Tailored trisubstituted chiral Cp\(
^*\)
Rh\(^{\text{III}}\) catalysts for kinetic resolutions of phosphinic amides\(^\dagger\)

Y. Sun\(^\ddagger\) and N. Cramer\(^*\)

A trisubstituted chiral Cp\(^*\) ligand family is introduced. Based on the disubstituted atropchiral Cp\(^*\) 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\(^*\) ligand portfolio.

Introduction

Molecules possessing a chiral phosphorus(\(\text{III}\)) as well as phosphorus(\(V\)) center\(^2\) are important compounds classes with widespread applications. The catalytic and stereoselective synthesis of molecules with chiral phosphorus centers received significant attention,\(^3\) 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.\(^4\) 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.\(^5\) For instance, we have recently reported the formation of cyclic phosphinic amides catalyzed by chiral Cp\(^*\)Rh\(^{\text{III}}\)-catalysts.\(^6,7\) 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\(^*\) are not accessible by this approach.

Herein, we report a flexible route to new trisubstituted Cp\(^*\) ligands. We showcase their potential for an enantioselective

**Scheme 1** Rh\(^{\text{III}}\)-catalyzed desymmetrization and kinetic resolution approaches for the synthesis P-chiral compounds.

**Scheme 2** Kinetic resolution by a difference in the cyclometalation rates \(k_2 > k_5\).

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Cp²RhIII-catalyzed C–H functionalization of racemic phosphinic amides through a kinetic resolution (Scheme 1). \( s \)-Factors of up to 50 were realized with the new tri-substituted Cp² ligands, largely outperforming any previous Cp² ligand.

Conceptually, both acyclic starting material enantiomers can coordinate to the Cp²RhIII 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate 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 RhIII-catalyst and substrate deuteration of unreacted starting material (see ESI† for details).

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 Cp² 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).\(^{11,12}\) Cp² ligands with other substitutions \( R^{10} \) were largely inferior (entries 2–5). We hypothesized that a new trisubstituted Cp² 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 [L6RhCl₂]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-butylcyclohexyl 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 equalled 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-1j and rac-1k (entries 12–13) as well as phosphonamidate esters rac-1n and rac-1o (entries 14–15) towards the

Table 1 Screening of the Cp² ligands for the kinetic resolution

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh</th>
<th>( T ) [h]</th>
<th>% Conv.(^{a})</th>
<th>( er ) 1a(^{b}) (% yield)</th>
<th>( er ) 2a(^{b}) (% 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 (42)</td>
<td>90.5 : 9.5 (48)</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>Rh7</td>
<td>8.5</td>
<td>52</td>
<td>97 : 3 (44)</td>
<td>93 : 7 (48)</td>
<td>50</td>
</tr>
<tr>
<td>12</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 µmol 1a, 75 µmol 5a, 5.0 µmol Rh7, 5.0 µmol (Br₂O₂), 0.10 mmol Ag₂CO₃, 50 µmol K₂CO₃, 0.25 ml in d-BuOH at 90 °C for the indicated time; \( \text{Ar} = 3,5-(\text{CF}_3)C_{6}H_{4} \). \(^{b}\) By 1H-NMR. \(^{c}\) By chiral HPLC, (isolated yield). \(^{d}\) With 30 µmol 5a.

Scheme 3 Synthesis of trisubstituted L6–L10 from L1.
resolutions conditions. 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 alkynes 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.

The P-chiral phosphinic amides were subsequently evaluated as chiral Lewis-bases in enantioselective reductive aldol...
additions\textsuperscript{37} between enone 6 and benzaldehyde (Scheme 4). Aldol adduct \textit{syn}-7 was obtained in 96:4 er with 13:1 \textit{syn}/\textit{anti} ratio using methyl-substituted 2a as the catalyst. In stark contrast, related phenyl-substituted phosphinic amide 8 obtained by the previous desymmetrization method\textsuperscript{38} provided isomer \textit{anti}-7 preferentially (1:4 \textit{syn}/\textit{anti}), with almost no enantioselectivity. Moreover, an enantiospecific access to corresponding \textit{P}III-compound was achieved by transfer reduction with \textit{P}(NMe\textsubscript{2})\textsubscript{3}, \textit{via} its thiophosphinic amide 9,\textsuperscript{18} providing 10 in 90\% yield and 99.5:0.5 er with retention of the configuration. Subsequent use of 10 as a ligand in rhodium catalyzed asymmetric hydrogenation\textsuperscript{19} of 11 provided reduced product 12 in 99\% yield and 86:14 er.

**Conclusions**

In summary, we have developed a new trisubstituted Cp\textsuperscript{x} ligand family. Based on our atropchiral Cp\textsuperscript{x} 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 \textit{s}-factors of up to 50. The superiority of them are showcased by kinetic resolutions amides providing access to compounds with stereogenic phosphorus(v) atoms. The ligand synthesis capitalizes on a late stage modification and expands the accessible ligand Cp\textsuperscript{x} ligand portfolio for further catalytic-enantioselective transformations with additional metals.

**Conflicts of interest**

There are no conflicts of interest to declare.

**Acknowledgements**

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**Notes and references**


5 (a) Z.-Q. Lin, W.-Z. Wang, S.-B. Yan and W.-L. Duan, \textit{Angew. Chem., Int. Ed.}, 2015, 54, 6265; (b) L. Liu, A.-A. Zhang, W. Fang, Z. Zhang, Z. Zuo, W.-X. Zhao, C.-L. Feng and...


Definiton s-factor: $s = \ln[(1-c)(1-\text{ee})]/\ln[(1-c)(1+\text{ee})]$ (c: conversion; ee: recovered substrate’ see).

The absolute configuration of recovered 1a was determined to be (S) by X-ray-crystallographic analysis.


CCDC 1588292 ([S]-1a) and 1588293 ([L6RhCl3]2) contain the supplementary crystallographic data for this paper.†


