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Enantioselective Intramolecular Reductive Heck Reaction with a Palladium/Monodentate Phosphoramidite Catalyst

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A palladium-catalyzed enantioselective reductive Heck reaction of enones using monodentate phosphoramidite ligands is described. \( \alpha,\alpha',\alpha''\)-trisubstituted arylboronates, and \( N \)-methyl dicyclohexylamine as reducing agent gives the reductive Heck product in high yields and enantioselectivities of up to 90%. The solvent plays an important role and in diethyl carbonate, the chemo- and enantioselectivity appeared to be the highest.

The transition-metal-catalyzed enantioselective conjugate addition of organometallics to activated alkenes is an attractive and widely applied method to create stereocenters.[1] A variety of organometallic reagents, for example, organoboron, -zinc, -aluminium, -silicon, -lithium, and -magnesium (Grignard) reagents have been used in combination with a plethora of Michael acceptors, and high levels of enantioselectivity have been achieved with a suitable chiral metal catalyst.[2] The enantioselective conjugate addition of hard organometallic compounds has been well explored in copper catalysis in particular,[3] whereas soft organometallics are mostly used in combination with rhodium[4] and palladium catalysts.[5] In sharp contrast, the direct use of the parent aryl or alkyl halides in enantioselective conjugate addition reactions is still underdeveloped although potentially more straightforward as it obviates the need for the preparation of the organometallic reagent. One reaction that can be used is the asymmetric Heck reaction, which, however, requires special substrates.[6]

The group of Cacchi[7] and our groups[8] extensively studied the palladium-catalyzed conjugate addition (also known as the reductive Heck reaction) of aryl iodides to enones and enals. In this process, the electrophilic halide acts as a nucleophile for which a stoichiometric reductant is needed. Until now, formates and trialkyl amines have been used successfully. Despite these developments, the asymmetric version of this reaction has been studied much less intensively, and an intermolecular version has not yet been reported. Nevertheless, a number of reports have appeared on the intramolecular version.[9] In 2007, Buchwald et al. reported the asymmetric reductive Heck reaction by using aryl triflates, nonaflates, and halides, using \( (R)-3,5\)-XylMeOBIPHEP as ligand.[9d] In most cases, moderate to good ee values were observed. In particular with aryl halides, the desired product was obtained in low yield and with moderate enantioselectivity. Jia and co-workers have developed an enantioselective arylation deoxygenation of indoles using a reductive Heck reaction with BINAP as ligand.[9e] Recently, Zhou and co-workers studied the same reaction using aryl halides, especially bromide and chloride, and found that spiro-di(1,1'-indanyl)bisphosphine (SDP)-type ligands were superior, affording 3-arylindanones with high ee.[9f] The use of 1 equiv. of benzoic acid with 3 equiv. of trialkylamine in ethylene glycol was crucial to obtain high yields as well as high enantioselectivities. Chiral 3-arylindanones are present in various natural products and are also used as intermediate to synthesize various bioactive molecules.[10] Other methods to prepare chiral 3-arylindanones through the cyclization of chalcone derivatives have also been reported.[11] Important examples include rhodium-catalyzed intramolecular asymmetric 1,4-addition of boryl substituted chalcones[12] and palladium-catalyzed Heck reaction of halogen substituted chalcones and their subsequent asymmetric reduction.[13] Since boryl substituted chalcones are prepared from the aryl halide precursor and the palladium-catalyzed cyclization reaction required two or more steps to obtain the desired product, it is advantageous to develop a novel method for the synthesis of chiral 3-arylindanones from easily accessible starting materials and a readily available chiral ligand in a single step fashion. Metal-catalyzed asymmetric cyclization reactions to prepare chiral 3-arylindanones[11] from different precursors, such as \( 2\)-alkenylbenzaldehyde[14a,b] and 2-cyclobutanone substituted arylboronates[14c] have also been described in the literature.

Monodentate phosphoramidite ligands form a readily available and easily tunable class of ligands that has proven...
successful in a variety of catalytic asymmetric transformations. Their use as ligands in the Heck reaction has been reported as well, including the successful use in an asymmetric Heck reaction (Scheme 1a). Although many reports on the use of chiral phosphoramidites as ligands in the transition metal-catalyzed asymmetric conjugate addition of organometallics have appeared, there is no report on their application in an asymmetric reductive Heck reaction.

Herein, we report the palladium-catalyzed intramolecular asymmetric reductive Heck reaction of chalcone 1 using chiral monodentate phosphoramidite ligands. Chalcone derivatives 1a-d are easily prepared from the readily available starting materials 1-(2-iodophenyl)ethan-1-one and the corresponding benzaldehydes through aldol condensation. After synthesizing 1, we studied the asymmetric reductive Heck reaction of 1a in the presence of 10 mol% Pd(OAc)$_2$ ligand (30 mol%), and N,N-dicyclohexylmethyamine as reducing agent (4.5 equiv.).

Our study commenced with a screening of chiral monodentate phosphoramidite ligands (Table 1). With the BINOL-based phosphoramidite L1 in chloroform at 65°C, the desired reductive Heck product 2a was obtained in a satisfying 81% yield but with a moderate 51% ee (entry 1). In addition, the competitive Heck product 3a was also formed in 11% yield. To improve the enantioselectivity in the formation of 2a and to suppress the formation of 3a, the reaction was examined in a variety of solvents (entries 2–5). Despite the moderate conversion, 1,2-dimethoxy ethane (DME) seemed to be more suitable than other solvents in terms of both selective formation of 2a and enantioselectivity (entry 4). Although 1,4-dioxane gave good conversion, the considerable amount of Heck product made it less effective (entry 5). The use of other solvents such as THF and 1,2-dichloroethane induced only moderate ee values.

In an attempt to identify a more selective ligand, we then screened the reaction with other chiral phosphoramidite ligands L2–L4 using DME as the solvent (entries 6–8). No promising results were observed with L2 and L3, however, if a,a',a''-tetraphenyl-1,3-dioxolane-4,5-dimethanol-derived phosphoramidite L4 was used as ligand, the reaction proceeded smoothly to afford 2a in 88% yield with 74% ee. Decreasing the temperature of the reaction led to an increase of the ee to 91%, though at the expense of the yield which was only 35% even after 72 h (entry 9). To improve the reaction rate and enantioselectivity, and keeping in mind the profound influence of the solvent, we also studied the effect of dialkyl

**Table 1.** Palladium-catalyzed intramolecular asymmetric reductive Heck reaction of chalcone 1a using monodentate phosphoramidite ligands. Variations in the ligand, temperature and the solvent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>Conv. [%]</th>
<th>YieldH [%]</th>
<th>ee [%]</th>
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<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>CHCl$_3$</td>
<td>65</td>
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<td>100</td>
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<td>15</td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td>THF</td>
<td>80</td>
<td>48</td>
<td>40</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>L1</td>
<td>DCE</td>
<td>80</td>
<td>24</td>
<td>45</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>L1</td>
<td>DME</td>
<td>80</td>
<td>24</td>
<td>55</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>L1</td>
<td>1,4-dioxane</td>
<td>80</td>
<td>48</td>
<td>81</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>L2</td>
<td>DME</td>
<td>80</td>
<td>48</td>
<td>46</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>L3</td>
<td>DME</td>
<td>80</td>
<td>6</td>
<td>100</td>
<td>86</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>L4</td>
<td>DME</td>
<td>80</td>
<td>52</td>
<td>100</td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>L4</td>
<td>DME</td>
<td>65</td>
<td>72</td>
<td>40</td>
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</tr>
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<td>10</td>
<td>L4</td>
<td>dimethyl carbonate</td>
<td>80</td>
<td>48</td>
<td>100</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>L4</td>
<td>diethyl carbonate</td>
<td>80</td>
<td>48</td>
<td>100</td>
<td>87</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>L5</td>
<td>diethyl carbonate</td>
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<td>24</td>
<td>100</td>
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<td>L5</td>
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<td>18</td>
<td>82</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>L1</td>
<td>diethyl carbonate</td>
<td>80</td>
<td>24</td>
<td>58</td>
<td>51</td>
<td>4</td>
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</table>

[a] All reactions were performed using 1a (0.22 mmol), catalyst (10 mol%), ligand (30 mol%), amine (1 mmol), in 2.0 mL of solvent and n-decane as internal standard for 6–72 h. [b] GC yields. [c] Isolated yield.
carbonate solvents, which have been advocated by the group of Börner for the use in asymmetric catalysis (entries 10–14).

With ligand L4, in combination with dimethyl carbonate as solvent, the reaction of 1a proceeded well to give 2a in 88% yield with 90% ee. Pleasingly, a higher enantioselectivity was observed with diethyl carbonate. Finally, changing the ligand to L5 but keeping diethyl carbonate as the solvent improved the reaction rate and enantioselectivity, giving 2a in 86% isolated yield with 90% ee in 24 h.

After having established the optimal reaction conditions, we studied the reaction with various chalcones (1b–d). As shown in Table 2, both electron-donating and withdrawing substituents are allowed in the β-phenyl substituent, although a slight decrease in the enantioselectivity was observed for electron withdrawing substituents. For instance, 1b gave the reductive Heck product in 80% yield with 90% ee, and the halide containing chalcones 1c and 1d gave the corresponding products 2c and 2d in good yield with 86% ee. We also examined the reaction with (E)-1-(2-bromophenyl)-3-phenylprop-2-ene-1-one 1e, in which the reductive Heck product 3e was obtained in 55% yield with 82% ee (Scheme 2). The low yield is a result of the poor conversion of 1e even after 3 days.

**Table 2.** The Pd(OAc)$_2$/phosphoramidite-catalyzed asymmetric reductive Heck reaction of 1.$^a$, $^b$

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
<td>2a</td>
<td>86%</td>
<td>90% ee</td>
</tr>
<tr>
<td>2b</td>
<td>80%</td>
<td>90% ee</td>
</tr>
<tr>
<td>2c</td>
<td>82%</td>
<td>86% ee</td>
</tr>
<tr>
<td>2d</td>
<td>91%</td>
<td>86% ee</td>
</tr>
</tbody>
</table>

$^a$ All reactions were performed using 1 (0.22 mmol), ligand L5 (0.066 mmol), Pd(OAc)$_2$ (10 mol%) and 1 mmol of N,N-dicyclohexylmethylamine in 2.0 mL of diethyl carbonate. $^b$ Isolated yields.

**Scheme 2.** Asymmetric reductive Heck reaction of (E)-1-(2-bromophenyl)-3-phenylprop-2-ene-1-one (1e).

Compared to earlier studies on the asymmetric intramolecular reductive Heck (AIRH) reaction,$^{9b}$ our present catalyst system is more effective in the enantioselective cyclization of (E)-2-iodochalcones and functions to a lesser extent with (E)-2-bromochalcones. In contrast to the method of Zhou et al.,$^{9d}$ we did not require an acid additive such as benzoic acid to obtain good yields and high enantioselectivities. Although Zhou’s catalytic system works very well with aryl bromides, affording 3-arylindanones with high ee, examples involving aryl iodides were not described. Our catalyst system provides an excellent opportunity to use aryl iodides in the AIRH reaction.

In conclusion, an efficient palladium-catalyzed enantioselective reductive Heck reaction of chalcones, using TADDOL-based monodentate phosphoramidite ligands, has been developed. Good yields and high enantioselectivities up to 90% are reached for the first time in an asymmetric reductive Heck reaction with monodentate ligands. The enantioselectivities are higher than those observed by Buchwald and co-workers$^{9d}$ but slightly lower than those observed by Zhou and co-workers.$^{9d}$ However, the ligand used here is substantially cheaper than the bisphosphines they use. In addition, the present method does not require the addition of stoichiometric benzoic acid. Another advantage is the use of diethyl carbonate as solvent (b.p. 90°C), which is much easier to remove than ethylene glycol (197°C). The reasons for the beneficial properties of diethyl carbonate as solvent with respect to reaction rate and enantioselectivity are currently unclear. Carbonates have been found to be beneficial solvents for a range of transition metal catalyzed reactions.$^{11d}$ It is possible to speculate that the relatively high polarity of the solvent paired with its low propensity to coordinate to the metal plays a role.

Extension of the scope of the reaction and the role of the solvent is currently under study.

**Experimental Section**

**General procedure for the asymmetric reductive Heck (ARH) reaction of 1.** In a flame dried Schlenk tube equipped with a septum and stirring bar, Pd(OAc)$_2$ (10 mol%, 0.022 mmol, 5.0 mg) and ligand L6 (30 mol%, 0.066 mmol, 43.5 mg) were dissolved in anhydrous diethyl carbonate (DEC, 1.0 mL) and stirred under nitrogen at room temperature for 5 min. Chalcone 1 (75 mg, dissolved in 1.0 mL of DEC; 0.224 mmol) was added, followed by the addition of N,N-dicyclohexylmethylamine (1 mmol), with constant stirring. Then, the Schlenk tube was placed into a preheated oil bath at 65°C and stirred for 30 min. Finally, the reaction mixture was heated to 90°C and stirred for 24 h. Upon completion (as judged by GC/MS), the reaction mixture was cooled down to room temperature, diluted with either diethyl ether or ethyl acetate, and filtered through a Celite and silica gel pad. The filtrate was concentrated and the residue was purified on silica gel chromatography to afford the desired product 2.

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