Enantioselective 1,4-addition of cyclopropylboronic acid catalyzed by rhodium/chiral diene complexes†

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† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data, and X-ray crystallographic data of compound 3a. CCDC 1047801. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc02140e

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Rhodium-catalyzed asymmetric addition of cyclopropylboronic acids to electron-deficient alkenes such as alkenylsulfones, enones, enoates, and nitroalkenes proceeded to give high yields of the corresponding 1,4-addition products with high enantioselectivity.

Asymmetric conjugate addition of organometallic reagents to electron-deficient alkenes catalyzed by Rh complexes is now well-recognized to be one of the most reliable methods for carbon–carbon bond formation introducing aryl and alkenyl groups with high enantioselectivity.1,2 On the other hand, asymmetric conjugate addition of allyl groups has been developed using Ni and Cu catalysts,3 and thus both catalytic systems perform a complementary role in the transition metal-catalyzed asymmetric conjugate addition reactions.4 The catalytic conjugate addition of simple alkyl metal reagents under the rhodium catalysis using organometallic reagents is difficult because an intermediate alkylrhodium(i) species having a β-hydrogen readily undergoes elimination to give a hydridorhodium species and an alkene.4

As rare examples of the rhodium-catalyzed addition reaction of alkyl metal reagents, we reported asymmetric methylation of imines by the use of Me2Zn or trimethylboroxine as a methylating reagent, where the β-hydrogen to be eliminated does not exist.5,6 von Zeischwitz and co-workers reported asymmetric 1,2- or 1,4-addition of Me3Al to cyclic enones catalyzed by a rhodium/binap complex.7 The stereoselective alkyl transfer from potassium benzylic trifluoroborates to aldehydes was also reported by Aggarwal and co-workers, where it is proposed that the reaction proceeds by direct migration of the benzylic group to the aldehyde without formation of a benzylrhodium species.8

In this context, we focused on the use of a cyclopropylrhodium(i) species for the conjugate addition, which may avoid the β-hydrogen elimination leading to the formation of a highly strained cyclopropane. The asymmetric addition of dicyclopentadienylzinc to aldehydes was reported by the use of a chiral amino alcohol.9

The diastereoselective addition of cyclopentadienyllithium or magnesium bromide to imines is achieved using a chiral auxiliary on the nitrogen.10 The Cu-catalyzed enantioselective addition of dicyclopentadienyllithium to a β-disubstituted nitroalkene was reported to give the addition product in low yield with low enantioselectivity.11,12

Here we report that the asymmetric addition of cyclopropylboronic acid to electron-deficient alkenes catalyzed by Rh/chiral diene complexes. To the best of our knowledge, this is the first example of the metal-catalyzed asymmetric conjugate addition of cyclopropylboronic acids.13

We found that a Rh complex coordinated with a diene ligand has high catalytic activity in the addition of cyclopropylboronic acid to an alkenylsulfone (Table 1). Thus, treatment of alkenylsulfone 1a with cyclopropylboronic acid (2, 2.5 equiv.) in the presence of [RhCl(cod)]2 (3 mol% of Rh) and K3PO4 (1 equiv.) in toluene at 60 °C for 12 h gave the addition product 3a in 60% yield (entry 1, Table 1). An enantioselective addition was achieved by the use of chiral diene ligands.14 A Rh complex coordinated with a ferrocenyl (Fc)-substituted diene ligand based on the tetrafluorobenzobarrelene (tfb) framework,15 which is a superior catalyst in the asymmetric addition of arylboronic acids to alkenyl sulfonyl compounds,16,17 displayed a high catalytic activity and enantioselectivity to give 3a in 96% yield with 97% ee (entry 2). Other tfb ligands substituted with phenyl (Ph) and benzyl (Bn), and bicyclo[2.2.2]octadienes L1 and L2,18 which are derived from a natural product, were less effective in the present addition reaction [entries 3–6]. The use of a rhodium-bisphosphine complex [RhCl((R)-binap)]219 did not give the addition product at all (entry 7). Cyclopropylboronic acid neopentylglycolate 2′ can also be used to give a 99% yield of 3a with 94% ee, although the reaction requires a higher reaction temperature (80 °C, entry 8). The absolute configuration of product 3a formed by the use of (S,S)-Fc-tfb* was determined to be S by X-ray crystallographic analysis.

The results obtained for the enantioselective addition of cyclopropylboronic acid (2) to several alkenyl sulfonyl compounds 1

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Rh-catalyzed addition of cyclopropylboronic acid 2 to alkynylsulfonyle 1a

\[ \text{[RhCl}(\text{L})_2]_{\text{(3 mol\% Rh)}} \text{ KPO}_4 (1 \text{ equiv}) \text{ toluene} 60^\circ\text{C} , 12 \text{ h} \]

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S,S)-Fc-tfb* (Fc: ferrocenyl)</td>
<td>96d</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>(S,S)-Fc-tfb* (Ben: benzylic)</td>
<td>43</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-Ph-tfb*</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-Bn-tfb*</td>
<td>10</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>(R)-L1</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>(R)-L2</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>(R)-Binap</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>(S,S)-Fc-tfb*</td>
<td>99</td>
<td>96</td>
</tr>
</tbody>
</table>

Reaction conditions: alkynylsulfonyle 1a (0.10 mmol), 2 (0.25 mmol), the Rh catalyst (3 mol\% of Rh), KPO4 (1 equiv) in toluene (0.4 mL) at 60°C for 12 h. d Determined by 1H NMR analysis using 1,4-dimethoxybenzene as an internal standard. e Determined by chiral HPLC analysis. f Isolated yield. g Not determined. h Cyclopropylboronic acid neopentylglycolate 2a was used instead of 2 in the presence of methanol (3 equiv.) at 80°C.

The addition of cyclopropylboronic acid to alkynylsulfonyl compounds 1

**Table 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-Tolyl</td>
<td>2-Furyl (1b)</td>
<td>97 (3b)</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>p-Tolyl</td>
<td>2-Thienyl (1c)</td>
<td>97 (3c)</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>p-Tolyl</td>
<td>3-Pyridyl (1d)</td>
<td>51 (3d)</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>p-Tolyl</td>
<td>CH2-C6H4 (1e)</td>
<td>78 (3e)</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>p-Tolyl</td>
<td>Butyl (1f)</td>
<td>94 (3f)</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>p-Tolyl</td>
<td>Benzyl (1g)</td>
<td>92 (3g)</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>2,6-Me2C6H4</td>
<td>Ph (1h)</td>
<td>80 (3h)</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>EtO</td>
<td>Ph (1i)</td>
<td>86 (3i)</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>N-Morpholyl</td>
<td>Ph (1j)</td>
<td>96 (3j)</td>
<td>98</td>
</tr>
</tbody>
</table>

Reaction conditions: alkynylsulfonyle 1a (0.20 mmol), 2 (0.50 mmol), [RhCl((S,S)-Fc-tfb*)]_{2} (3 mol% of Rh), KPO4 (1 equiv) in 1,4-dioxiane (for 1b-d, 1f, 1h; 0.8 mL) or toluene (for 1e, 1g, 1i, 1j; 0.8 mL) at 60°C for 24 h. e Isolated yields. f Determined by chiral HPLC analysis. g For 12 h. h NaPO4 was used instead of KPO4.

to give the corresponding addition products in good to high yields with high enantioselectivity (entries 4–6). Not only alkynyl sulfones, but also sulfonates (1b and 1i) and a sulfonamide (1j) can be applicable with high enantioselectivity (entries 7–9).

The enantioselective addition of cyclopropylboronic acid proceeded toward the other electron-deficient alkynes than alkynyl sulfones, where the higher enantioselectivity was observed with alkyl-substituted tfb ligands than that with Fc-tfb*. The reaction of hydroxorhodium/chiral tfb catalysts, the addition to nitroalkenes 4g-i were also applicable acceptors by the use of KF2 as a base instead of K3PO4 to give the corresponding addition products with 89% ee (entries 7–9).

The addition of cyclobutylboronic acid (6) or cyclopentylboronic acid (7) to alkynylsulfonyle 1a under the same reaction conditions as for cyclopropylboronic acid (2) did not take place and 1a was recovered intact (eqn (1)). On the other hand, the use of n-butylicboronic acid (8) gave only saturated sulfone 9 in 26% yield, indicating that the reduction of 1a proceeds via the formation of a hydridorhodium generated by β-hydrogen elimination of a n-butylicboronic acid species (eqn (2)). The results also imply that the transmetalation of the Rh with cyclobutyl- and cyclopentylboronic acid does not take place under the present reaction conditions.
Transfer of a substituted cyclopropyl group also took place under the rhodium catalysis (eqn (3) and (4)). Thus, the addition of a racemic cyclopropylboronate 10 having trans-2-phenyl to methyl vinyl ketone 4j in the presence of [Rh(OH)((S,S)-Fc-tfb*)]2 proceeded to give the addition product 11 in 68% yield (eqn (3)). The relative configuration of 11 was determined to be trans, indicating that the transmetalation and the following insertion took place with retention of the configuration.24 A kinetic resolution of the racemic 10 was also observed (10% ee with Fc-tfb* and 25% ee with Bn-tfb*). In the reaction of cyclopropylboronate 4j, migration of a cyclopropylrhodium(I) species to a reactive intermediate was not observed (eqn (4)).

In summary, we have developed Rh-catalyzed asymmetric addition of cyclopropylboronic acids to electron-deficient alkenes. The Rh complexes coordinated with chiral diene ligands based on a tetrafluorobenzobarrelene framework displayed high catalytic activity and enantioselectivity. The addition of a substituted-cyclopropyl group proceeded with the stereoretention, indicating that the transmetalation and the subsequent carboxylation proceeded with the retention of the configuration.

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Notes and references


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13 Cyclopropylboronic acid has been often used in Pd- and Cu-
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catalyzed coupling reactions, which include reductive elimination 
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23 The use of KHF\textsubscript{2} as an effective base was reported in the arylation of 
21 The use of Na\textsubscript{3}PO\textsubscript{4} instead of K\textsubscript{3}PO\textsubscript{4} inhibited the double bond 
isomerization of \textit{1g}. 
20 The solvent was selected depending on the substrates mainly due to 
the solubility problem. 
21 The use of Na\textsubscript{3}PO\textsubscript{4} instead of K\textsubscript{3}PO\textsubscript{4} inhibited the double bond 
isomerization of \textit{1g}. 
23 The use of KHF\textsubscript{2} as an effective base was reported in the arylation of 
23 The use of KHF\textsubscript{2} as an effective base was reported in the arylation of 
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stereoretention was observed, see: ref. 13a–c. The coupling reaction 
with inversion of the configuration of benzylboron reagents was also 
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