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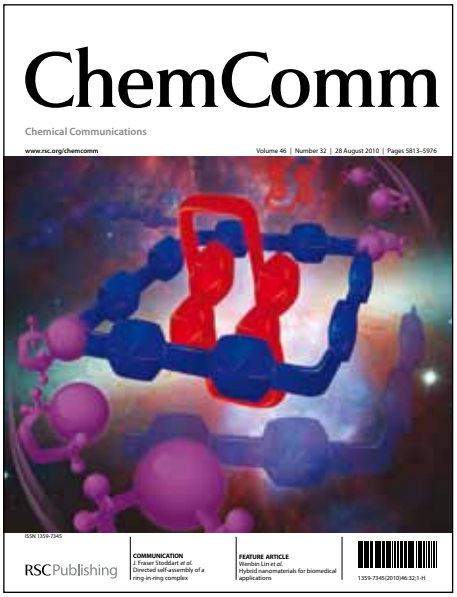

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ARTICLE TYPE

Rhodium / Phospholane-phosphite Catalysts give Unusually High Regioselectivity in the Enantioselective Hydroformylation of Vinyl Arenes.

Gary M. Noonan,[a] Christopher J. Cobley,*[b] Thomas Mahoney,[b] and Matthew L. Clarke*[a]

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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.[1] 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-phosphite ligands[2] have been amongst the most well-studied and proficient ligands for enantioselective hydroformylation.[3] This spurred us to prepare the hybrid phospholane-phosphite of two of the leading ligands available for enantioselective hydroformylation: Kelliphite[3a, 3o] and Ph-BPE.[3h] The resulting ligand, nicknamed BOBPHOS[4] was initially hoped to offer the *B*est *O*f *B*oth of these *PHOS*horus 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 enantioselectities 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.[5] 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,[2f] is that 5-15 % linear aldehyde by-product is often formed. Regioisomer and enantiomer ratios should be considered equally important in alkene additions,[6] 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*)-**1** can give desired isomer yields of 91%-94.8% under optimised conditions,[2f] Ph-BPE up to 94.9%,[3h] and BINAPHOS up to 82.7% (This can be improved to 90.2% for a derivative with different aryl groups,[2b] and 86.9% for a derivative with a P-NH function, Yanphos[2i]). 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.

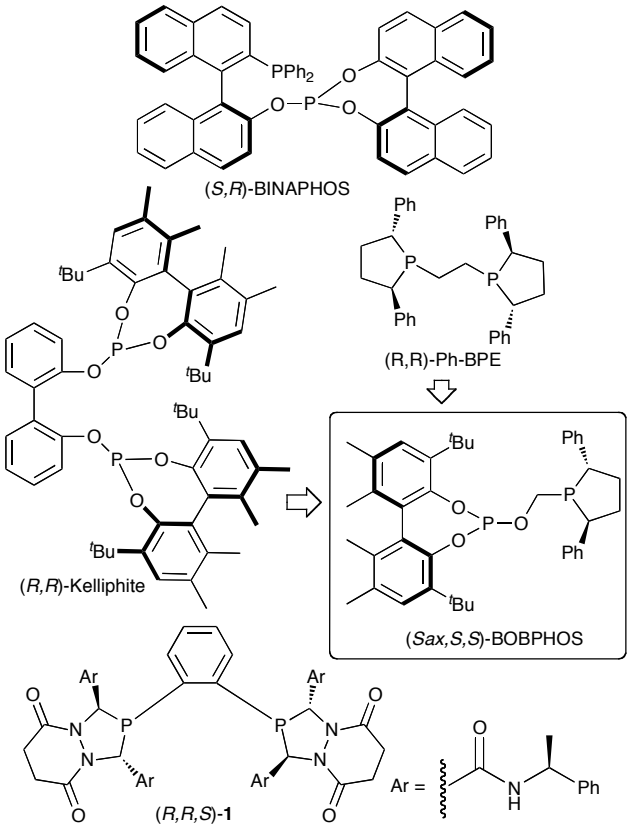
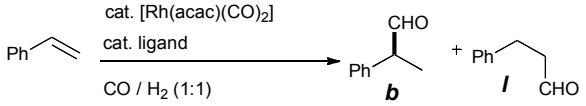


Fig. 1 Ligands for Enantioselective Hydroformylation.

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

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 Enantioselective hydroformylation of styrene catalysed by Rh / (*S,S,S*)-BOBPHOS.



Entry	Temp. (°C)	P (bar)	Time (h)	Catalyst (mol%)	Conversion[b] (%)	B/L[b]	ee[b]
1[c]	30	2.5	16	0.4	62	55	19
2	30	2.5	11	0.4	99	75	92
3	30	10	16	0.4	98	79	92
4[d]	35	3	4	0.25	>99	55	92
5[d]	35	14	15	0.25	>99	66	91
6[e]	50	3	3	0.05	>99	50	85
7	60	2.5	0.5	0.4	>99	25	82
8	60	10	1	0.4	>99	46	89
9[f]	50	10	5	0.025	>99	50	91
10[f]	65	12	6	0.01	>99	50	81

[a] 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 [styrene] = 0.3M in toluene except where noted. [b] Conversion and B/L determined by ^{1}H 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. [c] Mismatched (*R,S,S*)-BOBPHOS used as chiral ligand. [d] Ligand: Rh ratio of 2.5:1, 0.63M. [e] 4 M concentration. [f] 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 hydroformylations using the Rh/(*S,S,S*) BOBPHOS catalyst are negative order in syngas, 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 ^{1}H 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,[3a,7] 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 suitable for application in commercial processes.

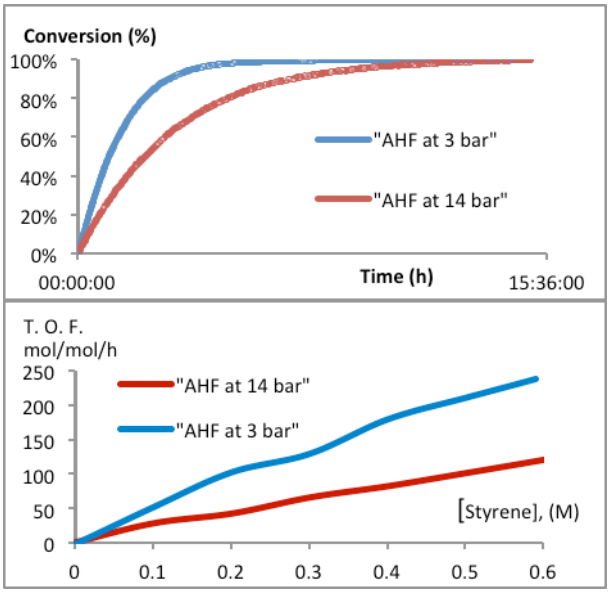


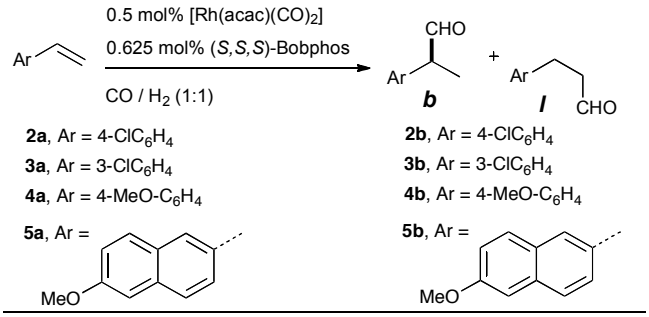
Fig. 2 Asymmetric hydroformylation of styrene at 3 and 14 bar respectively and 35 °C. Top: plot of Conversion versus time; Bottom: Plot of T. O. F. (measured at 0.1M intervals) versus substrate concentration.

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

observed for these substrates. Reactions were complete in several hours. To investigate if more electron donating vinyl arenes could be used, we also studied the hydroformylation of 4-vinyl anisole under solvent-free conditions and got excellent results with a desired isomer yield of 93.3%. 2-methoxy-6-vinyl-naphthalene also gave good results, although not quite matching the very best[2f] reported (Table 2, Entry 5 and 6).

In summary, The use of rhodium complexes of (*S,S,S*)-BOBPHOS as catalyst for the enantioselective hydroformylation of vinyl arenes enables very high desired isomer yields with good activity. The ability to give good activity at low pressures, the high solubility, and the ease of operation enable a solvent-free highly enantioselective hydroformylation at low catalyst loading directly delivering product of excellent purity. Projects studying the mechanism of action of this unusually selective catalyst, new related ligand systems and further applications are getting underway.

Table 2 Enantioselective hydroformylation of vinyl arenes catalysed by Rh / (*S,S,S*)-BOBPHOS.



Entry	substrate	Temp. (°C)	Time (h)	Catalyst (mol%)	Conversion[b] (%)	B/L[b]	ee[b]
1[c]	2a	30	3	0.5[c]	>99	>80	89
2	2a	30	3.5	0.5	>99	>80	89
3	3a	30	4.5	0.5	>99 [89]	>80	89
4[c,d]	4a	45	9	0.05	>99[89]	54	90
5	**5a**	30	6	0.5	>99 [96]	75	86
6[e]	**5a**	60	1	0.4	52 [46]	48	89

[a] The reaction times refer to either total reaction time, or if >99% complete, time after which >99% of gas was consumed. Constant pressure of 4 bar used, and a ligand : Rh ratio of 1.25 was used and [styrene] = 0.5M in toluene except where noted. [b] Conversion and B/L determined by ^{1}H NMR (alkyl protons either against cyclooctane internal standard or alkene protons), and confirmed by GC. >80:1 refers to either undetectable linear aldehyde or measured values of c. 99% branched aldehyde content. [Unoptimised yields of aldehydes of high purity (spectra in ESI)]. The ee was measured using capillary GC or HPLC (see ESI). [c] Ligand: Rh ratio of 2.5:1. [d] No solvent. [e] 0.4% Rh, 0.5% ligand.

Notes and references

[a] *School of Chemistry, University of St Andrews, EaStCHEM, St Andrews, Fife, UK. Fax: (44) 1334 463808; Tel: (44) 1334 463850; (corresponding author) E-mail: mc28@st-andrews.ac.uk.*

[b] *Author for industrial correspondance: ccobley@drreddys.com Chirotech Technology Ltd. Dr Reddys Laboratories (EU) Limited, 410 Cambridge Science Park, Milton road, Cambridge, UK, CB4 0PE.*

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

† 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)$_2$] 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 no-solvent+no activation process.

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

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