Tailored trisubstituted chiral Cp\textsuperscript{*}Rh\textsuperscript{III} catalysts for kinetic resolutions of phosphinic amides\textsuperscript{†}

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A trisubstituted chiral Cp\textsuperscript{*} ligand family is introduced. Based on the disubstituted atropchiral Cp\textsuperscript{*} ligand scaffold, the introduction of a bulky third substituent at the central position of the Cp ring leads to substantially increased selectivities for rhodium(III)-catalyzed kinetic resolutions and allowed for $s$-factors of up to 50. Their superiority is demonstrated by kinetic resolutions of phosphinic amides providing access to compounds with stereogenic phosphorus(V) atoms. The unreacted acyclic phosphinic amide and the cyclized product are both obtained in good yields and enantioselectivities. The ligand synthesis capitalizes on a late stage modification and expands the accessible ligand Cp\textsuperscript{*} ligand portfolio.

Introduction

Molecules possessing a chiral phosphorus(m\textsuperscript{ii}) as well as phosphorus(v) center\textsuperscript{a} are important compounds classes with widespread applications. The catalytic and stereoselective synthesis of molecules with chiral phosphorus centers received significant attention,\textsuperscript{b} but remains a challenging task. Additional and complementary methods for their selective preparations are highly desirable and would be synthetically very valuable. In this respect, catalytic enantioselective C–H functionalizations have emerged a complementary tactic to access chiral building blocks from simple starting materials.\textsuperscript{4} To the best of our knowledge, the synthesis of P-stereogenic centers by catalytic C–H functionalizations is so far limited to desymmetrization reactions of achiral precursors.\textsuperscript{5} For instance, we have recently reported the formation of cyclic phosphinic amides catalyzed by chiral Cp\textsuperscript{*}Rh\textsuperscript{III}-catalysts.\textsuperscript{5g,6,7} This desymmetrization approach is only suitable for substrates containing the same two aromatic substituents with identical prochiral C–H groups, thus restricting the obtainable structural diversity. Notably, acyclic P-stereogenic phosphinic amides\textsuperscript{a} are not accessible by this approach.

Herein, we report a flexible route to new trisubstituted Cp\textsuperscript{*} ligands. We showcase their potential for an enantioselective
Cp*Rh^III^-catalyzed C–H functionalization of racemic phosphinic amides through a kinetic resolution^a (Scheme 1). s-Factors of up to 50 were realized with the new tri-substituted Cp*Rh^III^ ligands, largely outperforming any previous Cp*Rh^III^ ligand.

Conceptually, both acyclic starting material enantiomers can coordinate to the Cp*Rh^III^ catalyst forming diastereomeric intermediates I and IV (Scheme 2). In the subsequent – likely rate-limiting step of the process – the matching enantiomer would undergo C–H activation leading to rhodacycle II much faster than IV to V, corresponding to \( k_2 \gg k_5 \). Experimental support of this assumption consists in the absence of ortho-C-deuteration of unreacted starting material (see ESI† for details). Rhodacycle II can further react with alkyne via III to deliver cyclic phosphinic amide 2a. The unreactive complex IV reverts back to the Rh^III^-catalyst and substrate 1a. Over time, the reacting enantiomer is removed from the starting material, getting enriched over time.

Results and discussion

The initial feasibility of the kinetic resolution was explored with racemic phenyl methyl phosphinic amide rac-1a and diphenyl acetylene (Table 1). Complex Rh1 with our standard second generation Cp* ligand (\( R = \text{OMe} \)) caused a moderate rate difference in the reaction of the two starting material enantiomers, correlating to an s-factor of 14 (entry 1).\(^{11,12} \) Cp* ligands with other substitutions \( R^{10} \) were largely inferior (entries 2–5).

We hypothesized that a new trisubstituted Cp*Rh^III^ ligand class with increased bulk may enhance the selection between matched and mismatched substrate. These ligands are straightforward prepared from L1 by condensation with a ketone forming the corresponding fulvenes 3 and 4 (Scheme 3).\(^{13} \) Reduction of 3 with LiAlH4 gave isopropyl-substituted ligand L6. X-ray crystallographic analysis of \([L6RhCl_2]_2\) showed the orientation of the installed isopropyl group.\(^{14} \) Moreover, facile addition of lithium organometallics across the fulvene double bond provided access to ligands L7–L10 with bulky tert-butyl analogues as third Cp substituent. The corresponding rhodium complexes were subsequently evaluated for the kinetic resolution. In this respect, Rh6 with an isopropyl group \( R' \) largely improved the s-value to 32 (entry 6). Rh7 featuring a larger tert-butyl group further improved the selectivity to an s-value of 42 (entry 7). Rh8 and Rh9 were slightly inferior (entries 8 and 9). Rh10 featuring a 1-tert-butyloxyhexyl group \( R' \) allowed for a significant reduction in reaction time to 3 h maintaining a high s value of 41 (entry 10). Moreover, the amount of diphenyl acetylene could be lower to 0.6 equivalents, improving the selectivity further (entries 11–12).

Next, the scope of the kinetic resolution procedure was evaluated (Table 2). Steric and electronic variations of \( R \) on the aryl group in the para- and meta-position had little influence on the reaction performance (entries 1–8). In all cases, the reaction of rac-1a–1h could be stopped at around 50% conversion. Both products were isolated in good to excellent enantioselectivities, resulting in s-values ranging from 26–50. An ortho-substituted aryl group (rac-1i) largely equaled the reaction rates of both starting material enantiomers and reduced the s-values. Besides variations of the aryl group, substituent \( R' \) can be varied, maintaining synthetically useful selectivities (entries 10–11). In addition to phosphinic amides, we evaluated phosphonodiamidates rac-1l and rac-1m (entries 12–13) as well as phosphonamidate esters rac-1n and rac-1o (entries 14–15) towards the synthesis.

### Table 1 Screening of the Cp*Rh^III^ ligands for the kinetic resolution^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh</th>
<th>( T ) [h]</th>
<th>% Conv.</th>
<th>er 1a(^a) (% yield)</th>
<th>er 2a(^a) (% yield)</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh1</td>
<td>8</td>
<td>54</td>
<td>91 : 9 (40)</td>
<td>85 : 15 (46)</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Rh2</td>
<td>10</td>
<td>60</td>
<td>78 : 22 (35)</td>
<td>81 : 19 (46)</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Rh3</td>
<td>32</td>
<td>30</td>
<td>63.5 : 36.5 (63)</td>
<td>84 : 16 (23)</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Rh4</td>
<td>32</td>
<td>18</td>
<td>57 : 43 (78)</td>
<td>77 : 23 (17)</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Rh5</td>
<td>32</td>
<td>54</td>
<td>68 : 32 (42)</td>
<td>76 : 24 (32)</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Rh6</td>
<td>10</td>
<td>55</td>
<td>98 : 2 (42)</td>
<td>89 : 11 (48)</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>Rh7</td>
<td>8.5</td>
<td>51</td>
<td>95 : 5 (46)</td>
<td>93 : 7 (46)</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>Rh8</td>
<td>5</td>
<td>55</td>
<td>98.5 : 1.5 (42)</td>
<td>89 : 11 (50)</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>Rh9</td>
<td>3</td>
<td>53</td>
<td>96 : 4 (44)</td>
<td>90.5 : 9.5 (48)</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>Rh10</td>
<td>3</td>
<td>55</td>
<td>99.1 : 0.9 (42)</td>
<td>90.5 : 9.5 (48)</td>
<td>41</td>
</tr>
<tr>
<td>11(^b)</td>
<td>Rh7</td>
<td>8.5</td>
<td>52</td>
<td>97.3 : 2.7 (44)</td>
<td>93 : 7 (48)</td>
<td>50</td>
</tr>
<tr>
<td>12(^b)</td>
<td>Rh10</td>
<td>4</td>
<td>51</td>
<td>95.5 : 4.5 (46)</td>
<td>94 : 6 (46)</td>
<td>47</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 50 \( \mu \text{mol} \) 1a, 75 \( \mu \text{mol} \) 5a, 5.0 \( \mu \text{mol} \) Rh7, 5.0 \( \mu \text{mol} \) (BzO)\(_2\), 0.10 \( \text{mmol} \) Ag\(_2\)CO\(_3\), 50 \( \mu \text{mol} \) K\(_2\)CO\(_3\), 0.25 \( \text{mL} \) in \( \text{dBuOH} \) at 90 °C for the indicated time; \( Ar = 3,5-(\text{CF}_3)\text{C}_6\text{H}_3 \). \(^b\) By \( 1\text{H-NMR} \). \(^c\) By chiral HPLC, (isolated yield). \(^d\) With 30 \( \mu \text{mol} \) 5a.

![Scheme 3](#)
The additional hetero atom on the phosphorus center had only a weak influence on the reactivity, whereas the s-values were lower with the current ligand system. The nature of alkyne 5 can be varied as well (Table 3). Whereas electron-rich diaryl alkyne 5b reacted less selective, unsymmetrically substituted internal alkyynes such as 5c, 5d and 5e provided comparable selectivities. Moreover, they are incorporated in a highly regioselective manner, giving 2ac, 2ad and 2ae with excellent regioselectivities.

In addition, we have as well investigated racemic phosphinic amide substrate rac-1p having two different aryl groups (eqn (1)). In this case, a parallel kinetic resolution becomes operative, yielding the two cyclic phosphinic amide products 2p and 2p′ in excellent yield and good enantioselectivity.

Table 2 Kinetic resolution of aryl phosphinic amides rac-1

<table>
<thead>
<tr>
<th>Entry</th>
<th>rac-1</th>
<th>R/R′</th>
<th>T [h]</th>
<th>Conv. b [%]</th>
<th>er 1′ (% yield)</th>
<th>er 2′ (% yield)</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rac-1a</td>
<td>H/Me</td>
<td>8.5</td>
<td>51</td>
<td>95 : 5 (46)</td>
<td>93 : 7 (46)</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>rac-1b</td>
<td>4-Me/Me</td>
<td>10.5</td>
<td>55</td>
<td>98 : 2 (42)</td>
<td>89 : 11 (50)</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>rac-1c</td>
<td>4-F/Me</td>
<td>10.5</td>
<td>55</td>
<td>98 : 2 (40)</td>
<td>90 : 10 (48)</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>rac-1d</td>
<td>4-Cl/Me</td>
<td>10.5</td>
<td>55</td>
<td>97 : 3 (40)</td>
<td>89 : 11 (45)</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>rac-1e</td>
<td>4-OMe/Me</td>
<td>8.5</td>
<td>54</td>
<td>99 : 1 (42)</td>
<td>91 : 9 (48)</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>rac-1f</td>
<td>4-NMe2/Me</td>
<td>9.5</td>
<td>42</td>
<td>83 : 17 (30)</td>
<td>95 : 5 (36)</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>rac-1g</td>
<td>3-Me/Me</td>
<td>10.5</td>
<td>58</td>
<td>99 : 1 (38)</td>
<td>85 : 15 (53)</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>rac-1h</td>
<td>3-Br/Me</td>
<td>14</td>
<td>55</td>
<td>99 : 1 (38)</td>
<td>91 : 9 (42)</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>rac-1i</td>
<td>2-Me/Me</td>
<td>10</td>
<td>53</td>
<td>79 : 21 (44)</td>
<td>77 : 23 (42)</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>rac-1j</td>
<td>H/Bn</td>
<td>4</td>
<td>59</td>
<td>99.5 : 0.5 (37)</td>
<td>84 : 16 (53)</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>rac-1k</td>
<td>H/(CH2)2OBn</td>
<td>6.5</td>
<td>51</td>
<td>93.7 : 7 (44)</td>
<td>93.3 : 7 (47)</td>
<td>29</td>
</tr>
<tr>
<td>12</td>
<td>rac-1l</td>
<td>H/pyrrolidinyl</td>
<td>5</td>
<td>57</td>
<td>89 : 11 (40)</td>
<td>79 : 21 (52)</td>
<td>9</td>
</tr>
<tr>
<td>13</td>
<td>rac-1m</td>
<td>H/morpholinyl</td>
<td>3.5</td>
<td>61</td>
<td>95 : 5 (37)</td>
<td>79 : 21 (55)</td>
<td>11</td>
</tr>
<tr>
<td>14</td>
<td>rac-1n</td>
<td>H/OMe</td>
<td>24</td>
<td>60</td>
<td>97.3 : 3 (37)</td>
<td>81 : 19 (55)</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>rac-1o</td>
<td>H/OPh</td>
<td>14</td>
<td>53</td>
<td>91 : 9 (44)</td>
<td>86 : 14 (48)</td>
<td>16</td>
</tr>
</tbody>
</table>

a Conditions: 0.10 mmol 1a, 0.15 mmol 5a, 0.10 mmol Rh7, 0.15 mmol (BzO)2, 0.20 mmol Ag2CO3, 0.10 mmol K2CO3, 0.25 M in tBuOH at 90 °C; Ar = 3,5-(CF3)C6H3. b By 1H-NMR. c By chiral HPLC, (isolated yield). d At 70 °C.

Table 3 Variation of the alkyne 5x

<table>
<thead>
<tr>
<th>Entry</th>
<th>5x</th>
<th>R1</th>
<th>R2</th>
<th>Conv. b [%]</th>
<th>er 1a′ (% yield)</th>
<th>er 2a′ (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>Ph</td>
<td>Ph</td>
<td>51</td>
<td>95 : 5 (46)</td>
<td>93 : 7 (46)</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>PMP</td>
<td>PMP</td>
<td>51</td>
<td>90 : 10 (46)</td>
<td>89 : 11 (46)</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>Bu</td>
<td>PMP</td>
<td>50</td>
<td>94 : 6 (46)</td>
<td>95 : 5 (46)x</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>iPr</td>
<td>PMP</td>
<td>43</td>
<td>82 : 18 (52)</td>
<td>94 : 6 (37)x</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>Bu</td>
<td>54</td>
<td>98 : 2 (43)</td>
<td>96 : 4 (48)x</td>
<td></td>
</tr>
</tbody>
</table>

a Conditions: 0.10 mmol 1a, 0.15 mmol 5a-d, 0.10 mmol Rh7, 0.20 mmol Ag2CO3, 0.10 mmol K2CO3, 0.25 M in tBuOH at 90 °C for 8.5 h; Ar = 3,5-(CF3)C6H3. b By 1H-NMR. c By chiral HPLC, (isolated yield). d rs = 18 : 1. e rs = 20 : 1.
resolutions amides providing access to compounds with ster-
upto 50. The superiority of them are showcased by kinetic
selectivities for kinetic resolutions and allowed for
central position of the Cp ring leads to substantially increased
shown that the introduction of a bulky third substituent at the

In summary, we have developed a new trisubstituted Cp ligand
family. Based on our atropchiral Cp ligand scaffold, we have
shown that the introduction of a bulky third substituent at the
central position of the Cp ring leads to substantially increased
selectivities for kinetic resolutions and allowed for s-factors of
up to 50. The superiority of them are showcased by kinetic
resolutions amides providing access to compounds with ster-
eogenic phosphorus(v) atoms. The ligand synthesis capitalizes
on a late stage modification and expands the accessible ligand
Cp ligand portfolio for further catalytic-enantioselective
transformations with additional metals.

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Conflicts of interest
There are no conflicts of interest to declare.
