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Supporting Information for:

**Rhodium – Mediated Asymmetric Hydroformylation using a Novel Bis  
(diazaphospholidine) Ligand\*\***

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This contains an abstract of the detailed results from the CATS evaluation service, together with additional kinetic data for the hydroformylation reactions. The report was prepared by Douglas Foster in June 1999.

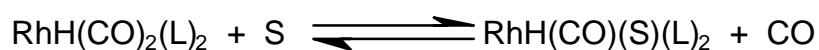
## **Introduction**

The ESPHOS diphosphine and SEMI-ESPHOS monodentate phosphine were tested under a variety of conditions for their ability to effect the asymmetric hydroformylation of vinyl acetate and styrene. The results are summarised in the Table.

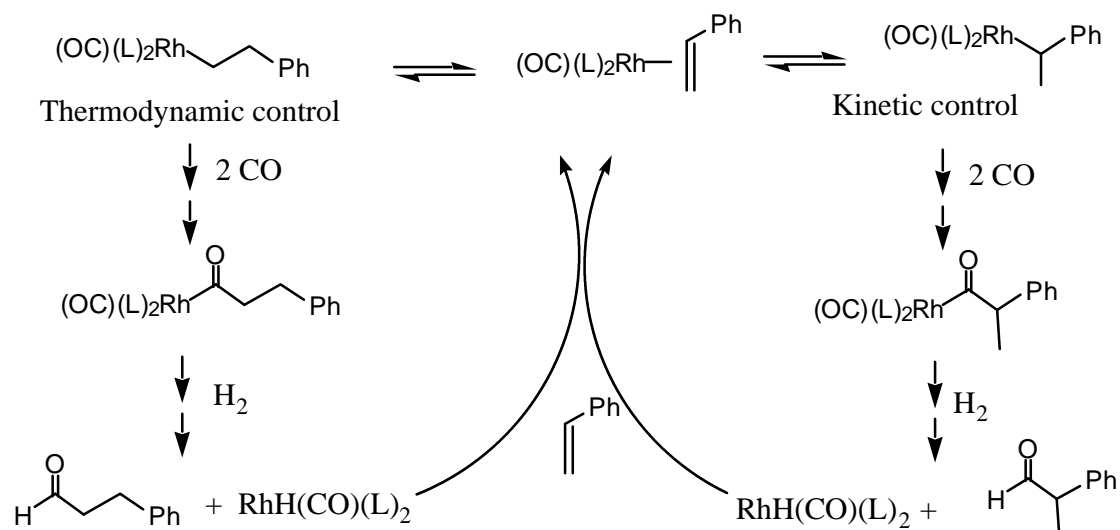
The reactions were carried out in a specially designed mini-autoclave fitted with a system for substrate or catalyst injection and for measuring kinetics at constant pressure. The ligand,  $[\text{Rh}(\text{CO})_2(\text{acac})]$  and toluene solvent were placed in the autoclave and flushed with  $\text{CO}/\text{H}_2$  before pressurising to several

bars below the operating pressure. The mixture was heated with stirring to the desired reaction temperature. The substrate was then introduced *via* the substrate injection facility and the pressure raised to the desired reaction pressure. It takes *ca* 90 seconds to stabilise the reaction conditions after the substrate injection. The pressure in the ballast vessel attached to the reaction vessel via a mass flow controller, which meters in gas to keep the constant pressure in the reactor, was monitored electronically with time. At the end of the reaction, the stirrer was stopped and the reactor cooled by plunging it into cold water. The liquid products were analysed by GC-FID (quantitative) and GC-MS (qualitative) using a chiral capillary column.

Generally speaking, heating the rhodium source and phosphine ligand under CO/H<sub>2</sub> leads to the rapid formation of the catalytically active species so that any reaction should start immediately the substrate is introduced, although for low pressure and temperature reactions formation of the active species may take longer leading to an induction period. There are two types of kinetic behaviour normally observed – first order in substrate or zero order in substrate and the order with respect to substrate gives information on the alkene binding step:



where L<sub>2</sub> is two monodentate or one bidentate ligand and S is the substrate. If this equilibrium does not lie totally to the right (which is usually the case), the reaction will be first order in substrate; if it does lie totally to the right it will be zero order. A complication occurs in our reactor at present in that at low CO/H<sub>2</sub> pressures (8 or 10 bar of CO/H<sub>2</sub>, gas diffusion into the liquid phase can become rate determining. When this occurs, the kinetics can give a misleading appearance of 0 order dependence on substrate concentration as well as misleading product distributions. There is a simple explanation for the change in product distribution observed when the reactant solution is ‘starved’ of CO during Rh catalysed hydroformylation reactions. The first step involves coordination of styrene followed by reversible rhodium bound H transfer to give both the straight and branched chain Rh-alkyl species, which because of the reversibility of the hydrogen transfer, are in equilibrium.



Now CO effectively acts as a ‘trapping’ agent to form Rh-CO-alkyl species (again both straight and branched alkyl chain) which upon H transfer from Rh, eliminate to form the observed products, 2- and 3-phenylpropanal. Now if the CO ‘trapping’ is faster or of a comparable rate to the reversible H transfer leading to equilibration of the branched and straight chain Rh-alkyl species, then increasing the CO conc. In solution will favour trapping of the kinetically favoured Rh-alkyl species (apparently the branched Rh-alkyl species) over the thermodynamically favoured straight chain (apparently) Rh-alkyl species. Conversely, ‘starving’ the solution of CO, will favour the formation of increased amounts of product from the thermodynamically favoured straight chain Rh-alkyl species, leading to a lowering of the aldehyde i:n ratio]. For the low pressure reactions I have been careful not to categorically state the order with respect to substrate as they may be diffusion limited, giving a false appearance of 0 order substrate concentration dependence.

## Analysis of Results

### Vinyl acetate

Optically active aldehydes are very important as precursors not only in biologically active compounds but also for new materials such as biodegradable polymers and liquid crystals. The ESPHOS ligand has demonstrated enormous potential for the asymmetric hydroformylation of vinyl acetate. The

chiral branched aldehyde, 2-acetoxypropanal, is a precursor for the Strecker synthesis of the amino acid threonine. The 2-acetoxypropanal product can be converted to 2-hydroxypropanal, a useful intermediate in the synthesis of steroids, pheromones, antibiotics and peptides. Both the ratio of branched to straight chain aldehyde and the enantiomeric excesses obtained using ESPHOS are comparable with the very best results seen in the literature (using BINAPHOS and BIHEMPHOS). SEMI-ESPHOS was not very active for the hydroformylation, even under forcing conditions. That ESPHOS produces virtually racemic product from the hydroformylation of styrene (see below) is somewhat surprising as the ligands BINAPHOS and BIHEMPHOS give large inductions during the hydroformylation of both vinyl acetate and styrene. However, asymmetric induction is usually higher in heterofunctionalised alkenes such as vinyl acetate, presumably due to the additional binding of the C=O bond of the substrate to the catalyst.

The **S-(-) enantiomer** (authentic synthesis) is the major enantiomer observed for the 2-acetoxypropanal product from ESPHOS catalysed hydroformylations, whereas the slight ee excess observed in one of the SEMI-ESPHOS catalysed hydroformylations (expt 9 of Table 1B) is the R enantiomer. The 2-acetoxy-1-propanol (2Ac1o1) arises from sequential hydroformylation of styrene to 2-acetoxypropanal followed by hydrogenation whereas the 1-acetoxy-2-propanol (1Ac2o1) arises from the isomerisation of 2Ac1o1 (primary product) into 1Ac2o1 (secondary product). It has also been observed that when the product samples (stored in sealed containers in the dark at room temperature) are re-analysed after a couple of months the 2Ac1o1 / 1Ac2o1 ratio falls considerably relative to that obtained on analysis of a fresh product mixture, presumably eventually reaching an equilibrium ratio. Since the hydrogenation of the aldehyde does not affect the chiral centre we can be sure that the major enantiomer in the 2-acetoxy-1-propanol, arising from ESPHOS catalysed hydroformylation reactions (followed by hydrogenation), is also the S enantiomer. However, various mechanisms can be suggested for the isomerisation of the 2-acetoxy-1-propanol into 1-acetoxy-2-propanol, some which invert the chiral centre and some which do not, so that we cannot be certain, at this time, which is the major enantiomer in the 1-acetoxy-2-propanol product. However, there are simple methods available which could be used to ascertain which is the major enantiomer for 1-acetoxy-2-propanol. For example, hydrolysis of a product mixture containing high amounts of both 1-

acetoxy-2-propanol and 2-acetoxy-1-propanol will give 1,2-propanediol. Now if both the acetoxypropanols are rich in the S enantiomer then (S)-1,2-propanediol will be the major enantiomer, whereas if the 1-acetoxy-2-propanol has been formed through a process which involves inversion of the chiral centre of 2-acetoxy-1-propanol then both the R and S enantiomers will be produced in large amounts.

The acetic acid (AA) will arise from the thermal decomposition of the expected linear aldehyde, 3-acetoxypropanal into propanal (acrolein) and acetic acid. This process has been observed by ourselves to occur at relatively low temperatures. The expected propanal is difficult to quantitate as it hydrogenates to propanal which overlaps with the solvent peak in our chiral GC analyses, but does appear to be present in similar quantities to the acetic acid. As such, the amount of acetic acid can be taken as a measure of the i:n ratio of aldehyde formation. It is interesting to note that many reports in the literature report directly the ratio of 2-acetoxypropanal : 3-acetoxypropanal. I suspect that many have confused 3-acetoxypropanal with acetoxyacetone, a minor product in the vinyl acetate hydroformylations employing ESPHOS but which is a more significant product in other work carried out in our laboratories. Interestingly, acetoxyacetone and 3-acetoxypropanal have very similar retention times on the chiral capillary column we have used in this work!

The best result so far obtained, by which time we had optimised our autoclave loading technique, is exemplified in expt 18. Vinyl acetate was hydroformylated employing the ESPHOS/Rh(CO)<sub>2</sub>(acac) catalyst system at 60°C and 8 bar of CO/H<sub>2</sub> (1:1) for 5 hours, to give 99% conversion with a 90% yield of the branched aldehyde, 2-acetoxypropanal, with 89% ee of the S enantiomer. This result might well be improved upon if conditions of temperature, pressure, CO:H<sub>2</sub> ratio and ESPHOS:Rh ratio were optimised. As already stated, this result in terms of ee and i:n ratio of aldehyde is already competitive with the best work in the literature.

Rhodium based catalysts usually give aldehydes as the only products from hydroformylation reactions, especially in aprotic solvents. The formation of some alcohol product may be due to the presence of the acetic acid. It would be interesting to follow up this work by carrying out the direct hydrogenation

of the chiral branched aldehyde to chiral alcohol *in-situ*, i.e. cool and vent the autoclave once the hydroformylation is complete and then pressurising with H<sub>2</sub> and optimise the conditions for hydrogenation.

## **Styrene**

Styrene hydroformylation is useful as a model for the asymmetric hydroformylations of vinyl aromatics in general. The hydroformylation reaction of vinyl aromatics lends itself, upon oxidation of the aldehyde, to the synthesis of a number of optically active non-steroidal antiinflammatory agents, 2-arylpropionic acids, for example, (S)-(+)-Ibuprofen, (S)-(+)-Naproxen and Suprofen.

Unfortunately, the results obtained with both ESPHOS and SEMI-ESPHOS are not particularly interesting with neither affording asymmetric induction in the branched aldehyde product, 2-phenylpropanal. It is interesting to note that both ligand systems give similar initial rates, in contrast to the hydroformylation of vinyl acetate where, as already noted above, SEMI-ESPHOS demonstrated very little activity compared with ESPHOS. That ESPHOS produces virtually racemic product from the hydroformylation of styrene was both disappointing and surprising given that the ligands BINAPHOS and BIHEMPHOS give large inductions during the hydroformylation of both vinyl acetate and styrene. It could be that heterofunctionalisation of the aryl group, face-binding to the catalyst, may be important and it would be of interest to consider this aspect in future work.

In summary, ESPHOS has demonstrated great potential for asymmetric hydroformylation reactions and is an excellent candidate for future work, including comparative studies in asymmetric hydrogenations

**Table 1** Asymmetric hydroformylation of alkenes catalysed by rhodium complexes.<sup>a</sup>

Substrate	Ligand	P:Rh	T / °C	p / bar	t / h	Initial Rate / Conversion mol dm <sup>-3</sup> s <sup>-1</sup> / %	Acetic acid yield / %	Aldehyde yield <sup>b</sup> / %	Aldehyde i:n <sup>c</sup>	Aldehyde e.e. / %	Alcohol yield <sup>d</sup> / %	Alcohol e.e. / %	
Vinyl acetate <sup>e</sup>	Esphos	1.5	80	40	3.0	2.2 x 10 <sup>-3</sup>	100	5.9	34.9	15.9	76(S)	58.8	84(S)
		1.5	80	40	1.0	3.4 x 10 <sup>-3</sup>	98.5	7.0	37.0	13.1	84(S)	54.5	88(S)
		1.5	60	8	3.0	2.3 x 10 <sup>-4</sup>	80.0	5.2	74.8	14.5	90(S)	0.6	-
		1.5	60	8	5.0	2.1 x 10 <sup>-4</sup>	98.9	5.4	90.3	17.3	89(S)	3.3	-
		1.5	50	8	21.0	7.2 x 10 <sup>-5</sup>	98.6	5.7	75.8	16.2	88(S)	17.1	89(S)
		1.5	30	100	17.0	-	23.6	2.0	21.6	10.8	93(S)	0	-
	Semiesphos <sup>f</sup>	3.0	80	40	8.0	-	4.2	3.1	1.1	0.3	-	-	-
		2.0	80	40	20.0	-	10.2	7.7	2.5	0.3	-	-	-
		2.0	120	40	6.0	-	5.5	2.7	1.9	0.7	-	-	-
		2.0	120	100	6.0	-	21.8	6.0	14.7	2.5	<2(R)	0.5	-
PPh <sub>3</sub>	3.0	80	40	4.5	1.0 x 10 <sup>-2</sup>	99.7	18.5	73.6	4.2	0	4.1	0	
	<hr/>												
Styrene <sup>g</sup>	Esphos	1.5	80	10	1.5	1.0 x 10 <sup>-3</sup>	99.6		98.9	3.5	0	-	-
	Semiesphos <sup>f</sup>	2.0	80	10	2.0	1.2 x 10 <sup>-3</sup>	91.3		85.0	1.5	<1	1.1	-
	PPh <sub>3</sub> <sup>h</sup>	3.0	80	10	1.0	1.9 x 10 <sup>-3</sup>	99.2		99.1	1.2	0	-	-

<sup>a</sup> Catalyst prepared *in situ* from [Rh(2,4-pentanedionato)(CO)<sub>2</sub>] (5 x 10<sup>-5</sup> mol) and the phosphine in toluene (4 cm<sup>3</sup>) containing substrate (1 cm<sup>3</sup>), autoclave stirring speed = 500 rpm. <sup>b</sup> For vinyl acetate reactions yield refers to 2-acetoxypropanal (1-acetoxypropanal decomposes under the reaction conditions to acetic acid and propenal) and for styrene reactions the yield refers to 2-phenylpropanal + 3-phenylpropanal. <sup>c</sup> Refers to aldehyde *formation* before aldehyde decomposition/hydrogenation - for vinyl acetate reactions, determined from the ratio of branched chain product (aldehyde + alcohol) : acetic acid and for styrene reactions, determined from the ratio of branched chain product (aldehyde + alcohol) : straight chain product (aldehyde + alcohol). <sup>d</sup> For vinyl acetate reactions refers to 2-acetoxy-1-propanol + 1-acetoxy-2-propanol and for styrene reactions to 2-phenyl-1-propanol + 3-phenyl-1-propanol. <sup>e</sup> Acetoxyacetone (0.3-0.6 %) is also a product. <sup>f</sup> Catalyst is unstable. <sup>g</sup> Acetophenone (<1 %) is also a product. <sup>h</sup> Increasing the stirrer rate to 1000 rpm gives a rate of 3.7 x 10<sup>-3</sup> and an i:n ratio of 2.9 for the aldehyde.