This is an Accepted Manuscript, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This Accepted Manuscript will be replaced by the edited and formatted Advance Article as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about Accepted Manuscripts can be found in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard Terms & Conditions and the ethical guidelines that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these Accepted Manuscript manuscripts or any consequences arising from the use of any information contained in them.
Rhodium / Phospholane-phosphite Catalysts give Unusually High Regioselectivity in the Enantioselective Hydroformylation of Vinyl Arenes.

Gary M. Noonan, Christopher J. Cobrely, Thomas Mahoney, and Matthew L. Clarke

Using the phospholane-phosphite ligand, BOBPHOS, almost perfect regioselectivities and high enantioselectivities (up to 92 % e.e.) are observed in Rh catalysed enantioselective hydroformylation of vinyl arenes. This can be achieved under solvent-free conditions.

Hydroformylation of alkenes is well documented as one of the most cost- and atom-efficient methods to produce aldehydes. A significant number of catalysts offering good to excellent enantioselectivity in asymmetric hydroformylation have now appeared, and since the seminal work on BINAPHOS/Rh hydroformylation catalysts, phosphine-phosphate ligands have been amongst the most well-studied and proficient ligands for enantioselective hydroformylation. This spurred us to prepare the hybrid phospholane-phosphite of two of the leading ligands available for enantioselective hydroformylation: Kelliphite and Ph-BPE. The resulting ligand, nicknamed BOBPHOS was initially hoped to offer the Best Of Both of these PHOShorus ligands, since Kelliphite/Rh catalysts display excellent activity under very mild conditions, even for internal alkenes, and Ph-BPE/Rh catalysts are very robust and give very good enantioselectivities for terminal alkenes such as styrene. Unexpectedly, Rh / BOBPHOS catalysts were found to favour the formation of branched aldehydes with high e.e. from simple terminal alkyl alkenes: a long standing issue for hydroformylation chemistry, since these substates normally favour the linear aldehyde. Given that 2-aryl-propanals are important chiral building blocks, most desirably accessed from cheap vinyl arenes, we have also studied enantioselective hydroformylation of styrene and a few of its derivatives using this catalyst. It is worth noting that several catalysts from the many published studies have already given good enantioselectivity in this reaction. However, an issue, as pointed out by Landis, is that 5-15 % linear aldehyde by-product is often formed. Regioisomer and enantiomer ratios should be considered equally important in alkene additions, so the product of % chemoselectivity, % regioselectivity and % enantioselectivity (enantiomer ratio): a ‘desired isomer yield’, is perhaps the best measure of synthetic utility. Using this measure, only one or two ligands stand out as being directly useful to the best of our knowledge. For example in styrene hydroformylation, the Landis ligands such as \((R,R,S)\)-I can give desired isomer yields of 91%-94.8% under optimised conditions, and Ph-BPE up to 94.9%, and BINAPHOS up to 82.7% (This can be improved to 90.2% for a derivative with different aryl groups, and 86.9% for a derivative with a P-NH function, Yphilhos). Here we report our preliminary findings that show that the Rh / BOBPHOS catalyst gives excellent performance in the hydroformylation of vinyl arenes, even under solvent-free conditions.

We initially did some screening experiments in the hydroformylation of styrene comparing the \((S,S,S)\) and \((S,R,R)\) isomers of BOBPHOS at 2 different pressures and temperatures. The results (Table 1, Entries 2 to 5) clearly

Fig. 1 Ligands for Enantioselective Hydroformylation.
establish BOBPHOS to give a ‘desired isomer yield’ (e.g. Table 1, Entry 2 = 94.7%) that is competitive with the best results ever recorded in the many studies on hydroformylation of styrene. The (S) enantiomer was formed preferentially as was the case with alkyl alkenes. Our alkyl alkene hydroformylation studies used low temperatures (16 °C) to maintain the high selectivity. However in this case, selectivity holds up reasonably well at higher temperatures.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>P (bar)</th>
<th>Time (h)</th>
<th>Catalyst</th>
<th>Conversion (mol%)</th>
<th>B/L</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>2.5</td>
<td>16</td>
<td>0.4</td>
<td>62</td>
<td>55</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>2.5</td>
<td>11</td>
<td>0.4</td>
<td>99</td>
<td>75</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>10</td>
<td>16</td>
<td>0.4</td>
<td>98</td>
<td>79</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>3</td>
<td>4</td>
<td>0.25</td>
<td>&gt;99</td>
<td>55</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>14</td>
<td>15</td>
<td>0.25</td>
<td>&gt;99</td>
<td>66</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>3</td>
<td>3</td>
<td>0.05</td>
<td>&gt;99</td>
<td>50</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>2.5</td>
<td>0.5</td>
<td>0.4</td>
<td>&gt;99</td>
<td>25</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>10</td>
<td>1</td>
<td>0.4</td>
<td>&gt;99</td>
<td>46</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>5</td>
<td>0.025</td>
<td></td>
<td>&gt;99</td>
<td>50</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>12</td>
<td>6</td>
<td>0.01</td>
<td>&gt;99</td>
<td>50</td>
<td>81</td>
</tr>
</tbody>
</table>

The reaction times refer to either total reaction time, or if >99% complete, time after which >99% of gas was consumed. Pressure is constant, a ligand : Rh ratio of 1.25 was used and [stylene] = 0.3M in toluene except where noted. Conversion and B/L determined by 1H NMR (alkyl) protons either against cyclooctane internal standard or alkene protons), and confirmed by GC. The ee was measured using capillary GC (see ESI), and in all cases the S enantiomer was the major isomer. Mismatched (R,S,S)-BOBPHOS used as chiral ligand. Ligand: Rh ratio of 2.5:1, 0.63M, 4 M concentration. No solvent, L:Rh = 2.5.

A large scale protocol would need lower catalyst loadings, or a very good recycling protocol, so some reactions were carried out at low loadings, and a kinetic analysis was carried out (Fig. 2 and E. S. I.). We were pleased to find that a reaction at 0.05 mol% at 4M concentration delivered >99% conversion in around 4 hours at just 50 °C with a peak T.O.F. of 950 in the early stages of the reaction. A plot of T. O. F. versus substrate concentration is a convenient graphical way to measure: the initial T. O. F., if catalyst activation is complete when substrate is added, and to detect if the reactions are diffusion-limited. In the low temperature asymmetric hydroformylations at 0.63 M concentration, the reactions of styrene, (and 4-chloro-styrene) are both pseudo first order in the alkene substrate, with the T.O.F. dropping evenly as its concentration decreases (Fig. 2). A plot of the natural log of [S] versus time also demonstrates this. On the other hand, the very highly concentrated reaction demonstrates kinetics that are in agreement with this being diffusion limited (see plot of T. O. F vs. [substrate] in ESI). However, as shown in Fig. 2, the asymmetric hydroformylation using the Rh/((S,S,S) BOBPHOS catalyst are negative order in styrene, so good rates are still achieved even if limited by solubility of syngas. This, along with the very high desired isomer yields, the high solubility and robustness of BOBPHOS / Rh catalysts prompted us to investigate solvent-free hydroformylation. The solvent in any chemical process is the most significant contribution to the environmental impact and a significant cost contributor whether disposed or recycled. It was pleasing to find that neat styrene can be hydroformylated using 0.025 mol% Rh pre-catalyst (with no activation) at just 50 °C and 10 bar pressure to give complete consumption of product within 6 hours, and maintain the excellent regio-, chemo- and enantioselectivity. A 1H NMR spectrum of the reaction ‘mixture’ is archived in the ESI and resembles a commercial sample (albeit contaminated with traces of Rh that would need to be removed in downstream reactions if used in a drug synthesis). While neat hydroformylations (and hydroformylation of mixtures of alkenes) are quite widely reported, the direct loading of a vessel with pre-catalyst, ligand and as-received-substrate in air, followed by the conversion to product of good purity seems of practical value. The best procedure we have discovered so far is shown in Table 1, entry 9, although we also note that an unoptimised neat reaction also worked using 0.01 mol% catalyst at 65 °C (T. O. F. = 2500 mol/mol/h), but gave lower e.e. In any case, the productivity we have observed is in the range of application in commercial processes.

![Fig. 2 Asymmetric hydroformylation of styrene at 3 and 14 bar respectively and 35 °C. Top: plot of Conversion versus time; Bottom: Plot of T. O. F. (measured at 0.1M intervals) versus substrate concentration.](image-url)

While many papers only report studies on styrene as a model substrate, some of the more synthetically useful publications also report other vinyl arenes. These can give less desirable results in some cases; in the case of asymmetric hydroformylation of 4-chlorostyrene and 4-methoxystyrene, the class-leading Landis ligands report a desired isomer yield down to 86.9% and 81% due to a drop-off in e.e. We studied alkenes 2a and 3a under the unoptimised low temperature conditions. The results obtained for the 3- and 4-chloro styrenes (desired isomer yield ~ 94-95%) appear to be the best...
We also note here that when we have used a significant excess of ligand (corresponding author) slightly faster than using the complex formed from [Rh(acac)(CO)] and BOBPHOS without large excess of ligand. Whether excess ligand prevents catalyst decomposition needs to investigated in our future mechanistic studies. We certainly recommend an excess of ligand for the 4 solvent no activation process.  

† We thank Dr Reddys Laboratories (UK), the EPSRC-Chemistry Innovation Network, and the Royal Society for funding.


Notes and references

40 a) School of Chemistry, University of St Andrews, EaSChEM, St Andrews, Fife, UK, Fax: (44) 1334 463808; Tel: (44) 1334 463850; (corresponding author) E-mail: e.coble@st-andrews.ac.uk

41 † Author for industrial correspondence: e.coble@drreddys.com

42 Chirotech Technology Ltd. Dr Reddys Laboratories (EU) Limited, 410 Cambridge Science Park, Milton road, Cambridge, UK, CB4 0PE

43 † Electronic Supplementary Information (ESI) available: [Full experimental details, further kinetic experiments, NMR and GC spectra]. See DOI: 10.1039/b000000x/00x

44 † We also note here that when we have used a significant excess of ligand (e.g. L:Rh of 2.5:1), rather than observe inhibition, the reaction proceeded slightly faster than using the complex formed from [Rh(acac)(CO)] and BOBPHOS without large excess of ligand. Whether excess ligand prevents catalyst decomposition needs to investigated in our future mechanistic studies. We certainly recommend an excess of ligand for the 4 solvent no activation process.

45 Only a couple of entries from table 1 were archived in a patent: G. M. Noonan, C. J. Cobley and M. L. Clarke, WO201201657A3.


