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Simple Oxazolidine Chiral Diene Ligands for Enantioselective Rh-Catalyzed Conjugate Additions.

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Abstract: Simple oxazolidine-based chiral diene ligands, ultimately derived from serine, have been synthesized using the Seebach self-regeneration of stereocentre strategy. The ligands have been used in the enantioselective Rh-catalyzed conjugate-addition of aryl boronic acids to cyclohexene. An efficient “in vacuo” reaction protocol has been developed as part of this study.

Key words: Diene, Chiral, Enantioselective, Rhodium, Oxazolidine

In recent years, there has been a pronounced level of interest in the design, synthesis and evaluation of chiral diene ligands for enantioselective transition metal-catalyzed transformations.1 Originally, Hayashi reported that rigid bicyclic dienes, such as 12 (Figure 1), acted as excellent chiral ligands for Rh(I)-catalyzed processes. Whilst ligand 1 is clearly a very effective ligand for asymmetric synthesis, accessing 1 is somewhat involved, including resolution of the racemic diene ligand. The report of 1 prompted the exploration of new areas of chemical space, and other laboratories accordingly sought to design efficient syntheses of new diene ligands avoiding the requirement for resolution. For example, the Carreira laboratory synthesized 21 from readily available chiral pool sources.

The rigid bicyclic scaffold of ligands 1 and 2 is arguably the key to their success in asymmetric synthesis contexts, therefore it is perhaps surprising that chiral diene ligands which offer much greater levels of conformational flexibility should act as competent ligands. Du has extensively reported on the synthesis and application of “simpler” ligand structures, for example, ligand 33 (Figure 1). Recently, the groups of Trost4 and Yu5 have reported asymmetric syntheses of ligands 4 and 5 respectively using transition-metal catalysis, however, in the case of 5, this ligand was not accessed as a single enantiomer. We felt that a significant level of structural scope existed to examine new ligand structures with syntheses offering diversity and if possible, both enantiomers accessible from inexpensive enantiopure chiral pool sources.

As part of our interest in synthesizing biologically relevant α- and β-amino acids,6 we have recently reported the use of serine-derived oxazolidines as highly stereoselective motifs for Ireland-Claisen rearrangements.7 The products from this rearrangement were unsaturated derivatives of biologically important unsaturated β,β′-dihydroxy α-amino acid products, offering large levels of structural diversity of alkyl- and allyl-allyl ethers, with allyl ethers 6a-b being representative (Scheme 1). We anticipated that ethers such as 6, derived from serine,10 could be readily transformed to diene ligands 7a-b as depicted in Scheme 1.

Prior to synthesizing 7a-b, esters 6a-b were complemented by three additional esters (6c-e) formed by the alkylation of 8 (Scheme 2). These additional ligands would offer the ability to probe steric and electronic sensitivity of the ligands in addition to being potentially simpler to synthesize. Accordingly, LHMDS-mediated enolization and subsequent reaction with electrophile formed oxazolidines 6c-e in excellent yield.11,12

Figure 1 Representative chiral diene ligands.

Scheme 1 Design principle for oxazolidinyl chiral diene ligands.
Oxazolidines \( 6a-e \) have been converted to diene ligands \( 7a-e \) through a synthetic sequence comprising of \( \text{LiAlH}_4 \)-mediated ester reduction, Swern oxidation and Wittig olefination (Table 1). It is worth noting that this three-step sequence was synthetically amenable, with only a single chromatographic purification required after the final Wittig methylenation reaction.

**Table 1** Ligand Synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \mathrm{R}^1 )</th>
<th>( \mathrm{R}^2 )</th>
<th>( \mathrm{R}^3 )</th>
<th>Yield (%)</th>
<th>( \text{ee} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{OEt} )</td>
<td>( \text{H} )</td>
<td>( \text{H} )</td>
<td>7a</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>OPMP</td>
<td>( \text{H} )</td>
<td>( \text{H} )</td>
<td>7b</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>( \text{H} )</td>
<td>( \text{H} )</td>
<td>( \text{7c} )</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>( \text{Me} )</td>
<td>( \text{H} )</td>
<td>( 7d )</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>( \text{H} )</td>
<td>( \text{H} )</td>
<td>( \text{Me} )</td>
<td>7e</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield over three steps.

With five diene ligands synthesized, we sought to determine their efficacy in an enantioselective transformation. The \( \text{Rh} \)-catalyzed addition of phenylboronic acid (\( 11a \)) to 2-cyclohexenone (\( 10 \)) was chosen as this reaction arguably acts as the benchmarking evaluation in the area of chiral diene ligand design. The conditions reported by Yu were chosen as a starting point because of the structural similarities of the ligands, i.e. the 5-membered ring skeleton in \( 5 \) and \( 7 \).\(^b\) In conducting the ligand screen it was observed that the reactions were proceeding sluggishly, and extended reaction times failed to achieve full conversion. Importantly though, on solvent removal at reduced pressure, any residual starting material was consumed. Consequently, a new operationally simple procedure was developed whereby on addition of \( 10 \), the reaction mixture was transferred to a rotary evaporator. The results from this ligand screen are presented in Table 2.

**Table 2** Ligand Screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \mathrm{T} ) (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
<th>( \text{ee} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>1 min</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>2(^a)</td>
<td>20</td>
<td>1 min</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>2.5 h</td>
<td>17</td>
<td>83</td>
</tr>
<tr>
<td>4(^b)</td>
<td>20</td>
<td>24 h</td>
<td>16</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>2.5 h</td>
<td>97</td>
<td>82</td>
</tr>
</tbody>
</table>

\(^a\) Complexation of \( \text{Rh} \)-catalyst and ligand 7 conducted at 50 °C prior to reaction. \(^b\) Reaction transferred immediately to rotary evaporator, set to 40 °C, on addition of \( 10 \).
aqueous work-up. Assayed using chiral stationary phase HPLC
(Chiralpak AD column). See Supporting Information for details.

Finally, a short study of boronic acid reaction partners
has been accomplished (Table 4). In the small sample
set presented, ligand 7c is seen to offer good
enantioselectivity with the highest observed selectivity observed with 4-fluorobenzeneboronic acid
(91% ee, entry 2, Table 4). The isolated yield of the
product derived from 4-acetylbenzeneboronic acid
(12e) is notably lower, even though the
enantioselectivity remains high (entry 5, Table 4).

Table 4 Boronic Acid Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>100 (12a)</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>4-FClH4</td>
<td>95 (12b)</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOC6H4</td>
<td>93 (12c)</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>1-Naphthyl</td>
<td>100 (12d)</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>4-AcC6H4</td>
<td>24 (12e)</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>4-ClC6H4</td>
<td>87 (12f)</td>
<td>83</td>
</tr>
</tbody>
</table>

* Assayed using chiral stationary phase HPLC. See Supporting
Information for details.

In conclusion, simple chiral diene ligands have been
synthesized from serine. The optimum ligand in this
study (7c) is synthesized via a self-regeneration
of stereocenters approach via allylation of a serine-
derived oxazolidine. As both enantiomers of serine are
commercially available and inexpensive, both
enantiomers of these ligands will be accessible.

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