CHAPTER 6 FLUOROUS BIPHASIC CATALYSIS

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6.1 Introduction

Biphasic systems, in which the catalyst is designed to be dissolved in a liquid phase which is immiscible with the product (either with or without a separate solvent) potentially provide some of the most attractive solutions to the problem of product separation in homogeneous catalysis.

In Chapter 5, aqueous biphasic systems were described. These are very elegant in that a water soluble catalyst is kept completely separate from the lypophilic product, except under conditions of fast stirring. Stopping stirring leads to rapid phase separation and the product can be collected by decanting. Such processes have been commercialised for short chain substrates, which have significant solubility in water, but it has been observed that the rates of reaction when using longer chain, less hydrophilic substrates are too low to be of commercial interest, presumably because mass transport limitations dominate the reaction.

Various other biphasic solutions to the separation problem are considered in other chapters of this book, but an especially attractive alternative was introduced by Horváth and co-workers in 1994.[1] He coined the term "catalysis in the fluorous biphase" and the process uses the temperature dependent miscibility of fluorinated solvents (organic solvents in which most or all of the hydrogen atoms have been replaced by fluorine atoms) with normal organic solvents, to provide a possible answer to the biphasic hydroformylation of long-chain alkenes. At temperatures close to the operating temperature of many catalytic reactions (60-120^{o}C), the fluorous and organic solvents mix, but at temperatures near ambient they phase separate cleanly. Since that time, many other reactions have been demonstrated under fluorous biphasic conditions and these form the basis of this chapter. The subject has been comprehensively reviewed,[2-6] so this chapter gives an overview and finishes with some process considerations.

Fluorous biphasic systems operate on the premise that the catalyst complex is preferentially soluble in the fluorous phase. This is achieved by synthesising fluorinated ligands that have a high weight-percentage of fluorine. It has been reported that for a complex to be preferentially soluble in fluorous solvents it must contain >60

D. J. Cole-Hamilton and R. P. Tooze (eds.), Catalyst Separation, Recovery and Recycling, 145–181.

wt% fluorine.[7] However, work by Hope and co-workers, has shown that this is not necessarily so. In fact, ligands with identical analytical composition, such as *para-, meta-* and *ortho-* isomers, may have very different solvent preferences. It is more important that the organic core is enveloped to ensure preferential fluorocarbon solubility rather than containing a specific wt% of fluorine atoms.[8] They also report that preferential solubility of a perfluorinated ligand does not immediately imply preferential solubility of the corresponding catalyst. Rábai and co-workers report that increasing the length of a single fluorous ponytail will be detrimental to the solubilities in both solvents[9] and an increase in the partition coefficients is observed when the number of fluorous ponytails attached to the ligand is increased. Provided that the partition properties of the solvent system are known (solubilities of one within the other), partition coefficients of solutes between fluorous and organic solvents can be calculated[10] with remarkable accuracy using a model which relies only on estimating the molar volume (V_b) and the modified non-specific cohesion parameter (δ_b') of the solute, both of which can be estimated using group contribution incremental methods. The value of the partition coefficient (P) depends on the size and non-specific vaporization energy (E_v') of the organic core of the solute as well as the length and number of attached fluorous ponytails. Generally, log P increases with the chain length and number of chains unless E_v' is very large, when either can lead to a decrease in partition into the fluorous phase. Some systems have been shown to give lower log P on increasing the chain length or number of fluorous chains,[11, 12] but these do not have very high values of E_v' for the organic core. So some modification of this aspect of the modelling is required. Clarke has recently published his findings with phosphino-amine fluorous soluble metal complexes.[13] He demonstrates that the addition of one fluorous ponytail to a $(C_6F_5)_2P$ fragment is sufficient to ensure a high partition co-efficient in perfluoromethylcyclohexane (PFMC)/toluene. Initially the synthesis of fluorous soluble ligands focussed on fluorinating known ligands, for example; fluorous analogues of triphenylphosphine in Vaska's complex[14] and Wilkinson's catalyst[15] or other triaryl phosphines.[16, 17] Further work investigating the influence of the position of these perfluoroalkyl modifying "ponytails" on the aryl ring has been undertaken by Hope and co workers.[18, 19]

With the catalyst immobilised in the fluorous phase, the substrate can be introduced either in solution, e.g. with toluene, or neat.[20] When heated, the two phases form a single homogeneous phase, which allows the substrate to be in intimate contact with the catalyst at all times. With the addition of reacting gases, reaction will occur at this elevated temperature and the catalyst and product are easily separated by cooling the mixture and decanting the product allowing easy reuse of the catalyst phase. The concept is shown schematically in Figure 6.1 for the hydroformylation of alkenes, which was the test reaction first reported by Horváth and co-workers.

Although temperature dependent solubility is generally used to affect the required phase transitions (miscible – immiscible), an alternative involves the use of CO_2 to affect the transition.[21] Being soluble in both organic and fluorous solvents, the CO_2 can render a biphasic system monophasic without raising the temperature. The concept has been demonstrated using hydrogenation and epoxidation of alkenes, and significant rate enhancements (50-70%) were observed at room temperature. Almost similar enhancements can, however also be achieved in the biphasic systems by using more

efficient stirring. The CO_2 approach may have particular appeal in systems where one of the substrates or products is thermally sensitive.

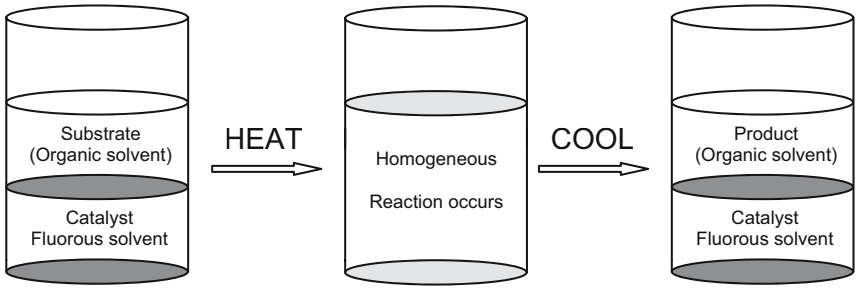


Figure 6.1 The fluorous biphase concept illustrated for the hydroformylation of an alkene (substrate) to an aldehyde (product)

The influence of the fluorous ponytails on the metal complex is an important factor to understand as the strongly electron withdrawing effect of the fluorine atoms may affect the behaviour of the phosphorus atom. A spacer group between the phosphorus and the fluorine tail is usually included in the ligand design. Generally this is an aryl or alkyl group that is effectively acting as a shield to the phosphorus and metal centre from the powerful electron withdrawing effect of the perfluoroalkyl tail. Horváth and co-workers studied the optimum length of an alkyl spacer group and found that the electronic properties of the ligand could be tuned by varying the length of the alkyl spacer group between the phosphorus atom and the perfluoroalkyl tail.[22] The results they reported from theoretical calculations implied that two methylene groups would provide sufficient shielding of the phosphorus atom, but in practice a C_2H_4 spacer does not entirely eliminate the electron withdrawing effect of the perfluoroalkyl tail. An alkyl spacer is expected to be a better insulator of electron effects than an aryl group, which may transmit electronic effects especially to the *o*- and *p*- positions of the ring. Insulation of the effects of the fluorous substituents on aryl groups can be achieved by using a C_2H_4 or $O(CH_2)_n$ (n = 1 or 5) [23] spacer between the aryl group and the fluorous tail, or by attaching the fluorous tail to a $SiCH_2CH_2$ spacer.[11, 24] Ligands such as $P(4\text{-}C_6H_4SiMe_{3\text{-}n}(CH_2CH_2C_6F_{13})_n)_3$ (n = 1-3) and $\{CH_2P(4\text{-}C_6H_4SiMe_{3\text{-}n}(CH_2CH_2C_6F_{13})_n)_2\}_2$ have been shown to be electronically very similar to PPh_3 and $Ph_2PCH_2CH_2PPh_2$ and sterically only marginally larger. Only the ligands with n = 3 are preferentially soluble in fluorous solvents, but the rhodium and nickel complexes tend to show much higher fluorophilicities because the coordination of multiple ligands encapsulates the organic centre of the molecule better. The fluorous content (wt %) actually decreases slightly for the complexes.

There has been great interest since Horváth's original paper, in synthesising new and more fluorous soluble ligands for various reactions. From the wide ranging topics published it would appear that the general consensus is that if the reaction can be carried out under homogeneous conditions, then it should be possible to fluorinate the ligands and perform the reaction under fluorous biphasic conditions. We now discuss the reactions that have been reported using fluorous biphasic systems.

6.2 Alkene Hydrogenation

Having successfully produced a fluorous analogue of Wilkinson's catalyst for the hydroboration of alkenes, Horváth and co-workers applied this complex {ClRh $[P(CH_2CH_2(CF_2)_5CF_3)_3]_3$} to the hydrogenation of a range of alkenes.[25] Using a PFMC/toluene biphasic system at 45ºC under a balloon pressure of H_2, the reaction of 2-cyclohexen-1-one showed clean conversion to cyclohexanone, 98% yield. Throughout the study, conjugated alkenes, terminal alkenes and disubstituted alkenes were tested. Separation of the toluene layer and reuse of the PFMC layer for further catalytic reaction of 2-cyclohexen-1-one showed a small drop in yield over 3 cycles (from 96 to 92%). However, for the reaction of 1-dodecene, by the third cycle a black solid had precipitated and any further hydrogenations suffered a substantial drop in rate. By recycling the catalyst solution into new vessels, the reaction proceeded normally. These results do not compare to those for the best homogeneous catalysts, but the ease of recycling the expensive catalyst, does make this a useful reaction system. Hope *et al* have also described a rhodium-catalysed hydrogenation of styrene in the fluorous biphase using a range of fluorinated ligands.[26] The purpose of this study was to investigate the effects of the perfluorocarbon solvent and the fluorous ponytail substituents on the catalytic system. The best rates were achieved with the fluorous ligand $P(4\text{-}C_6H_4OCH_2C_7F_{15})_3$, 201 mmol dm^{-3} h^{-1}, in a toluene/hexane/perfluoro-1,3-dimethylcyclohexane (PFDMCH) solvent system. No free ligand was observed in the organic phase and recharging the reactor with further fractions of substrate resulted in no effect on the catalytic activity, demonstrating a high catalyst stability and recovery.

Hydrogenation of 1-octene was also carried out by van Koten and co-workers using analogues of Wilkinson's catalyst containing $P(4\text{-}C_6H_4SiMe_2(CH_2CH_2R_f))_3$ (R_f = C_6F_{13} or C_8F_{17}).[27, 28] Comparison of this catalyst with $[RhCl(PPh_3)]$ and with $[RhCl(P(4\text{-}C_6H_4SiMe_3)_3]$ under monophasic conditions in $PhCF_3$ showed that the $SiMe_3$ substituent slightly increased the reactivity compared with H, but that the fluorous tail reduced the activity back to the same as that using PPh_3 as the ligand. The ligands with the fluorous ponytails showed good activity under fluorous biphasic conditions (1-octene/PFMC) at 80 ^oC for the hydrogenation of 1-octene and the fluorous phase could easily be separated from the product by cooling below 25^oC. Over 8 cycles using the ligand with $R_f = C_8F_{17}$ and carrying out the separation at 0^oC, the rate of reaction increased from 177 catalyst turnovers h^{-1} to 600 h^{-1}, but this was largely attributed to loss of significant amounts of the fluorous solvent into the organic phase. When the lost fluorous solvent was replaced for the 8th run the rate reduced to 155 h^{-1} (87.5% of the initial rate). ICPAAS analysis showed that the overall leaching corresponded to 1% of the Rh after 9 cycles (0.1% after the first cycle, c.f . 0.3% after the first cycle with the ligand with $R_f = C_6F_{13}$). The phosphine leaching to the organic phase was much more significant (1.3% and 8% per cycle for $R_f = C_8F_{17}$ and C_6F_{13} respectively).

Rhodium complexes of triarylphosphines containing an OCH_2 spacer (Figure 6.2) have been used for hydrogenation of methyl *(E)*-cinnamate in Galden D100 (mainly perfluoroctane) or FC-77(mainly C_8 containing fluorocarbons)/ethanol.[23] Generally speaking the reactions were slow (<100 turnovers h^{-1}); they could be recycled twice but the reaction half-lives increased with time. Rhodium and phosphine leaching were of

the order of 0.4 and 1.55% respectively for ligands with only one ponytail. Although when the ponytail was in the 2-position, the leaching was much higher (2.8 and 5.6%) because the steric congestion of this ligand inhibited coordination. Leaching was lowest (0.1 and 0.5% in the second and third runs) for the ligand with two ponytails (as was the reaction rate). Higher leaching and lower rate in the first run were attributed to difficulties with coordinating the bulky ligand.

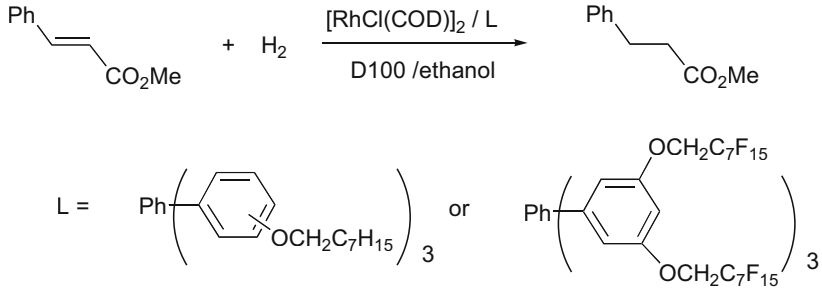


Figure 6.2. Fluorous biphasic hydrogenation of methyl *(E)*-cinnamate catalysed by rhodium complexes.[23]

Fluorous solvents are of very low polarity so it would be expected that ionic compounds would not dissolve readily in them. However, ionic rhodium catalysts have been used successfully in fluorous biphasic systems. $[Rh(COD)(Ar_2PC_2H_4PAr_2)]BF_4$ ($Ar = 4\text{-}C_6H_4SiMe_2(CH_2)_2C_6F_{13}$)] is active for the hydrogenation of 1-octene and partial hydrogenation of 1-octyne.[29] In the case of 1-octene in acetone, the lower rate of alkene isomerisation than for the unsubstituted analogue means that the fluorous compound is a better hydrogenation catalyst. This has been attributed to aggregation, which has also been observed for other analogues in which there is an Me_3Si- or $Me_2Si(C_8H_{17})$- substituent, but to a lesser extent. 1-octyne was hydrogenated (40°C, 1 bar H_2) under fluorous biphasic conditions with phase separation at 0°C.

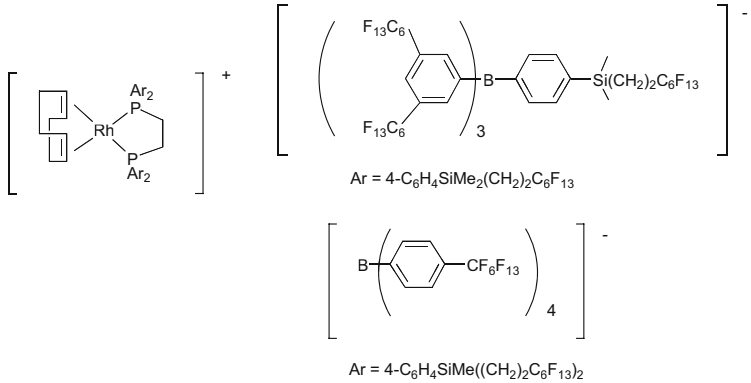


Figure 6.3. Fluorous soluble ionic catalysts for the hydrogenation of 1-octene.[30]

Better retention into the fluorous phase was observed when using a polar fluorous solvent and hexane (>99.82%, insoluble catalyst emulsified in homogeneous reaction mixture) than when using a PFMC and acetone (97.5%), as expected for the ionic

catalyst. Phosphine leaching was very similar to that of rhodium in this case suggesting that the diphosphine remains coordinated throughout the reaction. Turnover frequencies for these reactions were low (10-30 h^{-1}) and the selectivities to *cis*-4-octene were 60-70%. The other main product was 4-octyne (15-17%). Using similar cations, but heavily fluorinated anions (Figure 6.3) the catalysts were fully soluble in the fluorous biphasic mixture and could be recycled with only 1% losses after the hydrogenation of 1-octene.[30] The complex containing more fluorous tails on the diphosphine and $[B(4\text{-}C_6H_4C_6F_{13})_4]^-$ was the more active hydrogenation catalyst.

(R)-BINAP ligands bearing fluorinated substituents (Figure 6.4) have been prepared by Hope and co-workers.[31] The ruthenium complexes of the two ligands were compared with Ru-*(R)*-BINAP for the asymmetric hydrogenation of dimethyl itaconate in methanol at room temperature and 20 bar H_2 with a substrate/catalyst ratio of 2000. The enantioselectivity of the compound, to the *(S)*-enantiomer, was unaffected (>95% each) by the addition of the perfluoroalkyl groups. However, they did affect the conversions, only 42% with Ru-(B) and 83% with Ru-(A) compared to 88% conversion with the non-fluorous analogue, the more electron-withdrawing ponytails lowering the activity of the catalyst. Theses reactions were not carried out under fluorous biphasic conditions.

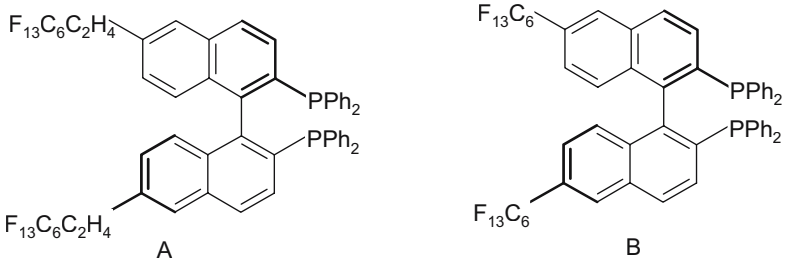
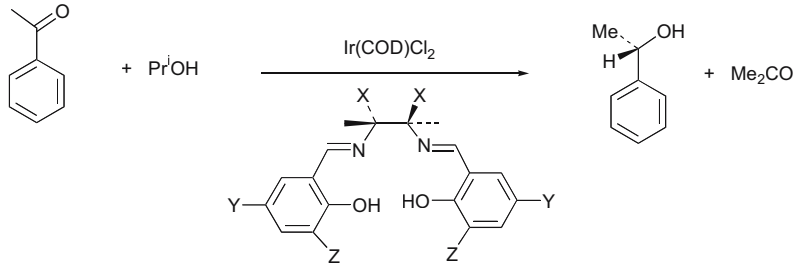


Figure 6.4. (R)-BINAP ligands used in ruthenium catalysed asymmetric hydrogenation of dimethyl itaconate.[31]



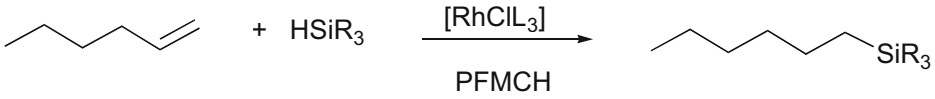
X	Y	Z		e. e.
Ph	C_8H_{17}	H	**1a**	0
Ph	C_8H_{17}	Bu^t	**1b**	56
X_2				
$(CH_2)_4$	C_8H_{17}	Bu^t	**2a**	5
$(CH_2)_4$	3,5-$C_6H_3(C_8H_{17})_2$	Bu^t	**2b**	10
$(CH_2)_4$	C_8H_{17}	C_8H_{17}	**3**	47

Figure 6.5. Transfer hydrogenation of acetophenone in Galden D-100.[32, 33]

The asymmetric transfer hydrogenation of acetophenone by 2-propanol has been carried out in Galden D-100 (mainly perfluorooctane) using iridium complexes of salicaldehyde diaminoethane Schiff bases as ligands (Figure 6.5).[32, 33] High yields (>90%) with enantiomeric excess up to 57% were observed when the reactions were carried out at 70°C. These e. e.'s are higher than observed with non-fluorous analogues (<22%), but the catalyst was destroyed during the reaction so that the recovered fluorous phase was much less active giving an e. e. of only 6%. The organic phase was also active, but not enantioselective. Other ketones and ≈–diketoesters were also reduced with e. e. between 18 and 60%.

6.3 Alkene Hydrosilation

Complexes of the form $[RhCl(P(4\text{-}C_6H_4SiMe_{3\text{-}n}((CH_2)_2C_8F_{17})_n)_3]$ have been used for the fluorous biphasic hydrosilation of 1-hexene (Figure 6.6) in PFMC without an additional organic solvent (alkene:silane = 2:1).[34] The reactions were monophasic at the reaction temperature (reflux), but the more fluorinated catalyst was not completely soluble in the monophasic mixture. It was redissolved in the PFMC phase, which separated on cooling to room temperature. Reaction rates were similar to those obtained using $[RhCl(PPh_3)_3]$ in benzene. Reactions were carried out for 15 min and the fluorous phase was recycled twice, with 100% conversion of the silane being observed in each case. However, ICPAAS analysis showed that, for less fluorous catalyst, rhodium and ligand leaching were high (12 and 19% respectively), whilst the retention of the more fluorinated catalyst was better (1.7 and 2.2%). In an interesting variant of the fluorous biphasic principle, fluorinated alkenes were hydrosilated with e.g. $HSiMe_2Cl$ using $[RhCl(PPh_3)_3]$ in benzene or toluene. The fluorous product could be extracted using FC-72 (a mixture of perfluoro hexanes) and the organic phase containing the catalyst recycled. Rhodium and phosphorus were undetectable (<1 ppm) by ICPAAS in the fluorous phase.



$L = P(4\text{-}C_6H_4SiMe_{3\text{-}n(}CH_2)_2C_8F_{17})_n$

Figure 6.6. Hydrosilation of alkenes under fluorous biphasic conditions.[34]

6.4 Alkene Hydroboration

Fluorous biphasic catalysis (FBC) has been applied to the rhodium-catalysed hydroboration of alkenes and alkynes by Horváth and co-workers.[15, 35] This was achieved by synthesising a fluorous analogue of Wilkinson's catalyst $[RhCl(PPh_3)_3]$, using the perfluorinated phosphine $[P(C_2H_4C_6F_{13})_3]$. The modified catalyst was highly soluble in PFMC and $CF_3C_6H_5$, slightly soluble in THF and acetone, but insoluble in other organic solvents. The catalyst was effective at a loading of 0.01 – 0.25 mol%,

affording turnover numbers (TON) as high as 8500. The reaction was carried out in PFMC without an added organic solvent as it was observed that the reactions occurred more rapidly in the absence of a non-fluorous solvent. A high degree of catalyst recovery was observed in repeat reactions of norbornene although some loss of catalyst was indicated by a drop in yield and TON, 90% yield with TON 854 in the first run compared to 83% yield and TON 785 in the second run. In their later paper,[35] this catalyst loss was studied further and quantitatively by atomic absorption analysis, the rhodium loss was found to be 0.4% per cycle, for the Rh complex bearing the above ligand. However, the Rh complex with $[P(C_2H_4C_8F_{17})_3]$ only showed a loss to the organic phase of 0.2% per cycle. It was also noted that after three cycles, the perfluorohexyl complex deposited a black solid and accordingly the activity dropped, suggesting decomposition of the catalyst. Low catalyst loading and Rh loss do make this a favourable method of hydroboration of alkenes and alkynes especially due to the ease of separation of the products from the fluorous phase.

6.5 Alkene Hydroformylation

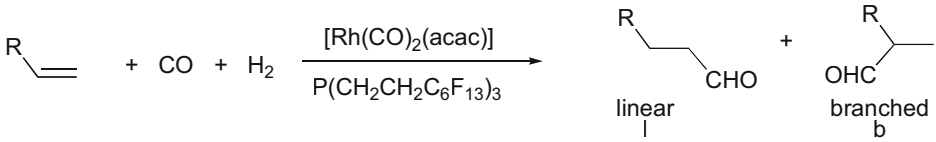


Figure 6.7. Hydroformylation of an alkene using a rhodium complex bearing a fluorous ponytail.[1, 22]

In his original paper introducing FBC,[1] the reaction Horváth chose to demonstrate the principle was the hydroformylation of 1-decene (Figure 6.7 ($R = C_8F_{17}$). Due to the lack of fluorous soluble ligands available, the synthesis of a new fluorinated phosphine was also necessary, $P(CH_2CH_2(CF_2)_5CF_3)_3$ was chosen. PFMC was used as the fluorous phase, toluene as the organic phase and the catalyst was prepared *in situ* from the Rh precursor $[Rh(acac)(CO)_2]$ and the phosphine. After 24 hours, they report that only trace amounts of conversion products were observed by GC analysis indicating that very little catalytic species has leached from the fluorous phase throughout the initial reaction. In a later paper by the same authors,[22] further investigation of the shielding of the phosphine from the electron-withdrawing fluorous tail indicated that, although it does not completely shield the effects, a $-C_2H_4-$ group between the phosphine and fluorous tail provides sufficient shielding. A kinetic investigation carried out on this reaction showed it to be first order in both [Rh] and 1-decene. Increasing $[P(C_2H_4C_6F_{13})_3]$ increased the l:b ratio but decreased the activity of the hydroformylation, which is consistent with the known negative order in [phosphine] for hydroformylation reactions. This paper also reports the semi-continuous hydroformylation of 1-decene, recycling the catalyst phase in nine successive runs. A slight rise in activity and a slight decrease in l:b ratio (4.5 – 3.5) and selectivity to aldehydes, 91.5% to 88.3% were observed, with a corresponding rise in isomerisation from 7.8% to 11.0%. These results are as expected if phosphine is being lost to the organic phase as the reaction has a negative order in [phosphine] and the linear selectivity is lower at lower [phosphine]. The Rh loss from the fluorous phase was

measured as 4.2% over 9 runs. This is equivalent to 1.18 ppm Rh loss/mol aldehyde. Being a trialkyl phosphine and not very bulky, very high [phosphine] (0.3 mol dm^{-3}) was at required for high l:b ratios (7.8:1) in the product aldehyde. The catalytic system was also tested for the hydroformylation of ethene using FC-70 (predominantly perfluoro compounds with 15 carbon atoms) as the fluorous solvent under continuous flow operation and gave a selectivity of 99.3% to propanal. This reaction was successfully carried out for two months with no loss in activity, but the product was removed in the gas phase.

Various groups have studied fluorous analogues of triphenylphosphine in attempts to increase the linear selectivity. Masdeu-Bultó and co-workers have reported the successful fluorous biphasic hydroformylation of 1-octene using a Rh complex with the fluorinated phosphine $P(C_6H_4\text{-}4\text{-}OCH_2C_7F_{15})_3$.[36] Rh/P = 5, at 80ºC and 40 bar. The biphasic solvent system used was PFMC/toluene (60/40, v/v). After 1 hour of reaction a conversion of 98% with an aldehyde selectivity of 97% was achieved. The l:b ratio was 2.6:1% . However, on recycling the catalyst solution, a drop in the aldehyde selectivity was observed without a drop in conversion, indicating a loss of ligand to the organic/product phase. On cooling, the toluene phase was observed to be slightly coloured symptomatic of catalyst leaching from the fluorous phase. By increasing the temperature of separation from 10ºC to 50ºC, the separation improved. Reusing this catalyst phase allowed three recycles with little reduction in aldehyde selectivity observed (99%, 97% and 91%). After the first recycle, analysis of the product phase showed Rh and P in the toluene phase and traces of aldehyde are reported as being observed by GC analysis in the fluorous phase. An increase of the substrate/Rh ratio from 500/1 to 2000/1 showed a lower conversion, 20%, after 1 hour, as expected, but the selectivity to aldehydes remained high, 94%. By removing the toluene from the reaction an increase in activity (68% conversion in 1 h) was observed, this effect has also been observed by others.[20]

Hope and co-workers have synthesised a large number of perfluorinated ligands and carried out testing of these ligands in the hydroformylation of 1-hexene[37] using $[Rh(acac)(CO)_2]$ as the precursor and a P/Rh ratio of 3. After I h in a high pressure reactor using a 1:1 organic:fluorous solvent mixture, 70ºC, 20 bar CO/H_2(1:1) the fluorous analogue of triphenyl phosphine, $P(4\text{-}C_6H_4C_6F_{13})_3$, gave 89.2% selectivity to aldehydes, with an l:b ratio of 3.8 compared with values for triphenylphosphine of 98.2% selectivity and l:b ratio of 3.1. Further studies[20, 38] on this ligand with 1-octene as the substrate demonstrated that using $[Rh(acac)(CO)_2]$ (2 mmol dm^{-3}) and $[P(4\text{-}C_6H_4C_6F_{13})_3]$ (20 mmol dm^{-3}) at 60ºC and 20 bar in PFMC, an l:b ratio of 6.3:1 (selectivity to linear aldehyde = 80.9%) could be obtained with a turnover frequency of 4 400 h^{-1} and with 99.95 and 96.7% retention of rhodium and phosphine into the fluorous phase. The rhodium retention is better than that of the phosphine because the form of the catalyst at room temperature, where the separation was carried out, is $[RhH(CO)(P(4\text{-}C_6H_4C_6F_{13})_3)_3]$, anchoring it into the fluorous phase by 9 fluorous ponytails.[39] Higher rates and more Rh leaching were observed at higher reaction temperatures. By omitting the organic solvent, higher rates, linear selectivity and retention into the fluorous phase were observed. Even though the system becomes biphasic under the reaction conditions at 20% conversion,[40] the kinetics were first order up to at least 80% conversion,[20] showing that mass transport does not become

rate determining provided that the mixture is stirred efficiently. The rate and selectivity are much better than those obtained using PPh_3 under the same conditions. This is due to the electron withdrawing effect of the fluorous tail, which is transmitted to the rhodium centre *via* the phenyl ring. The higher binding constant of the fluorinated ligand than PPh_3 accounts for the better linear selectivity at low phosphine loadings. This conclusion is supported by the observation that the selectivity under comparable conditions but with less phosphine (80°C, 30 bar, P:Rh = 3) for this system is higher (l:b = 3.5)[20] than for the analogous ligand with an $–OCH_2$- spacer (80°C, 40 bar, P:Rh = 5, l:b = 2.6).[36] although it should be noted that toluene, which may reduce the l:b ratio was present in the latter system. In the presence of toluene under slightly milder conditions and with the lower P:Rh ratio (70°C, 20 bar, P:Rh = 3) the selectivity of the complex without the spacer was still higher (l:b = 3.8).[37] The high rates, selectivities and the omission of the organic solvent meant that this system was chosen for more detailed studies in a continuous flow system (see Section 6.13).[41, 42]

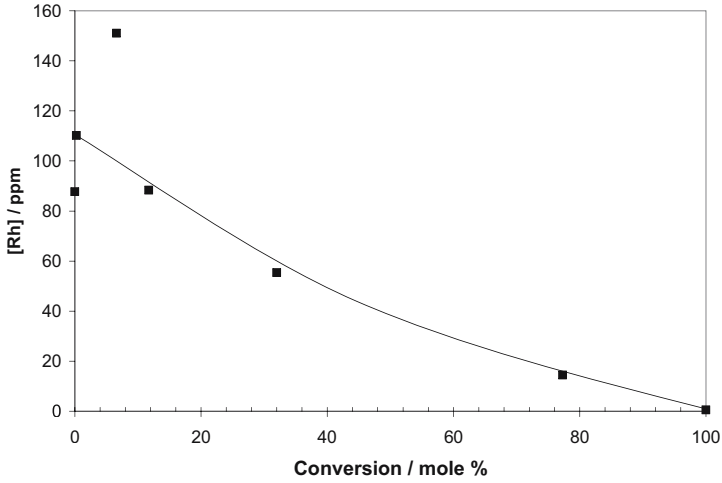


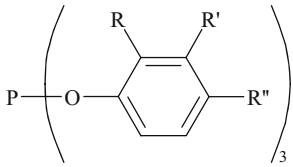
Figure 6.8. Concentration of rhodium in the organic phase as a function of conversion during the hydroformylation of 1-octene catalysed by Rh/ $[P(4\text{-}C_6H_4C_6F_{13})_3]$.[41]

A comparison between $[P(4\text{-}C_6H_4C_6F_{13})_3]$, $[P(4\text{-}C_6H_4C_8F_{17})_3]$ and $[P(3,5\text{-}C_6H_4(CF_3)_2)(4\text{-}C_6H_4C_6F_{13})_2]$ suggests that a catalyst bearing the ligand containing the C_8 fluorous ponytail undergoes only 10% of the leaching of the other two ligands, whilst their activities (first order rate constant, $k = 1.9 \times 10^{-3}$, 1.3×10^{-3}, 2.5×10^{-3} s^{-1}) and selectivities (l:b = 6.3, 6.7 and 4.7 respectively) are similar.[8] Other studies have shown that the retention of the catalyst within the fluorous phase is very dependent upon the conversion, being much enhanced at high conversions (see Figure 6.8).[43]

The fluorinated analogue of triphenyl phosphate, $P(O(C_6H_4C_6F_{13})_3$, also performed well in the hydroformylation of 1-hexene when compared with $P(OPh)_3$ with a selectivity of 82.3% and l:b ratio of 6.4 compared to 92.0% and 2.9 respectively.[8] This represented one of the first examples of phosphite ligands being used for hydroformylation in fluorous biphasic catalysis. Further optimisation[20, 38] of this system in perfluorodimethylcyclohexane (PFDMCH) using 1-hexene and 1-octene

showed that high rates and linear selectivities (l:b up to 9.9:1) could be achieved, but alkene isomerisation was always *ca.* 13%, whilst leaching of Rh (>2.5%) and phosphine (>4%) were much higher than for the phosphine analogue. This leaching, which was much worse when toluene was present, was attributable to degradation of the phosphite, either through direct reaction with the aldehyde, or through reaction with water formed by aldol condensation of the product. Either would produce complexes in which one or more fluorous tails had been removed, so that the fluorous solubility would be reduced.

Mathivet *et al* have extended this work on phosphites in the hydroformylation of higher alkenes under fluorous biphasic conditions.[44, 45] They have synthesised and studied the affect of a number of ligands with the fluorous ponytails in various positions on the aryl group, Figure 6.9. The two ligands with a single fluorous ponytail, **A** and **B**, partition in a solvent mixture of 1-decene and $C_8F_{17}H$ in a 5/95 ratio and the ligand with two fluorous tails, **C**, partitions with a ratio of 1/99. There is likely to be some loss of ligand through leaching throughout the reaction as all the ligands dissolve to some extent in the substrate.



A: R= $C_2H_4C_8F_{17}$, R'=R"= H

B: R=R'= H, R"= $C_2H_4C_8F_{17}$

C: R= R"= $C_2H_4C_8F_{17}$, R'=H

D: R = C_8F_{17}, R' = R" = H

E: R =H, R' = C_8F_{17}, R" = H

F: R = R' = H, R" = C_8F17

G: R = CH_3, R' = H, R" = C_8F_{17}

H: R = C_8F_{17}, R' = H, R" = C_8F_{17}

J: R = C_8F_{17}, R' = H, R" = COC_7F_{15}

Figure 6.9. Fluorinated ligands used in the rhodium catalysed hydroformylation of alkenes.[44, 45]

The three ligands were tested in the hydroformylation of 1-decene with no organic solvent using only $C_8F_{17}H$ at 80°C under 40 bar CO/H_2 (1:1) and run to 100% conversion. **A** and **C** are both sterically hindered and gave similar results, 100% conversion was achieved quickly after 15 and 12 min respectively with an aldehyde selectivity of 85% in both cases, this results in TOFs of 10 000 and 11 000 h^{-1}. The unhindered ligand **B** achieved 100% conversion in 30 minutes, but showed a higher aldehyde selectivity of 95%, TOF 3900 h^{-1}. Results with **B** and various terminal alkenes demonstrate the high selectivity of this phosphite to aldehyde formation. Catalyst recycling was also considered. Using 1-decene as the substrate allowed direct comparison with Horváth's work. Each reaction was run for just 10 minutes and the first three runs for each ligand show a slight increase in conversion with the fourth run showing a marked drop for ligand **A**, however the selectivities for each ligand dropped slightly in each cycle. In the fourth recycle, the organic phase was noted as being yellow in colour, which indicates that leaching of Rh is occurring. The reason for the differences in results between the various ligands lies in the steric hindrance that exists

with ligands **A** and **C**, which will result in only one phosphite coordinating to the Rh making the active species [$HRhL(CO)_3$] and allowing facile binding to the alkene, causing the fast reaction. The single ligand makes the catalyst less selective, whereas **B** is more similar to the triphenyl phosphite modified catalyst, which forms the bis phosphite. In order to try to overcome some stability issues with these ligands, further syntheses of ligands **D-J** were carried out and reported in a second paper.[44] An investigation of the effect of the position of the fluorous group on the ring **D-F** show that the activity increases as the fluorous group gets closer to the phosphorus (TOF of 10 000 h^{-1}, 6300 h^{-1} and 3500 h^{-1} for **D, E** and **F**). Conversely, aldehyde selectivity increases as the fluorous group moves away from the phosphorus atom; thus the *para*-substituted phosphite shows the highest selectivity towards aldehyde (71%, 80% and 85% for **D, E** and **F**). It is also noted from the comparison of **C** and **H** that the removal of the ethyl spacer group has a marked effect on the aldehyde selectivity (85% and 46% respectively). This is perhaps due to the electronic effect of the fluorous tail on the metal or may simply be due to the steric hindrance of the ligand about the metal centre. Again the hydroformylation of internal and different terminal alkenes was examined using **E.** It was found that decreasing the length of the substrate caused the activity, l:b ratio and aldehyde selectivity to increase (see Table 6.1)

Recycling of the ligands was investigated for ligands **D, E** and **J**. over four recycles the conversions dropped for all three phosphites, however the most marked decrease was with **E** (<10% conversion in the fourth recycle). The selectivity of the catalysts to aldehyde products did not decrease so drastically but a decrease in the selectivity of **E** was most notable in the second recycle. This suggests that some leaching of the three phosphites to the organic phase does occur.

TABLE 6.1**.** The results of hydroformylation reactions carried out using rhodium complexes ligand **E** (Figure 6.9).[44, 45]

Alkene	TOF / h^{-1}	l:b	Selectvity to aldehyde / %
1-hexene	7800	6.5	94
1-octene	6900	6.3	87
1-decene	6300	5.8	80

Another approach to the fluorous biphasic hydroformylation of alkenes has been investigated by Xiao and co-workers using a fluorous soluble polymer catalyst.[46] The poly(fluoroacrylate-*co*-styryldiphenylphosphine) ligands are of the form shown in Figure 6.10. Neither ligand is soluble in normal organic solvents but both are soluble in fluorinated solvents. The hydroformylation of 1-decene was performed in a batch reactor using a solvent mixture of hexane-toluene-PFMC (40:20:40) (the hexane proved necessary to form a homogeneous phase under the reaction conditions). The catalyst was formed *in situ* from [$Rh(acac)(CO)_2$] and the ligand (P/Rh = 6) under CO/H_2 (30 bar, 1:1). The results showed a turnover frequency of 136 mol aldehyde (mol Rh h)$^{-1}$ and a selectivity to aldehyde of 99%, the l:b ratios of 4.8 (polymer **a** in Figure 6.10) and 5.9 (polymer **b** in Figure 6.10) are also competitive with those obtained from homogeneous hydroformylation reactions in conventional solvents. The recycling of the catalyst phase was carried out in the hydroformylation of 1-hexene. Three consecutive reactions were carried out and a 1 ppm loss of Rh was observed for

each recycle. However, by the end of the third run all PFMC had leached to the product phase, which in turn caused loss of ligand and catalyst to the product phase.

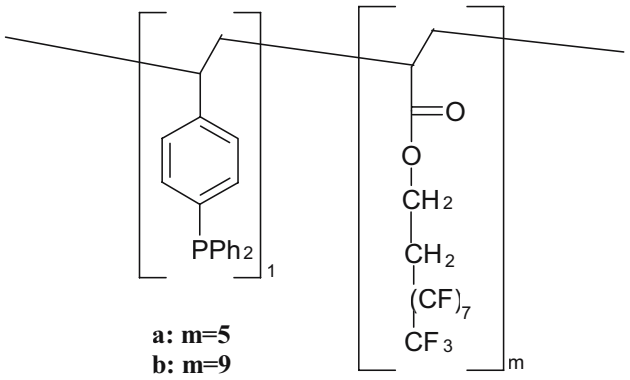


Figure 6.10. Fluorous polymers with bound PPh_3 used in the hydroformylation of 1-hexene.[46]

Ojima and co-workers[47] have reported fluorinated analogues of BINAPHOS, an unsymmetrical bidentate ligand having one phosphine and one phosphite donor, for rhodium-catalysed asymmetric hydroformylation. Unlike the previous papers, this deals with the hydroformylation of styrene, which preferentially forms the branched product. This is desirable because the linear product has no chiral centre and because the branched product is a possible intermediate in the formation of ibuprofen type anti-inflammatories. The ligands were found to be preferentially soluble in toluene over PFMC, possibly due to the aromatic nature of the naphthalene groups and the slightly low fluorine content. All ligands displayed good solubilities in perfluorotoluene (PFT).

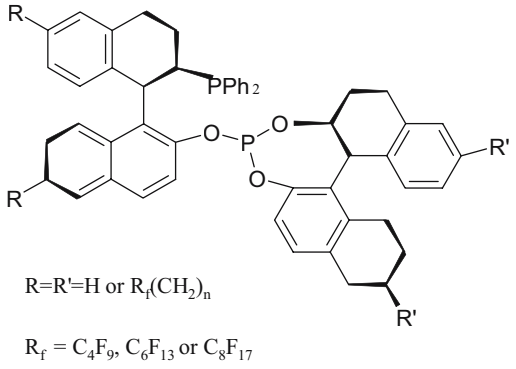


Figure 6.11. (S,R)- $[C_6F_{13}(CH_2)_3]_2$-BINAPHOS and related ligands used in the rhodium catalysed asymmetric hydroformylation of styrene.[47]

The hydroformylation reactions were carried out in a number of different solvent systems, Table 2, at 50-60°C and 40 bar CO/H_2 (1:1) using the (S,R)- [*n*-$C_6F_{13}(CH_2)_3]_2$-BINAPHOS ligand, Figure 6.11. After 18 hours in the PFMC/toluene system, 100% conversion was achieved with 100% selectivity to aldehydes of which 92% were

branched, with an enantiomeric excess of 85%. With only PFMC as solvent only 88% conversion was observed, with a b:l ratio of 94:6 and an e. e. of 87%. Changing the fluorous solvent to PFT showed 73% conversion after 16 hours with 100% selectivity to aldehydes of which 91% were the branched form with an overall e. e. of 82%.

TABLE 6.2. The Rh/*(S,R)*- [n-$C_6F_{13}(CH_2)_3]_2$-BINAPHOS catalysed hydroformylation of styrene.[47]

Solvent System	Styrene:Rhodium	Time (h)	Conv. (%)	b/l	e. e. (%)
PFMC/Toluene	2235	24	84	91/9	90
PFMC/Toluene	1042	18	100	92/8	85
PFMC	1042	18	88	94/6	87
PFT	2235	2	11	91/9	94
PFT	2235	16	73	91/9	82

6.6 Alkene Epoxidation

The large amounts of molecular oxygen that can be dissolved into fluorous solvents, together with their oxidation resistance makes them potentially very suitable solvents for oxidation reactions. Fish and co-workers reported the synthesis of a novel perfluorinated triazacyclononane (TACN) ligand, shown in Figure 6.12, which is soluble in perfluoroalkanes.[48] Using this ligand along with a fluorinated carboxylate synthon, $[M(O_2C(CH_2)_2C_8F_{17})_2]$ (where M is Co or Mn), they have successfully carried out the epoxidation of a variety of alkenes, in a fluorous biphasic system. The suggested form of the catalyst produced *in situ* is $[C_8F_{17}CH_2CH_2CO_2M\text{-}\{(C_8F_{17}(CH_2)_3)_3TACN\}]^{2+}$. The reactions were carried out in perfluoroheptane with the substrate acting as the organic layer, in an oxygen barosphere in the presence of *tert*-butyl hydroperoxide (TBHP). Alkenes bearing allylic hydrogens gave the highest yields under these conditions. Removal of the upper, organic layer and adding new cyclohexene and TBHP provided similar results to the first run, showing that leaching of the catalyst into the organic phase was negligible, but no quantitative data was provided. $[CuCl\{(C_8F_{17}(CH_2)_3)_3TACN\}]$ is also active for alkene oxidation by Bu^tOOH/O_2 in perfluoroheptane at room temperature (biphasic).[49] The best results were obtained with cyclohexene, which gave cyclohexanone and cyclohexanol (78:22) in 435% conversion based on Bu^tOOH, O_2 being responsible for the majority of the oxidation. The catalyst was recycled twice with the yield dropping to 75% and 50% of that obtained in the first run, suggesting catalyst instability or leaching. Cyclohexane could be oxidised to cyclohexanone and cyclohexanol and toluene to benzaldehyde using the same system, but the yields were very low 97.5 and 17% based on Bu^tOOH respectively. These values represent catalyst turnover numbers of 5 and 13 respectively. A copper complex of bipyridine bearing fluorous ponytails, which also contained fluorinated carboxylate groups, was not successful in these oxidation reactions. The organic phase was blue at the end of the reaction and conversions were very low.

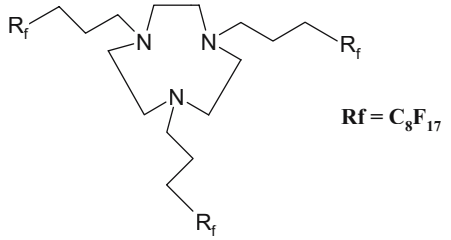


Figure 6.12. Fluourinated TACN ligand used in epoxidation reactions.[48]

Pozzi and co-workers have also reported a fluorous soluble cobalt complex, which is active in the aerobic epoxidation of alkenes in a fluorous biphasic system (FBS).[50] The ligand used in this complex was a fluorinated tetraarylporphyrin, with eight perfluorooctyl chains shown in Figure 6.13. The cobalt complex was dissolved in perfluorohexane and added to a solution of the alkene with 2-methylpropanal (aldehyde: substrate = 2:1) at room temperature.

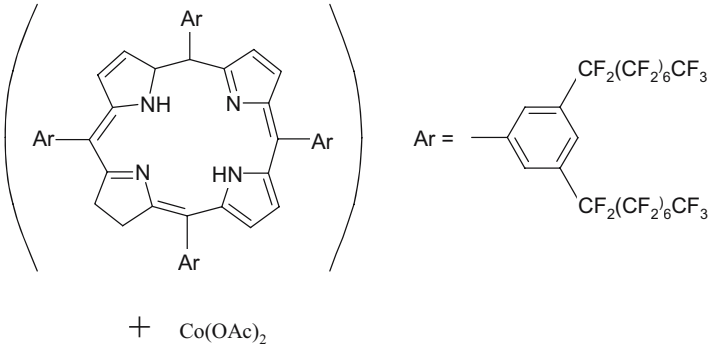
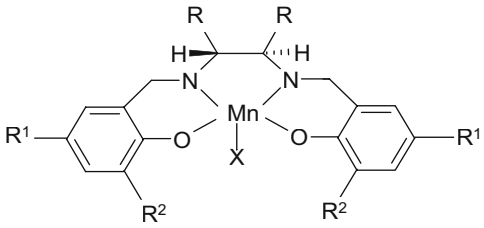


Figure 6.13. Fluorinated porphyrin ligand used in the cobalt catalysed aerobic oxidation of alkenes.[50]

The yields for reactions of unsubstituted terminal alkenes were lower than for substituted alkenes but they were still reasonable and could be increased further by increasing the aldehyde:alkene ratio. Total conversions of substrate were reported with epoxide selectivity as high as 95% in some cases. The FBC system allows for a much higher substrate:catalyst ratio (1000:1) than the non-fluorous epoxidation reported (20:1) previously. Recycling the fluorous layer once showed no reduction in conversion or selectivity.

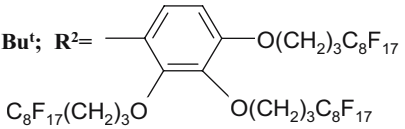
Further efficient ligands for the epoxidation of alkenes have been reported by Pozzi, but using PhIO as the oxidant and pyridine *N*-oxide as an additive in FBS.[7, 51-53] Chiral (salen)Mn complexes have been synthesised, which are soluble in fluorous solvents and active in the epoxidation of a variety of alkenes. The catalysts were of the form shown in Figure 6.14.



1 R_2 = **-$(CH_2)_4$-; R^1= R^2 = - C_8F_{17}; X = Cl^-**

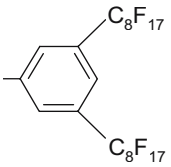
2 **R = Ph; R^1= R^2= -C_8F_{17}; X=Cl^-**

3 **R_2 = -$(CH_2)_4$-; R^1= Bu^t; R^2=**



X= $C_7F_{15}COO^-$

4 **R_2 = -$(CH_2)_4$-; R^1= Bu^t; R^2=**



X = $C_7F_{15}COO^-$

Figure 6.14. Chiral salen complexes used in the asymmetric epoxidation of alkenes.[7]

1 and **2** were initially reported in 1998 although the free ligands were soluble in diethyl ether and ethanol the Mn-complexes were insoluble in organic solvents. The FBS allowed a much smaller catalyst:substrate ratio (0.005:0.33 mol dm^{-3}) compared to other homogeneous systems and provided good yields of epoxides (up to 85%); no significant decrease in activity was observed when the fluorous phase was recycled a second time. However, only the epoxidation of indene showed high enantioselectivity (92%). The low enantioselectivity (<15%) of the ligands **1** and **2** was attributed to the low steric hindrance of the perfluoroalkyl groups, as well as possible inefficient shielding of the strong electron-withdrawing effect of these fluorinated groups. Further work and synthesis produced **3** and **4** as "second generation (salen)Mn^{III} complexes. They were, indeed, more enantioselective than the original complexes. In the case of 1,2-dihydronaphthalene, the e. e. increased from 10% to 50% with the second-generation complexes. Further investigation of the catalyst was carried out and it was found that the fluorous layer could be recycled up to three times after the first reaction, but the catalytic activity dropped significantly in the fourth run. This was attributed to oxidative decomposition of the catalyst and was indicated by the gradual disappearance of the characteristic UV-Vis-absorption bands of the (salen)Mn^{III} from the fluorous layer and their non-appearance in the organic layer.

The same catalysts have been investigated for the asymmetric oxidation of dialkyl sulfides using PhIO as the oxidant in CH_3CN:perfluorooctane.[54] Although the conversions (>80%) and selectivities to sulfoxides (>90%) were generally good, and the more heavily fluorinated catalysts could be recycled 4 times with only small drops

in activity, which were attributed to oxidation rather than leaching, the e. e.'s in these reactions were poor (<20%).

6.7 Other Oxidation Reactions

Knochel and co-workers have reported biphasic aerobic oxidation of aldehydes, sulfides and alkenes, using nickel and ruthenium catalysts with a perfluorinated 1,3-diketone ligand, see Figure 6.15.[55] The nickel complex, when reacted with aldehydes in a toluene/perfluorodecalin reaction mixture at 64°C, provided yields of the expected carboxylic acids of 71-87%. The same catalytic system was active for the oxidation of sulphides, but required the presence of isobutyraldehyde and the nickel catalyst did not oxidise alkenes. The ruthenium form of the catalyst in $C_8F_{17}Br$ was active in the epoxidation of disubstituted alkenes. After "several" recycles, the ruthenium complex was recovered in 95% yield. The catalytic leaching was small as yields of 70% were still obtained after 6 runs, but this corresponds to a drop in yield from 87% - 70% over the six recycles. Quantitative data of the metal loss to the organic phase is desirable for comparison with other systems. Using the same fluorinated diketonate ligand, Knochel and co-workers have also reported a fluorous biphasic system for the Wacker oxidation of alkenes to aldehydes, suitable for a variety of alkenes.[56] The catalyst system was a palladium (II) complex of the same fluorinated ≈–diketonate, as shown in Figure 6.15. Reactions were carried out in $C_8F_{17}Br$ with the substrate in benzene and *tert*-butylhydroperoxide as the oxidant. Although a wide variety of alkenes was tolerated in this system, aliphatic alkenes required longer reaction times than styrene derivatised substrates (8-20 h compared with 2-5 h). The catalyst for the reaction of 4-methoxystyrene was reused 8 times and initially gave yields of 4-methoxyacetophenone of 78% but dropped to 72% yield in the 8th recycle, which indicated low catalyst leaching to the organic solvent. The catalyst was also active for the epoxidation of some activated disubstituted alkenes.

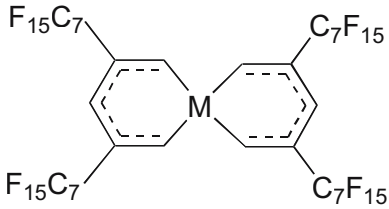


Figure 6.15. Perfluorinated ≈–diketonate complex used for a variety of oxidation reactions (M = Ni)[55] or Wacker oxidation (M = Pd).[56]

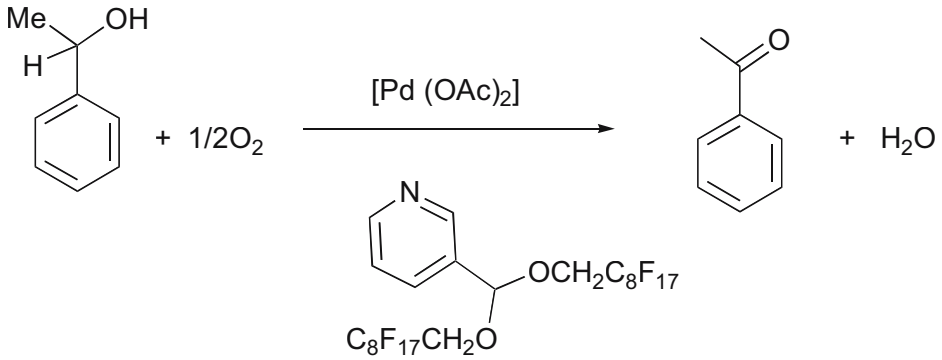


Figure 6.16. Aerobic oxidation of 1-phenylethanol catalysed by palladium complexes of a fluorous pyridine in toluene/perfluorodecalin.[57]

Uemura and co-workers have reported the aerobic oxidation of alcohols to aldehydes and ketones using palladium complexes containing pyridines with fluorous tails in a toluene/perfluorodecalin biphasic system at 80°C, using molecular sieves to remove the generated water.[57] Some catalyst decomposition occurred, but this was minimised by using excess pyridine ligand. Generally the organic phase contained palladium, but using the ligand shown in Figure 6.16, the organic phase was colourless. Inductively coupled plasma optical emission spectroscopy (ICPOES) analysis showed that only 0.8% of the palladium leached to the organic phase during oxidation of 1-phenylethanol to acetophenone. Recycling could be carried out 3 times, but the yield dropped form 90 to 74% even though extra ligand was added before the third cycle. A wide range of primary and secondary alcohols was oxidised in yields usually >75%. 4-Nitrobenzyl alcohol is oxidised to the corresponding aldehyde using air and TEMPO (1-oxy-2,2,6,6-tetramethylpiperidine) in perfluoroheptane in the presence of $[Cu(O_2CCH_2CH_2C_6F_{17})\{R_f(CH_2CH_2)_3TACN]$ at 90°C, when the system is monophasic.[49] Yields >90% can be obtained and cooling to room temperature allows phase separation and reuse of the catalyst. Using 6 mol % TEMPO in each run, the catalyst could be recycled 7 times with yields >90% for the first 5 cycles. Thereafter the yield dropped to 51 and 8% in runs 6 and 7.

Copper complexes synthesised *in situ* from $[CuBr(SMe_2)]$ and bipyridine bearing $-(CH_2)_4C_8F_{17}$ in the 5 and 5' positions are also active for the oxidation of a wide range of primary and secondary alcohols to aldehydes and ketones by air in the presence of TEMPO under fluorous biphasic conditions ($C_8F_{17}Br$/PhCl at 90°C).[58] Yields were generally very high (>80%). For 4-nitrobenzyl alcohol, the yield of aldehyde was 93% after 1.5 h. The fluorous phase was separated and reused 7 times. In the eighth run, the yield of 4-nitrobenzaldehyde was still 86%. Sterically hindered alcohols are rather unreactive in this system, but this allowed the selective oxidation of *cis*-4-methylcyclohexanol to the corresponding ketone in the presence of *trans*-4-methylcyclohexanol, which remained essentially unreacted.

Pozzi has also reported a fluoro-functionalised tetraazacyclotetradecane macrocycle, which is selectively soluble in fluorocarbons and active in the fluorous biphasic oxidation of hydrocarbons.[59] This ligand (Figure 6.17) was produced whilst

trying to generate a simple method of synthesising fluorous ligands. Both the copper and cobalt complexes of this ligand, using CuCl and the cobalt salt of pentadecafluorooctanoic acid ($Co(C_7F_{15}COO)_2$) as precursors, catalysed the oxidation of saturated and unsaturated hydrocarbons. The copper complex gave slightly higher yields and higher ketone selectivities in the oxidation of cyclooctane (80% yield, 80% cyclooctanone, 20% cyclooctanol). The Co complex only gave 30% yield, (76% ketone selectivity), but both complexes performed similarly in the oxidation of cyclohexene to give cyclohex-2-en-1-one and cyclohex-2-en-1-ol. Recycling the fluorous layer, in the cyclooctane oxidation and the Co catalysed oxidation of cyclohexene, showed no drop in activity implying negligible catalyst leaching, but the activity of the Cu catalyst for the oxidation of cyclohexene dropped to 50% on the second cycle (c.f. 80% on the first cycle).

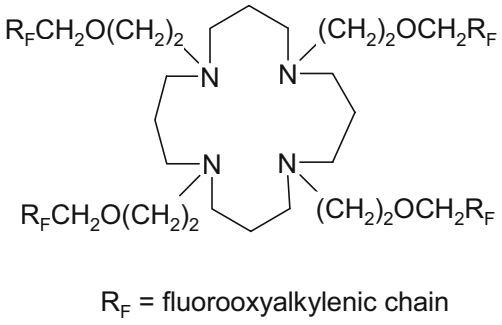
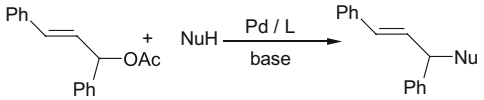


Figure 6.17. Fluorinated macrocycles used for the cobalt or copper catalysed oxidation of saturated or unsaturated hydrocarbons.[59]

6.8 Allylic Alkylation



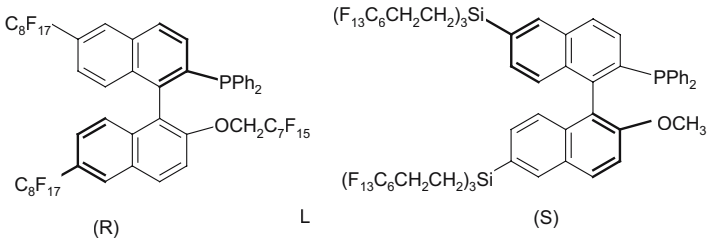


Figure 6.18. Palladium catalysed allylic alkylation using fluorinated ligands.[60, 61]

Maillard *et al* have reported perfluorous analogues of MOP (methoxynaphthyldiphenyl phosphine), see Figure 16.18, and their application in palladium catalysed allylic alkylation.[60, 61] Due to the somewhat low fluorine content in these ligands, (R) 56.0 wt% fluorine, (S) 56.88 wt% fluorine, they are slightly soluble in THF and toluene, which will result in loss of the ligand during reaction and would involve further separation steps to recycle the ligand fully. The ligands were used in Pd-catalysed allylic alkylation but they gave low enantioselectivities (0-37%) for various solvent/base systems. An attempt to recycle the catalyst was made. However, the second run only gave a conversion of 24% as opposed to 100% in the initial run. This drop in activity was attributed to significant leaching of the ligand to the organic phase and is unavoidable unless the fluorine content of the ligands can be increased.

Bayardon and Sinou have reported the synthesis of chiral bisoxazolines, which also proved to be active ligands in the asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate, as well as cyclopropanation, allylic oxidations and Diels-Alder reactions.[62] The ligands do not have a fluorine content greater than 60 wt% and so are not entirely preferentially soluble in fluorous solvents, which may lead to a significant ligand loss in the reaction system and in fact, all recycling attempts were unsuccessful. However, the catalytic results achieved were comparable with those obtained with their non-fluorous analogues.

6.9 Heck, Stille, Suzuki , Sonagashira and Related Coupling Reactions

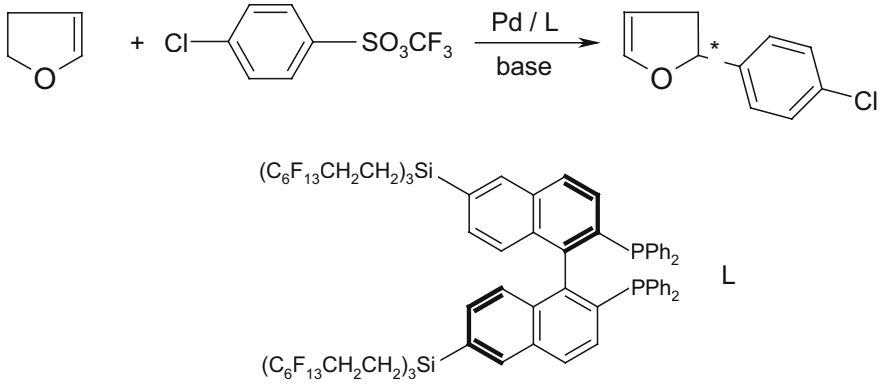


Figure 6.19. Heck coupling catalysed by fluorinated *(R)*-F_{13}BINAP palladium complex.[63]

Nakamura *et al* applied fluorous chiral BINAP ligands to the asymmetric Heck reaction.[63] R-F_{13}BINAP, see Figure 6.19, is easily air oxidised, but in a benzene/FC-72 biphasic system, the Heck coupling of 2,3-dihydrofuran with 4-chlorophenyl triflate occurred with high enantioselectivity (93%), but low yield (39%). Reuse of the fluorous phase gave a 2% yield, most likely because of deactivation of the catalyst by ligand oxidation, TLC monitoring of the reaction showed the ligand to be oxidised in the fluorous phase, but there may also be some catalyst leaching to the organic phase. Compared with the original reaction with non-fluorous BINAP in

trifluoromethylbenzene, the e. e. was much higher (90% e. e. F_{13}-BINAP, 76% e. e. BINAP). Therefore, overcoming the air sensitivity of the fluorous BINAP would provide a highly competitive system for Heck couplings.

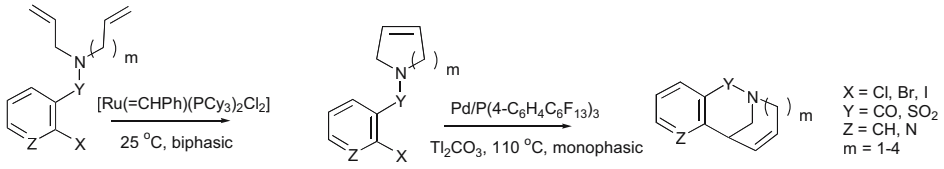


Figure 6.20. Tandem ring-closing metathesis and Heck coupling for the formation of bridged ring systems.[64]

Heck coupling has also been used in tandem with ring closing metathesis to give bridged ring systems (Figure 6.20).[64] In conventional solvents, the Heck catalyst poisoned the ruthenium catalyst used for the ring-closing metathesis. However, by carrying out the reaction in a fluorous biphasic system with a standard metathesis catalyst but a fluorinated palladium catalyst for the Heck reaction, the catalysts could be kept separate during the low temperature ring-closing metathesis, but on heating the system became monophasic, thus allowing the Heck reaction to proceed. Yields were significantly better (37-67%) than in a homogeneous system (0-37%) for reactions where the Heck reaction could be carried out under relatively mild conditions, but more forcing conditions led to decomposition of the fluorous tagged palladium complex. This method for keeping incompatible catalysts separate may have potential for a range of reactions.

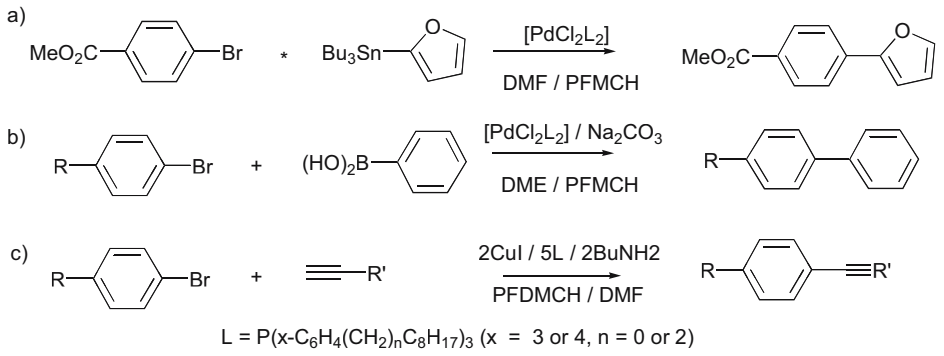


Figure 6.21. a) Stille,[65] Suzuki[66] and Sonigashira[67] coupling catalysed by complexes of fluorous analogues of PPh_3 (R = NO_2, COMe, CO_2Et or OMe; R' = Pr^i_3, Ph or CMe_2OH)

Stille,[65] Suzuki[66] and Sonigashira[67] couplings (Figure 6.21) have also been successfully carried out under fluorous biphasic conditions. Stille couplings of a variety of electron poor aryl bromides and electron rich aryl stannanes catalysed by $[PdCl_2(P(x\text{-}C_6H_4(CH_2)_nC_8F_{17})_3)_2]$ (x = 3, n = 0; m = 4, n = 0 or 2) were carried out in DMF/PFMC at 80°C in the presence of LiCl.[65] The reaction shown in Figure 6.21a gave 90% conversion with all three catalysts and could be repeated at least 6 times with

minimal loss of activity. Reactions using 2-tributylstannylanisole were less successful and could not be recycled, probably because the ortho methoxy group inhibited the coordination of the ligand.

The same palladium complexes have been successfully employed for the Suzuki coupling (Figure 6.21b) of a wide range of aromatic bromides (electron rich and electron poor) with phenylboronic acid.[66] Using 1.5 mol% of catalyst in PFMC/1,2-dimethoxyethane, at 75^{o}C, >90% conversion was achieved in 2 h. The catalysts were recycled 5 times, in most cases without appreciable loss of activity. At lower catalyst loadings (0.1 mol%) using an electron rich bromide and an electron rich aryl boronic acid, the conversions were high (100%) in the first run, but diminished substantially on recycling, generally to <10% by the third or fourth run.

The Sonigashira couplings (Figure 6.21c) were carried out using copper (I) iodide in PFDMCH/DMF in the presence of $BuNH_2$ at 100^{o}C over 4 h.[67] The best results (>98% conversion, recycled twice with little loss of activity) were obtained with electron poor substrates (R = NO_2 or CO_2Me in Figure 6.21) and $Pr^{i}_{3}SiC$ CH. For less electron rich substrates and the other alkynes, yields were between 10 (R = OMe, R' = CMe_2OH) and 80% and for the electron poor substrates yields fell off dramatically on recycling.

Knochel and Betzemeier have described palladium(0) - catalysed cross coupling between arylzinc bromides and aryl iodides as a facile method of forming carbon-carbon bonds and retaining the expensive catalyst for reuse.[68] The perfluorinated phosphine used in this reaction was $P(C_6H_4\text{-}4\text{-}C_6F_{13})_3$ in a toluene/$C_8F_{17}Br$ solvent system. The Pd catalyst was preferentially soluble in fluorous solvents and reuse of this phase did not cause any significant change in the reaction yield. The presence of the electron-withdrawing perfluoroalkyl groups has a positive effect on the reaction. The activity of the catalyst was in fact higher than with the non-fluorous catalyst $[Pd(PPh_3)_4]$. This is explained by the electron-deficient phosphine favouring reductive elimination in the cross-coupling reaction. This is obviously an important effect, which is likely to be utilised further.

6.10 Asymmetric Alkylation of Aldehydes

Chan and co-workers have synthesised perfluoroalkyl-BINOLs and shown them to be active ligands for titanium catalysed asymmetric carbon-carbon bond formation[69, 70] (the best one for fluorous biphasic reactions is shown in Figure 6.22). The reaction was carried out in perfluoro(methyldecalin)/hexane. PhCHO were dissolved in hexane along with the $Ti(O^{i}Pr)_4$ and added to a solution of the ligand in perfluoromethyldecalin. The catalyst complex was formed *in situ* when the homogeneous phase was formed at 45ºC and Et_2Zn was then added. After the reaction, the mixture was cooled to 0^{o}C to induce phase separation. Although there was no apparent loss of the *(S)*-R_fBINOL to the organic phase in repeated cycles, addition of $[Ti(O^{i}Pr)_4]$ was required with every cycle. The catalyst containing four C_8F_{17} substituents was recycled nine times without substantial loss of yield or drop in e. e., but it should be noted that although the 2nd – 9th cycles had yields of 80-70%, the first cycle had a yield of only 69%. This may indicate inadequate formation of the catalyst Generally, this system provided yields of 50-80% with e. e.'s as high as 58%. It was

observed that the more electron deficient substrate, 4-chlorobenzaldehyde, reacted slightly faster than the electron neutral benzaldehyde and in turn the more electron rich substrate, 4-methoxybenzaldehyde, reacted more slowly.

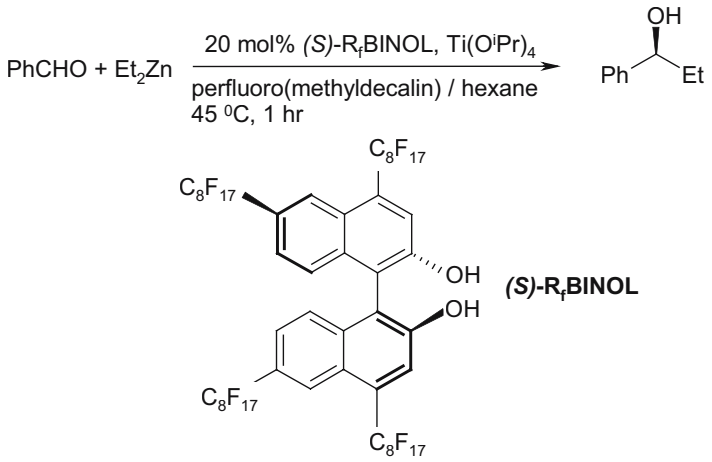


Figure 6.22. Asymmetric alkylation of benzaldehyde catalysed by a titanium complex of *(S)*-R_fBINOL.[69, 70]

Simultaneously, Takeuchi and co-workers reported another chiral fluorous BINOL, active in a similar reaction. However, their isomer is the (R)-R_fHBINOL[71] as shown in Figure 6.23. The ligand was dissolved in FC-72 (a perfluorous solvent containing primarily compounds with 6 carbons) along with [Ti(O-*i*Pr)$_4$]. Diethyl zinc in hexane was added to this and the solution was cooled to 0^{o}C before adding a benzaldehyde solution in toluene, thus creating an organic phase consisting of toluene and hexane. Under these conditions, the system is biphasic at all times. The organic phase was removed and quenched, before isolating the product. This system produced a higher enantioselectivity than Chan's (>80% compared to 58% e. e. respectively) with comparable yields. Repeat cycles using the fluorous phase showed a slight drop in yield and e. e. over 5 recycles. Again the yield obtained in the first run was lower (81%) than those achieved in the subsequent runs (89-87%). Unusually, the ligand loss to the organic phase has also been reported, 0.2 mmol of the ligand was recovered from the organic layer per cycle. From this data, the authors conclude that the asymmetric catalyst is present in the organic phase and that the asymmetric reaction must occur in this phase. Separating the organic and fluorous layers and performing the reaction in each, showed some catalytic activity in the organic phase, however a lower e. e. was achieved, than when using the fluorous phase or the biphasic system, suggesting a lower concentration of catalyst present in this phase than the fluorous phase.

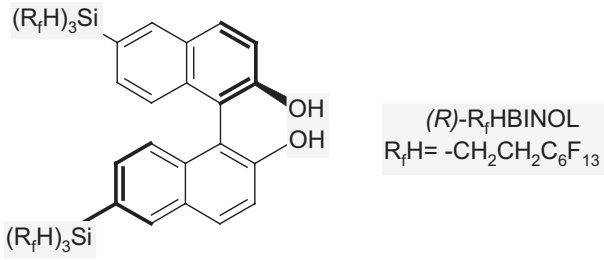


Figure 6.23. (R)-R_fHBINOL used in the asymmetric alkylation of benzaldehyde.[71]

Using $AlEt_3$ in place of Et_2Zn in the reaction shown in Figure 6.24, but carried out at 53°C afforded higher e. e. (63% rising to 82% at run 5) and high conversions (59% in the first run, rising to 88% in the third), but it was again confirmed that additional [$Ti(OPr^i)_4$] was needed for each run.[70] Higher enantioselectivities were obtained using zinc aminothiolates of the kind shown in Figure 6.24 ($R_2 = (CH_2)_4$, n = 10, e. e = 94%).[72] The reactions were carried out in PFMC/hexane at room temperature and the catalysts could be recycled up to 4 times, although the e. e. dropped steadily after the second run to 29% in the fifth run.

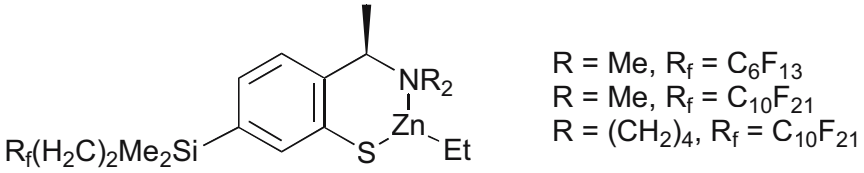


Figure 6.24. Alternative catalysts for the asymmetric alkylation of benzaldehyde.[72]

High enantioselectivities could be obtained using [$Ti(OPr^i)_4$] and a BINOL ligand modified with $CH_2CH_2C_6F_{13}$ only in the 6 and 6' positions in the allylation of benzaldehyde using 3-tributylstannylpropene (Figure 6.25).[73] This system did not give good results in either the organic or the fluorous solvent alone, but in the biphasic system (hexane/FC72, FC72 mainly contains C_6 fluorinated hydrocarbons) it gave 85% yield with 90.1% e. e. Very similar results were obtained using a C_8F_{17} chain (Yield 83%, e. e. 89.8%), but in a much shorter time (5 h c. f. 10 h for the ligand shown in Figure 6.25). Studies of different aldehyde substrates showed that good yields and e. e.s are only obtained from electron withdrawing aromatic aldehydes.

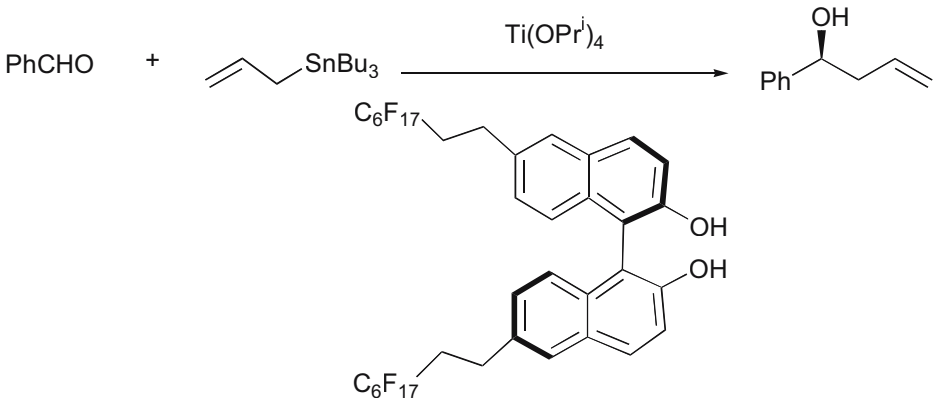


Figure 6.25. Asymmetric allylation of benzaldehyde catalysed by a fluorinated Ti/BINOL complex under fluorous biphasic catalysis.[73]

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6.11 Miscellaneous Catalytic Reactions

Another fluorous biphasic system, which showed desirable results was reported by Biffis and co workers[74] who described the preferential silylation of primary alcohols using $[Rh_2(PFTD)_4]$, (PFTD = perfluorotetradecanoate). Ligands of lower carbon number were found to leach to the organic (CH_2Cl_2) phase during the reaction. The best results were obtained with a DCM/FC-77 (mainly C_8 containing fluorocarbons) solvent system, at room temperature, 1 mol% catalyst and a 1:1 alcohol to silane ratio for 6 hours. This gave a yield of 68%, which was not as good as the non-fluorous reaction (96% yield in 3 h). Catalyst decomposition caused a decrease in yield by the second recycle of the fluorous layer. An interesting property of the system was observed when a range of alcohols was tested and the preference for primary alcohols over secondary and hydrophilic alcohols became apparent.

Endres and Maas have also described the use of rhodium(I) perfluoro carboxylates, see Figure 6.26, as active catalysts in the carbenoid reaction of diazoacetate with toluene in a toluene-PFMC solvent system.[75] Both catalysts are insoluble in toluene. The complex containing the aryl carboxylic acid gave a total yield of 71% and the other complex a total yield of 78%. Decomposition of both catalysts was observed. This explains why only partial catalyst recovery could be made. In a more recent paper,[76] further perfluorinated chains have been attached to the dirhodium complex, introducing spacer groups. Only the ligand with $R_f = CH_2C_6F_{13}$ was soluble in PFMC. The spacer group had been introduced to minimise the electronic effect of the electron withdrawing fluorous ponytail on the dirhodium complex, in order that it more resembled its non-fluorous analogue, $[Rh_2(OAc)_4]$. The polar carboxylate groups make these fluorinated catalysts different from others reported, which are generally non-polar. These complexes are also soluble in THF and diethyl ether at room temperature, which causes the catalyst to leach to the organic phase during a reaction. Unfortunately, this study shows the limitations of the fluorous analogue of Rh-catalysed carbene transfer. As the electron-withdrawing effect has to be restricted, two

or more methylene spacer groups are required, but this in turn makes the catalyst insoluble in fluorous solvents. Clearly fluorous biphasic catalysis does have its limitations.

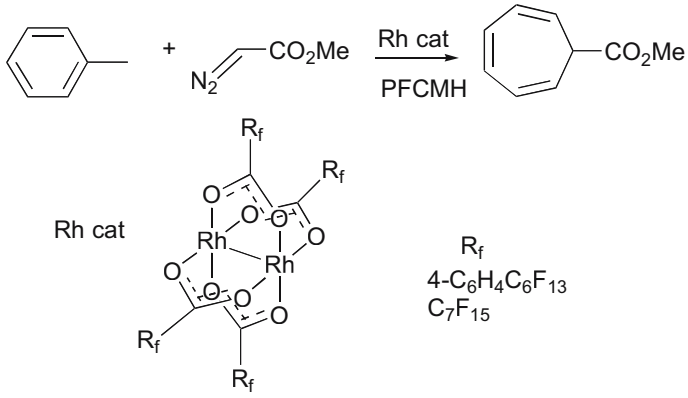

Figure 6.26. Carbene reaction catalysed by rhodium(II) complexes containing fluorinated carboxylates.[75, 76]

6.12 Fluorous Catalysis without Fluorous Solvents

Wende and Gladysz have investigated the reaction of a perfluorinated catalyst system in the absence of any fluorous solvent.[77] This system catalyses the conjugate addition of alcohols to methyl propiolate under homogeneous conditions in *n*-octane at 65°C (Figure 6.27). The fluorinated phosphine, $P(C_2H_4C_8F_{17})_3$, without metal, shows temperature dependent solubility in n-octane such that it is essentially insoluble at -30°C and it is reported that >97% phosphine recovery is made every run. Through synthesis of a large number of fluorous ligands, it was observed that the solubilities of these compounds increased with increasing temperature. The process simply relies upon the same concept as an ordinary FBS, whereby at room temperature there are two phases, in this case solid and liquid; at reaction temperature a single homogeneous solution is formed and upon cooling the solid catalyst is again precipitated and can easily undergo a heterogeneous separation. However, if there is incomplete conversion, unreacted substrate and the organic solvent still have to be removed from the final product.

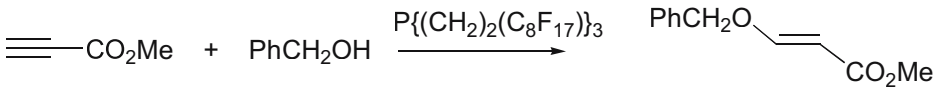

Figure 6.27. Conjugate addition of benzyl alcohol to methyl propiolate catalysed by a fluorous phosphine without a fluorous solvent.[77]

The reaction was carried out by combining the phosphine ligand $\{P(C_2H_4C_8F_{17})_3\}$, the alcohol and methyl propiolate in *n*-octane at room temperature, the authors report no visual dissolution of the phosphine. On heating to 65°C a homogeneous phase was attained. After 8 hours the sample was cooled to –30°C and the phosphine precipitated. The sample was kept at –30°C whilst the supernatant liquid was removed. It is unclear why the phosphine undergoes a colour change during the reaction. Before heating it is a white solid and the authors report that most samples on cooling precipitated an orange solid, which upon recycling often darkened to red. For benzylic alcohol ($PhCH_2OH$) a yield of 82% was achieved in the first cycle. This was maintained for three recycles but in the fifth cycle, dropped to 75%. Interestingly, by omitting the *n*-octane from the reaction and making this a totally solvent free system, the initial yield rose to 99% and was maintained for two further recycles before dropping to 95% in the fourth run. By total omission of any solvent, not only is the cost reduced but also the process becomes much more environmentally friendly. There has been some work published by other groups working on a similar principle, these include catalysed condensations of carboxylic acids and amines to amides,[78] transesterifications[79] and benzoylations of alcohols and esterifications of carboxylic acids.[80] This is an interesting approach from an economic point of view as there is no unnecessary expense on costly fluorinated solvents. However, it would appear that a phase change of the catalyst at or above the collection temperature, to provide a much less soluble form of the catalyst could provide even greater advantages. Such systems do not appear to have been reported.

6.13 Continuous Processing

Yoshida *et al* recently reported the development of a continuous flow reaction system using a fluorous biphasic system.[81] They report the acetylation of cyclohexanol and the Baeyer-Villiger reaction of 2-adamantanone using fluorous biphasic conditions (see Figures 6.28 and 6.29. The acetylation of cyclohexanol employed a fluorinated catalyst, ytterbium(III) bis(perfluorooctanesulfonyl)amide, PFMC at 40°C. The organic phase was made up of a solution of cyclohexanol in toluene to which was added acetic anhydride. This organic mixture was continuously added to the stirred tank reactor and once part filled with reaction mixture the mixture overflowed to a decanter (25°C) where separation occurred. Once this decanter had filled the organic phase began to overflow to the product tank whilst the fluorous phase could be recycled to the reactor (see Figure 6.30). The product was analysed by GC and the results showed conversion was maintained at >90% over 500 hours (nearly 3 weeks) with less than 2 ppm ytterbium in the organic phase.

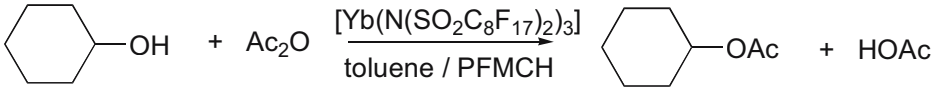

Figure 6.28. Acetylation of cyclohexanol carried out continuously under fluorous biphasic conditions for 500 h.[81]

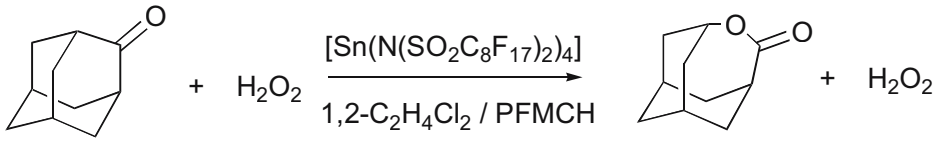

Figure 6.29. Baeyer-Villiger reaction carried out continuously over 200 h under fluorous biphasic conditions.[81]

In order to see if the reaction system was suitable for water forming reactions the Baeyer-Villiger reaction of 2-adamantanone with 35% aqueous solution of H_2O_2 was investigated. Using tin(IV) bis(perfluorooctanesulfonyl)amide in 1,2-dichloroethane/PFMC a conversion in the region of 50-60% was achieved with a high selectivity. This reaction was run for 200 hours. The success of these reactions indicates what may be possible with future continuous flow fluorous biphasic systems, however no high pressure or gas substrates were involved in these reactions.

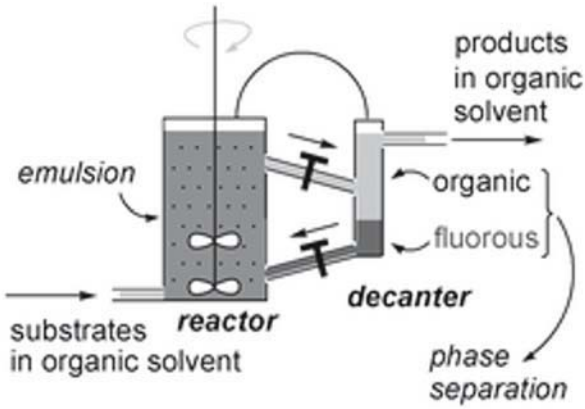

Figure 6.30. Schematic diagram of a reactor used continuously for up to 500 h for fluorous biphasic reactions without gaseous reagents.[81] (A. Yoshida et al, *Development of the continuous-flow reaction system based on the Lewis acid-catalysed reactions in a fluorous biphasic system*, Green Chemisty, 5, (2003), 555) *Reproduced by permission of The Royal Society of Chemistry.*

A reactor which allows the continuous operation of fluorous biphasic reactions involving gases has been described by Manos, Hope, Cole-Hamilton and co-workers and demonstrated in the hydroformylation of 1-octene catalysed by complexes formed *in situ* from $[Rh(CO)_2(acac)]$ and $P(4\text{-}C_6H_4C_6F_{13})$.[41-43] Shown schematically in Figure 6.31, gases and fresh substrate are continually fed to the continuously stirred tank reactor (CSTR), which contains the catalyst dissolved in PFMC. All the time, the mixture is being removed through a dip tube, and flow controller (capillaries) to a gravity separator. The phases separate and the organic phase is allowed to overflow through a tube into a collection vessel, whilst the fluorous phase is continuously fed back into the reactor *via* an HPLC pump.

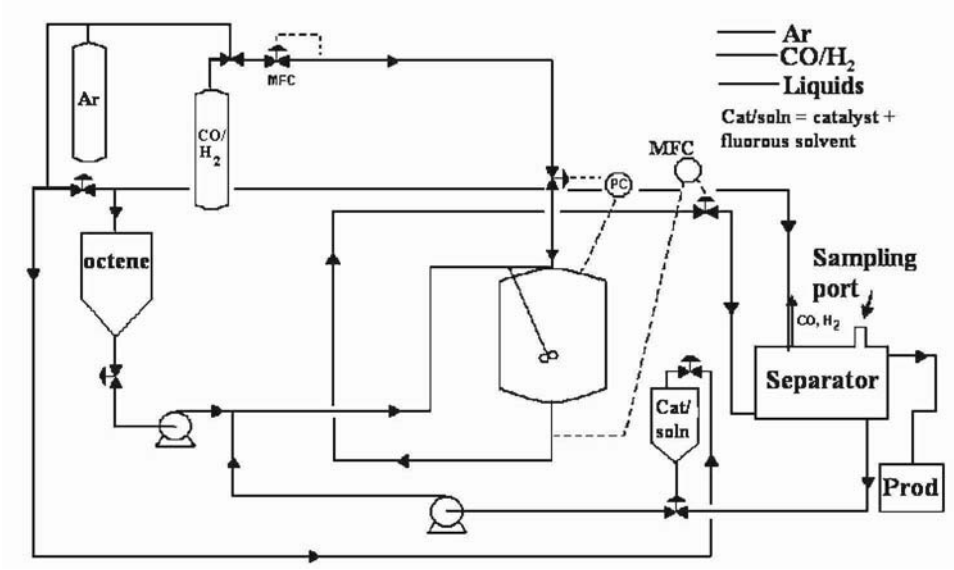

Figure 6.31. Schematic diagram of continuous flow reactor for fluorous biphasic reactions under gas pressure.[42]

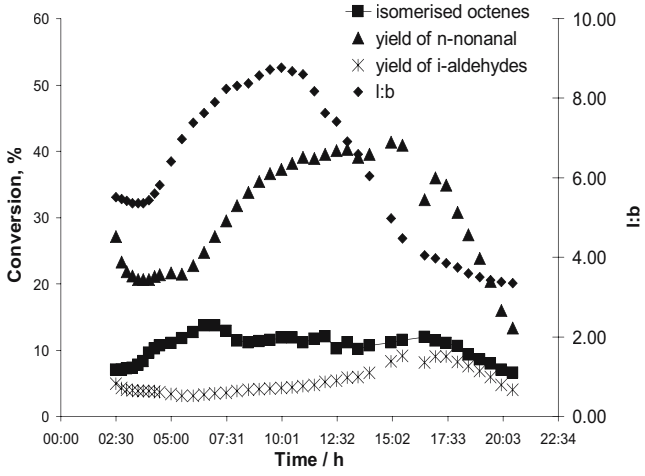

Figure 6.32. Results for the continuous hydroformylation of 1-octene catalysed by Rh/ $P(4\text{-}C_6H_4C_6F_{13})_3$ in fluorocarbon solvents.[42]

Studies of the phase behaviour at ambient temperature within the separator [43] show that there is significant solubility of the product nonanal within the fluorous phase and *vice versa*. Although this does not present a problem for the nonanal (it will simply be recycled to the reactor and create a steady state, it does mean that fluorous solvent is always being lost. The loss of the fluorous solvent (2.8 mol% into pure nonanal), as for the catalyst and the free ligand [41] is much more significant at low conversion, so

optimum results should be obtained if the reaction is run at high conversion. This is a fundamental problem with a continuous flow CSTR since some substrate will always enter the reactor and pass straight out of it without having significant contact with the catalyst. A possible solution to this problem, involving two parallel batch reactors is discussed below. In order to work at as high conversions as possible, the hydroformylation reaction was run in batch mode (all flows turned off) at the start of the continuous run and again once the reaction mixture had passed through the system and just filled the separator. Figure 6.32 presents the results obtained in a continuous run.[42]

The drop in conversion at the start of the reaction represents the lower conversion expected in the flow system than in the batch reaction. Since the steady state conversion in this case was low, it was expected that phosphine and rhodium would leach significantly to the organic phase (which indeed was yellow). Loss of rhodium should cause a decrease in rate, whilst loss of phosphine should cause an increase because the reaction is negative order in [phosphine]. As discussed above, the phosphine leaches more than the rhodium, hence the increase in rate over the period 5-10 h. Once the [phosphine] drops below a certain level, complexes of the form $[RhH(CO)_n(P(4\text{-}C_6H_4C_6F_{13})_3)_{3-n}]$ (n = 2-3) will start to form. These have fewer ponytails than $[RhH(CO)(P(4\text{-}C_6H_4C_6F_{13})_3)_3]$ and will leach more heavily, accounting for the reduction in rate at 17-20 h. The l:b ratio is high throughout the main part of the reaction (7:1), but this may in part be attributed to the high levels of isomerised alkene (the branched alkyl intermediate in hydroformylation reactions can lead to the branched aldehyde (reaction with CO) or to isomerised alkene (≈-hydrogen abstraction), so that high isomerisation can give high l:b ratios, see Figure 6.33)[82]. The high levels of isomerisation in this continuous reaction has been traced to inefficient stirring in the reactor.[41] Although leaching was a major problem in this reaction, the catalyst performed >15 000 turnovers at an average rate of 750 h^{-1} over the 20 h period of the reaction.[42]

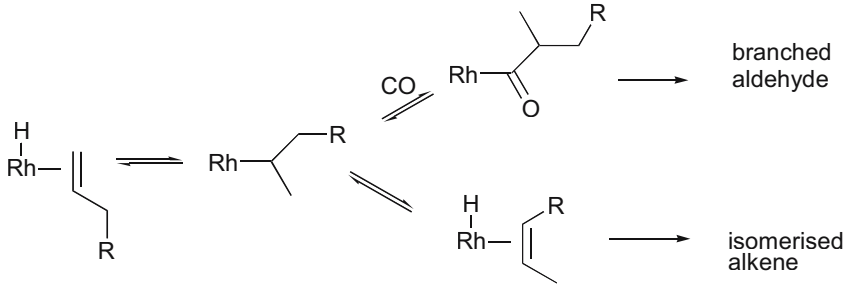

Figure 6.33. Relationship between isomerisation and branched aldehyde formation during hydroformylation reactions

Figure 6.34 shows another continuous reaction.[41] In this case, more catalyst solution was fed when the reaction rate slowed (represented by the dots in the figure) so that the conversion was up to 70% for part of the reaction. The l:b ratio was very high (13:1) for much of the reaction, but interestingly dropped because of a drop in isomerisation

activity at the highest conversions. Paradoxically this suggests that the gas mixing is better at high conversion, when the phases are better separated. Perhaps it reflects the higher concentration of rhodium in the active phase of the two-phase system.

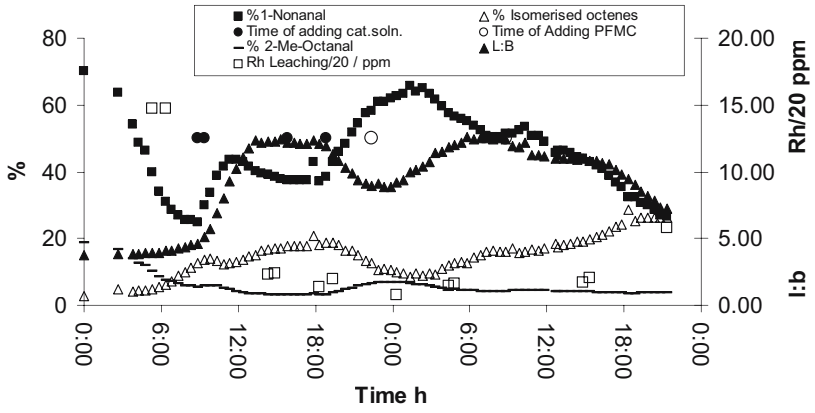

Figure 6.34. Results from the hydroformylation of 1-octene carried out under continuous flow conditions with extra catalyst solution addition.[41]

The drop in conversion at the start of the reaction is much greater than expected just on the basis of transferring from a batch to a continuous reaction. It occurs because there is also substantial leaching of rhodium (300 ppm) at the start of the reaction, either because the catalyst has not preformed properly or because there is oxygen in the system and some of the phosphine is oxidised. Rhodium leaching increases at the end of the reaction (115 ppm), presumably because phosphine is lost to the organic phase and there is insufficient to keep the catalyst as $[RhH(CO)\{P(1\text{-}C_6H_4C_6F_{13})_3\}_3]$, but is about 20-30 ppm for most of the reaction.

The main conclusions to be drawn from this study are that the reactor design works well, and that steady state continuous flow operation requires excellent mixing of the gases and two liquid phases and high conversions. Improvements in the catalyst (ligand) are required to reduce leaching still further, but commercialisation will also require a different reactor design or more than one CSTR in series.

6.14 Process Synthesis for the Fluorous Biphasic Hydroformylation of 1-Octene

The fluorous biphasic concept was first tested on the hydroformylation of 1-decene[1] and has been used more for this type of reaction than for any other. A continuously operational reactor - separator system using 1-octene as the substrate has been reported.[41, 42] The major problem that is encountered is that the fluorous solvent, ligand and catalyst all show some solubility in the organic phase. Significant advantages have been demonstrated when the reaction is carried out without an additional organic solvent.[20] This improves the reaction rate and selectivity as well as the retention of ligand and catalyst in the organic phase. In a commercial plant it would

also remove one complete separation step, that of the product from the organic solvent. Certain other advantages compared with triphenylphosphine also accrue if the fluorous pony-tail is attached in the 4-position of the phenyl ring, as in $P(4\text{-}C_6H_4C_6F_{13})_3$. The electron withdrawing nature of the fluorous substituent increases both the rate of reaction and the selectivity to linear aldehyde.[20] This means that lower phosphorus loadings are required (Rh:P = 1:10, compared with 1:150-300 in commercialised PPh_3 systems)[83] to achieve l:b ratios of 6:1 in batch processes (10:1 in some continuous reactions and a linear selectivity of 81% compared with 83-90% for commercialised propene hydroformylation using PPh_3. It should be noted that propene cannot give isomerised alkene and *ca.* 4% of 1-octene is isomerised during the fluorous biphasic hydroformylation. For comparison, commercialised cobalt based hydroformylation processes can give linear selectivities of 10:1, but 10% of alkene is lost to hydrogenation so that the selectivity to linear aldehyde product is again *ca.* 81%.[83]

The fact that less ligand is required when using the fluorous substituent not only saves in terms of ligand cost, but it also means that the reaction can be carried out with very high rates at low temperature. At 70°C, the turnover frequency (TOF) is 4400 h^{-1} compared with 500-700 in commercial propene based systems, which are operated at 100°C.[20] This in turn should mean that ligand degradation, one of the chief repetitive costs of the processes using PPh_3, should be greatly reduced. One possible disadvantage of omitting the organic solvent is that phase separation occurs under the reaction conditions at *ca.* 20% conversion. This might appear to negate the major advantage of the fluorous biphasic system (homogeneous reaction conditions), but kinetic measurements have shown that the reaction remains first order way beyond this conversion and even as far as 80% conversion.[20]

Even when omitting the organic solvent, some leaching of the ligand and the catalyst still occurs. Catalyst retention is improved because the form of the catalyst, which is present in the separator $[RhH(CO)(P(4\text{-}C_6H_4C_6F_{13})_3]$ contains the maximum number of fluorous substituents and hence is most fluorophilic.[41] It is also very much dependent on the degree of alkene conversion to aldehyde because the fluorous ligand and catalyst have very much higher solubility in 1-octene than in nonanal.[41] It is clear from Figure 6.8 that reactions should be conducted to 100% conversion if leaching of the expensive catalyst and ligand are to be minimised. This could be achieved by using stirred tank reactors in series or in parallel. In Figure 6.35, we show the use of two tank reactors (**R1** and **R2**) operating in parallel, both feed from the same supplies and both are attached to the same collecting vessel (**C**) attached to the same separator. This design allows the reactions to be carried out to high conversion in batch mode and allows for the bulk of the catalyst solution to be in the reactor under the conditions for which it has been optimised at all times. By tunrng off the stirrer each reactor also acts as the separator. Since only the product phase is withdrawn from the reactor, the catalyst solution is not itself heated and cooled, so heat losses can be minimised. A heat exchanger (**HE**) is proposed for using the heat from the product leaving the reactor to preheat the fresh substrate. Because the product phase is withdrawn hot from the reactor, a small amount of fluorous solvent (up to 4 mole %) [40] and catalyst will be dissolved in it. On cooling in the heat exchanger and separator, where dissolved gases will also be vented and recycled, the small amount of fluorous

solvent and catalyst will separate. It will be recycled to the reactors once it has built up to a significant level. The reactors would be operated in batch mode with a reaction time of 20 min followed by a settling, separation and refilling period also of 20 min. The two reactors would be operated in orthogonal cycles, so that the size of the collecting tank can be reduced to a minimum.The reactors would have feeds for the alkene, the fluorous solvent/catalyst solution and systems for recycling the unreacted gases and the small amount of catalyst solution that separates in the collecting vessel. The product solution will be passed from the collecting vessel to a single fractionating column (**D**), where the isomerised alkene, dissolved fluorous solvent and two aldehyde products will be fractionally separated. The recovered fluorous solvent (expected to be as much as 2.8 mol % [43]) will be returned to the reactor, whilst the isomerised alkenes will be burnt as fuel. The complete system is shown schematically in Figure 6.35.

To produce 100 000 tonnes of nonanal per year (25% down time, 100% conversion of substrate, 80% selectivity to nonanal) requires a production rate from the reactors of 19 tonne h^{-1}, so that each batch must be 6.3 tonnes. Assuming a 1:1 ratio by volume of fluorous solvent:liquid substrate and a 75 % loading, each reactor must have a volume of 20 m^3. If the distillation column were fully integrated into the system it would be required to handle 19 tonnes aldehyde h^{-1}. An increase in selectivity to the linear product, which could be achieved using careful ligand design would reduce the reactor size by up to 25%.

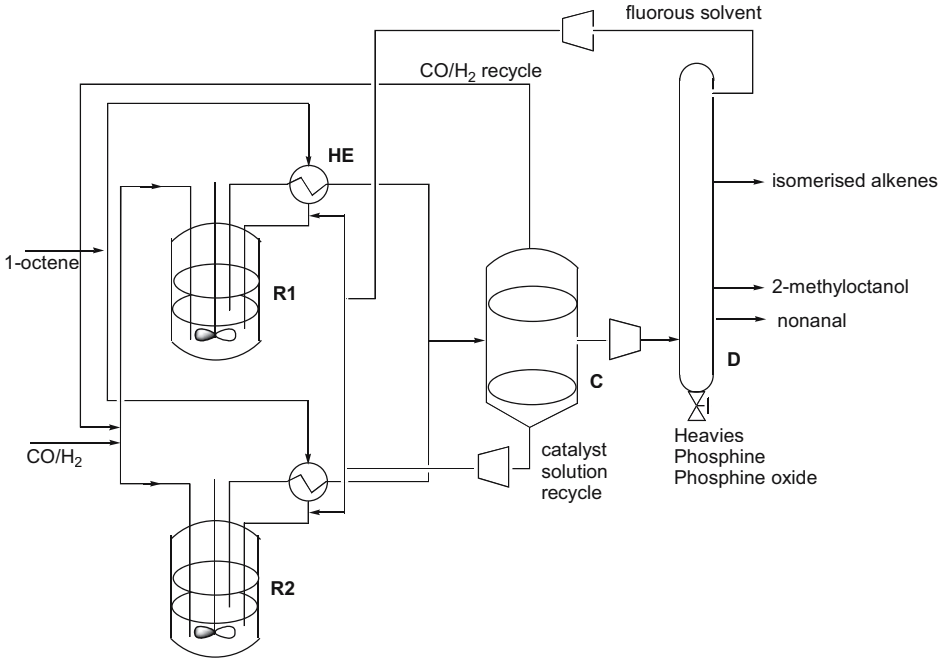

Figure 6.35. Schematic design of a full-scale fluorous biphasic reactor for the hydroformylation of 1-octene

The main costs of the process are in the fluorous solvent and in the ligand. The total estimated cost of the ligand will be of the order of 150 000 € for 30 kg. If we assume that the rhodium losses can be reduced to 1 ppb (this will require improved ligand design) and that ligand losses may be 10 times this (0.12 g tonne^{-1}), the added cost for the ligand replenishment will be 60 000 €, increasing the cost of the nonanal by 0.6 € per tonne. Although some of the fluorous solvent (*ca*. 0.2 mol%) will be dissolved in the product, it is expected that almost all of this will be recovered in the distillation unit and recycled. The total cost of the inventory of the fluorous solvent is 3.5 M€ (based on a current quotation for 25 tonnes of 140 € kg^{-1}), but this could be reduced to <30 € kg^{-1} (0.75 M € for 25 tonnes) if perfluorohexane were used as the solvent. This is a capital investment, and a loss of 1% per annum would increase the cost of the nonanal by 0.35 € tonne^{-1} (0.075 € tonne^{-1} using perfluorohexane). Even though the solvent and the ligand are very expensive, realistic estimates of losses that might be obtainable on optimisation of the reaction suggest that the major additional cost to the final price of the nonanal will still be because of rhodium losses (1 € tonne^{-1}). These costings are collected in Table 6.3.

TABLE 6.3. Process for optimized nonanal production of 100 000 tonnes y^{-1} using perfluoromethylcyclohexane in a fluorous biphasic system [a]

		Total cost / k€	Cost of replenishment / k€ y^{-1}	Increased cost of nonanal / € tonne^{-1}
T / ºC	70			
p / bar	20			
Organic:fluorous (v/v)	1			
Reactor volume / m^3	20			
Collecting vessel volume	20			
Rhodium inventory / kg	2.5	1000	100	1
Ligand inventory / kg	30	150	60	0.6
Fluorous solvent inventory / tonne	25	750	7.5	0.075
Synthesis gas : alkene ratio	1.2			
Selectivity to linear product / %	80			
Isomerised alkene / %	4			
Fluorous solvent in organic phase g kg^{-1}	3			

[a] Based on 25% down time, perfluorohexane as fluorous solvent and P(4-$C_6H_4C_6F_{13}$)$_3$ as the ligand.

6.15 Conclusions

The fluorous biphasic concept, which was first suggested by Horváth in 1994, has now been applied to a very wide range of catalytic reactions, in many cases with the recycling of the catalyst being demonstrated. In most cases there is a fall off of conversion with reuse and significant leaching of ligand and metal containing catalyst, although in some cases very good catalyst retention does appear to have been demonstrated by ICP analysis and by successive experiments. Two different types of continuous reactor have been developed for laboratory demonstration on a small scale, one with and one without the capacity for handling pressurised gases. Two reactions

have been operated, both without gaseous reagents, continuously for up to three weeks with no noticeable loss in activity, suggesting that the technique should definitely be considered for scale-up. Preliminary costings using realistic price estimates suggest that losses of fluorous ligand and of fluorous solvent during the commercial hydroformylation of long chain alkenes would not greatly inflate the costs of the process, despite the high costs of these chemicals. The major renewable cost would still be from loss of rhodium.

6.16 Acknowledgement

We thank Sasol Technology (UK) Ltd and the EPSRC for a studentship (C. R. M.).

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