% (Table 1, entry 1). As already observed for the addition of arylboronic acids to aldehydes, the reaction is rather sensitive to electronic effects both in substrate and arylboronic acid. Addition of the less nucleophilic para-chlorophenylboronic acid 2b gave the corresponding tertiary alcohol 3b in even lower yield, but with a slightly higher enantioselectivity.

Fig. 1 Trifluoromethyl substituted diarylmethanols.

Fig. 2 Phosphoramidite (S)-L.
higher selectivity of 72% ee (entry 2). To our delight, the activated para-chloro-substituted substrate 1b and arylboronic acid 2a could be converted into the corresponding tertiary alcohol with 96% yield and 68% ee (entry 3).

With these results in hand, the scope of the reaction was investigated. Also the addition of phenylboronic acid (2d) proceeded to full conversion and the alcohol 3b could be obtained in 90% yield with 79% ee (entry 5). Electron donating substituents on the aryl-group of the boronic acid 2 increased the rate of the reaction, whereas the presence of electron-withdrawing substituents decreased the rate of the reaction (entries 3 and 4).

Determined by chiral HPLC. The absolute configuration of the products is unknown. Conditions could be optimized to 3 mol% of catalyst and 2 equivalents of arylboronic acid without affecting the outcome of the reaction (entries 3 and 4).

Table 1  Enantioselective rhodium/phosphoramidite-catalyzed asymmetric arylation of 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate R</th>
<th>Boronic acid</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a H 2a</td>
<td>3a</td>
<td></td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>1a H 2b</td>
<td>3b</td>
<td></td>
<td>28</td>
<td>72</td>
</tr>
<tr>
<td>3a</td>
<td>1b Cl 2a</td>
<td>3c</td>
<td></td>
<td>96</td>
<td>68</td>
</tr>
<tr>
<td>4b</td>
<td>1b Cl 2c</td>
<td>3d</td>
<td></td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>1b Cl 2d</td>
<td>3b</td>
<td></td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>1b Cl 2e</td>
<td>3e</td>
<td></td>
<td>94</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>1b Cl 2f</td>
<td>3f</td>
<td></td>
<td>91</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>1b Cl 2g</td>
<td>3g</td>
<td></td>
<td>52</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>1b Cl 2h</td>
<td>3h</td>
<td></td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>1b Cl 2i</td>
<td>3i</td>
<td></td>
<td>69</td>
<td>76</td>
</tr>
</tbody>
</table>

Reactions were performed on 0.178 mmol scale in 2.5 mL of MTBE at reflux for 16 h with 3.0 equiv of arylboronic acid (2) with a catalyst generated from 5 mol% [(C2H4)2Rh(acac)] and 12.5 mol% (S)-L. Isolated yield after column chromatography. Conditions could be optimized to 3 mol% of catalyst and 2 equiv of arylboronic acid without affecting the outcome of the reaction.

Notes and references


