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Hydroformylation in fluorous solvents

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Abstract

The hydroformylation of long chain alkenes under fluorous biphase conditions and in neat perfluorocarbon solvents is reviewed. Special emphasis is placed upon the authors' evaluation of the steric and electronic influence of perfluoroalkylation on catalyst activity, regioselectivity and retention in the fluorocarbon phase.

Keywords: Fluorous; Hydroformylation; Rhodium; Phosphine

1. Introduction

The temperature-dependent miscibility of highly fluorinated and organic solvents underlying the fluorous biphase approach to catalyst/product separation, originally introduced by Horváth and Rábai [1] has been exploited in a wide range of reactions and processes and the area has been extensively reviewed [2–6]. However, the process that has elicited the greatest interest, as measured by the number of publications and highlighted in Horváth and Rábai's original work, is the hydroformylation of long chain alkenes.

Cobalt-carbonyl catalysts, employed in the first commercial process for the hydroformylation of alkenes in the 1950's [7] were superceded by the introduction of phosphine ligands, that offered enhanced hydrogenation to alcohols coupled with improved regioselectivity to the linear (*n*-) product, and these technologies are still in use today [8]. More recently, more selective rhodium-phosphine catalysts have replaced these cobalt-based catalysts in the hydroformylation of propene [9], where the volatile butanal product can be readily distilled directly from the reactor. However, their thermal instability has precluded the application of these rhodium catalysts for the hydroformylation of longer chain alkenes. The opportunity for facile catalyst/product separation without distillation offered by the fluorous biphase approach is, therefore, attractive and accounts for the considerable effort directed towards fluorous-phase soluble rhodium catalysts for hydroformylation. In this mini review, the progress in fluorous-based hydroformylation catalysis is charted leading to important conclusions on the viability of this approach.

2. Results and discussion

Although the environmental persistence and high cost of highly fluorinated solvents are likely to be key factors in the potential commercialization of a fluorous-based hydroformylation process, academically there are four, linked, factors that have defined progress in this area: (i) ease of ligand synthesis, (ii) fluorous phase compatibility, (iii) reaction regioselectivity and (iv) rhodium leaching levels. Three classes of phosphorus(III) ligands have been evaluated and it is convenient to consider each class separately.

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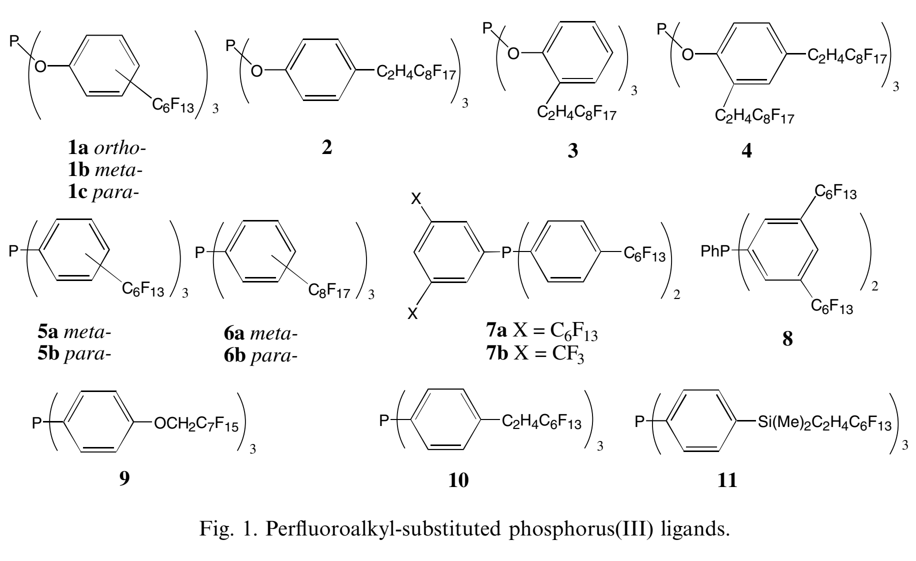
2.1. Trialkylphosphines

The trialkyl phosphine, $P(C_2H_4C_6F_{13})_3$, can be prepared in high yield by the reaction of PH_3 with $CH_2{=}CHC_6F_{13}$ [1,10,11], or via the reaction of PCl_3 with either a Grignard [12,13] or an alkyl zinc reagent [14]. The ligand partitions almost exclusively (99:1) into the fluorous phase of a $CF_3C_6F_{11}$(PP2):toluene two-phase system [11] and has been shown to generate the desired $[HRh(CO)L_3]$, by solution phase NMR experiments, on reaction with $[Rh(CO)_2(acac)]$ under syngas [10]. Horváth and Rábai initially outlined the hydroformylation of 1-octene in a toluene/PP2 two phase system at 100 °C under 10 atm CO/H_2 (1:1) using a catalyst generated in situ from $[Rh(CO)_2(acac)]$ and the trialkyl phosphine (1:40) which gave an 85% conversion to aldehydes with an n/i ratio of 2.9 [1]. In a subsequent full paper [15], an in-depth analysis of hydroformylation under fluorous biphase conditions generated a series of important conclusions. Here, the hydroformylation of 1-decene and ethylene were investigated with the same rhodium catalyst (generated in situ) under both batch and semi-continuous conditions at 100 °C and 1.1 MPa CO/H_2 (1:1) in a 50/50 vol% toluene/PP2 biphase. Whilst the regioselectivity is comparable to that for the analogous catalyst based on triphenylphosphine, the catalytic activity is an order of magnitude lower. The reaction, as expected, is first-order in both rhodium and alkene and is inhibited by excess phosphine. The regioselectivity increases with phosphine concentration such that the best n/i ratio (7.8:1) is obtained at a P:Rh ratio of approximately 100:1 ($[\text{ligand}] = 0.3\ \text{mol dm}^{-3}$). The long-term stability of this catalyst under these conditions is significantly greater than that for the catalyst based on triphenylphosphine such that the semi-continuous experiments were highly successful with total turnovers of up to 35,000 during nine cycles with only 1.18 parts per million (4.2%) loss of rhodium per mol of product(s), that arises from the low solubility of the catalyst in the organic phase.

2.2. Triarylphosphites

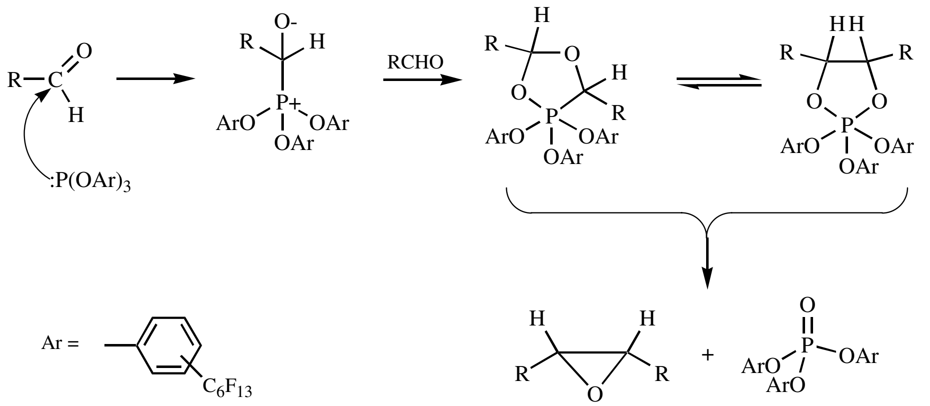
Two groups have evaluated the application of perfluoroalkylated triarylphosphites for fluorous-based rhodium-catalysed hydroformylation of alkenes [6, 16–18]. *Ortho*-, *meta*-, *para*-substituted and *ortho*/*para*-disubstituted ligands (Fig. 1), which can be prepared in very high yields from the condensation of the requisite perfluoroalkylated phenols with PCl_3 [12,18–20] have all been evaluated in catalysis, and differ by the presence/absence of an additional C_2H_4 spacer unit. The phosphites with one perfluoroalkyl group per aryl ring partition 95:5 in 1-decene:1*H*-perfluorooctane [18] or toluene:perfluoro-1,3-dimethylcyclohexane (PP3) [21] biphases, whilst (**4**) partitions 99:1 in the 1-decene:1*H*-perfluorooctane biphase [18].

The hydroformylation of 1-hexene or 1-octene in a toluene:PP2 biphase at 70 °C under 20 bar CO/H_2 (1:1) using a catalyst generated in situ from $[Rh(CO)_2(acac)]$ and (**1b**) or (**1c**) gave 84–95% conversions to aldehydes with n/i ratios up to 8.4:1 [6,17]. However, catalyst decomposition at elevated temperatures and surprisingly high rhodium and phosphorus leaching levels even at 70 °C (39% and 47%, respectively) at the end of the reactions appeared to be inconsistent with their first order kinetics. The most reasonable explanation is the acid catalysed addition of the phosphite to the aldehyde product to give the polar phosphonate (Scheme 1) which has a low partition coefficient in the fluorous phase [22,23]. Similar catalyst decomposition was reported by Mathivet et al. in the hydroformylation of 1-decene in a toluene/1*H*-perfluorooctane biphase at 80 °C under 40 bar of syngas using a catalyst generated in situ from



1a *ortho-*
1b *meta-*
1c *para-*
2
3
4
5a *meta-*
5b *para-*
6a *meta-*
6b *para-*
7a X = C_6F_{13}
7b X = CF_3
8
9
10
11

Fig. 1. Perfluoroalkyl-substituted phosphorus(III) ligands.



Scheme 1. Postulated mechanism for the decomposition of perfluoroalkylated phosphites by reaction with the aldehyde product.

[Rh(CO)$_2$(acac)] and (**2**) [18]. Poor regioselectivity (*n*/*i* 0.9) for the *ortho*-derivatised ligand (**1a**) in hydroformylation was attributed to steric crowding on coordination [21]. However, inclusion of the additional C_2H_4 spacer in (**3**) and (**4**), appears to overcome some of these problems with regioselectivities of 2:1 reported for the rhodium catalysed hydroformylation of 1-decene using either ligand [18]. In addition, the presence of the perfluoroalkyl groups in the *ortho*-positions, appears to inhibit the phosphonate decomposition pathway for these ligands, although reduction in catalytic activity and rhodium leaching are observed after four catalytic cycles.

Both groups recognized that the partition of the ligand and/or catalyst into the organic phase could be decreased by eliminating the organic solvent entirely and carrying out the hydroformylation in neat perfluorocarbon solvents [17,18]. In these experiments, the alkene substrate is completely miscible with the solvent whilst the aldehyde product phase separates. An additional advantage, commercially, in this approach is that the product does not need to be separated, in a second step, from an organic solvent such as toluene, after separation from the catalyst. However, whilst the hydroformylation of 1-octene using the catalyst based on (**1b**) the *n*/*i* ratio could be improved to 9.9:1 and the leaching of rhodium to the product phase decreased by a factor of 10, the problem of ligand decomposition by reaction with the aldehyde product could not be eliminated, and so this catalyst system could not be used in multiple experimental cycles.

2.3. Triarylphosphines

Perfluoroalkylated triarylphosphines with 1, 2, 3 or 4 perfluoroalkyl groups connected directly to the aryl rings in the *ortho*-, *meta*-, *para*- or *bis*-*meta*-positions, or with additional –C_2H_4–, –OCH_2– or –$SiMe_2C_2H_4$– spacer groups to ameliorate the electronic influence of the perfluoroalkyl substituents (Fig. 1), have been prepared via a variety of routes [2–6,12,24]. It is well established that triarylphosphines give much better regioselectivity in rhodium-catalysed hydroformylation reactions than trialkylphosphines [25,26], and we have focused our attention in this area. As indicated elsewhere [27], greater than 60% by weight fluorine is an approximate rule of thumb for the preferential solubility of a molecule in a perfluorocarbon solvent and the solubility of these triarylphosphines in the fluorous phase of a toluene:PP3 biphase certainly increases with the number and length of the perfluoroalkyl substituents (Table 1). However, the partition functions do not correlate exactly with the percent by weight fluorine and the exact positioning of the fluorous ponytails is also crucial. Furthermore, although Horváth has suggested [15] that aryl phosphines may be less suitable for fluorous biphase catalysis because their higher polarity might make them more soluble in the organic phase than trialkyl phosphines, (**6b**) and (**7a**) partition into the fluorous phase as well as Horváth's trialkylphosphine.

Table 1
Partition functions and electronic data for triarylphosphines

Phosphine	% Fluorine by weight	Partition function[a]	$^1J_{PSe}$/Hz[b]
11	50	73:27[c]	(774)[d]
7b	59	48:52	801
10	57	47:53	767
5b	61	15:85	791
5a	61	11:89	796
8	64	10:90	806
9	59	9:91	759
6b	64	1:99	793
7a	64	1:99	803

[a] Determined gravimetrically from 0.100 g of ligand stirred in a biphase consisting of toluene (2 cm^3) and PP3 (2 cm^3) at 25 °C. Presented % toluene:% PP3.

[b] Coupling constant for phosphine selenide dissolved in ether at 25 °C.

[c] Data taken from [35].

[d] Value estimated from the linear correlation of $^1J_{PtP}$ (for *cis*-[$PtCl_2L_2$]) vs $^1J_{PSe}$ (for Se = L) [36]. $^1J_{PtP}$ (for *cis*-[$PtCl_2L_2$]) taken from [37].

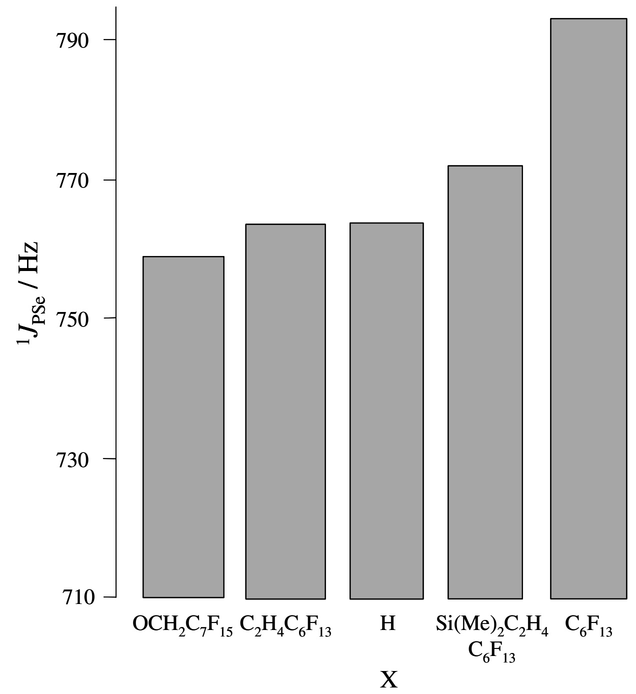


Fig. 2. $^1J_{PSe}$ with substituents X in $Se{=}P(C_6H_4\text{-}4\text{-}X)_3$.

There has been considerable interest in the donor properties of perfluoroalkylated triaryl phosphines. Although our earlier studies [28] used the variation in $^1J_{PtP}$ as a measure of the effectiveness of the electronic insulator, this function is significantly influenced by steric effects for the *ortho*- or *meta*-substituted phosphines [29,30]. A more accurate probe, following oxidation of the ligand, is the $^1J_{PSe}$ coupling constant of the phosphorus(V) selenides (Table 1) [31], which indicates that the length and substitution pattern of the perfluoroalkyl substituents have little influence on the σ-donor properties of the phosphorus atoms. This probe also allows a comparison of the relative efficiencies of the additional spacer units (Fig. 2). Taking this electronic data alongside the partition functions of the ligands suggests that, for hydroformylation at least, direct attachment of the perfluoroalkyl substituents to the aryl rings would be expected to give the greatest regioselectivity [22] and the highest catalyst retention in the fluorous phase. Indeed, a recent study on the hydroformylation of 1-octene in either a toluene/PP2 two phase system or neat PP2 at 80 °C under 40 atm syngas using a catalyst generated in situ from $[Rh(CO)_2(acac)]$ and (**9**) (1:5) gave, at best, an *n*/*i* ratio of just 2.8:1 with significant loss of rhodium to the product phase [32].

In our work, initial screening of the hydroformylation of 1-hexene in a toluene/PP3 two phase system at 70 °C under 20 atm CO/H_2 (1:1) using a catalyst generated in situ from $[Rh(CO)_2(acac)]$ and (**5b**) (1:3) gave a 98% conversion to aldehydes with an *n*/*i* ratio of 3.8 [33]. Elimination of the organic phase, as highlighted previously in the hydroformylation studies using the triaryl phosphites, offers significant improvements in the retention of both rhodium and phosphorus in the fluorous phase. In the studies on the hydroformylation of 1-octene in neat PP2 at a range of temperatures between 70 and 90 °C under 20 atm CO/H_2(1:1) using the same catalyst with Rh:(**5b**) ratios of 1:3 and 1:10 gave conversions between 95% and 98% with *n*/*i* ratios of 3.0–6.3 (Table 2) [16,17]. Crucially, rhodium leaching levels as determined by ICPMS were excellent. For example, only 0.05% of the rhodium loaded could be detected in the product phase at the best regioselectivity (*n*/*i* 6.3; conditions rhodium:phosphine 1:10; 70 °C). Clearly, two beneficial aspects of the fluorous approach are working in tandem in these experiments. The low phosphine loading, 20 $mmol\,dm^{-3}$ (cf. 152 $mmol\,dm^{-3}$ used by Horváth et al. [15] to obtain the same level of regioselectivity), important for commercialisation in view of the cost of the perfluoroalkylated ligand, offers high linear regioselectivity without compromising the rate of the reaction whilst at the same time affording excellent retention of the catalyst in the fluorous phase.

At first glance, the comparable and higher partition functions of ligands (**6b**) and (**7a**) into the fluorous phase would be expected to offer enhanced catalyst retention, but the actual factors involved are not straightforward (Table 2). Rhodium leaching levels for the catalyst derived from (**7a**) are virtually identical to those from our

Table 2
Hydroformylation of 1-octene at 20 bar CO/H_2 (1:1)[a]

Phosphine	Conversion[b] (%)	Octane[c] (%)	Isom[c] (%)	Branc[c] (%)	*n*-Nonanal[c] (%)	*l*/*b*[d]	Rate constant[e] (s^{-1})	Rh loss[f]
5b	97.8	0.4	3.7	12.8	80.9	6.3	1.9	7292
6b	93.1	0.4	2.7	11.9	78.2	6.7	1.3	729
7a	98.5	0.4	3.3	16.9	77.9	4.7	2.5	7486

[a] Reaction conditions: solvent – PP2 (4 cm^3); temperature 70 °C; catalyst generated in situ from $[Rh(CO)_2(acac)]$ and ligand, Rh:P ratio 1:10; time – 90 min.

[b] Conversion (100% – % residual 1-octene).

[c] Percentage of product by mole fraction. Isomerised products generally >95% 2-octene; Branched products = 2-propylhexanal + 2-ethylheptanal + 2-methyloctanal, generally >95% 2-methyloctanal.

[d] *l*/*b* = ratio of linear to all branched aldehyde products.

[e] All reactions were found to be 1st order in [1-octene] to over 80% 1-octene consumption.

[f] Rhodium loss to the organic product as ppm by weight.

benchmark catalyst derived from (**5b**) whilst those for (**6b**) are significantly better. At the same time, whilst the regioselectivities and reaction rates for the catalysts derived from (**5b**) and (**6b**) are comparable, the reaction rate and regioselectivity for that derived from (**7a**) are higher and lower respectively [26,32]. The most reasonable explanation rests with the increased steric bulk associated with *meta*-perfluoroalkylation [29]. It is well established that several, related, species are known to exist under hydroformylation reaction conditions, including $[RhH(CO)L_3]$ (**I**), $[RhH(CO)_2L_2]$ (**II**) and $[RhH(CO)_3L]$ (**III**) [22,34]. Therefore, if the bis-*meta*-substituted ligand is sufficiently bulky, the catalyst rests with less phosphine ligands than that with the *para*-substituted ligands, and so higher reaction rates and lower selectivities would be expected [22]. Furthermore, there would be poorer catalyst retention in the fluorous phase, since the catalyst would have fewer fluorous ponytails: 8 (**II**; L = **7a**) cf. 9 (**I**; L = **5b**, **6b**) or 4 (**III**; L = **7a**) cf. 6 (**II**; L = **5b**, **6b**). Further experiments to validate this hypothesis and identify the catalytically active species under process conditions are underway.

3. Conclusions

By omitting the organic phase, hydroformylation of long chain alkenes using rhodium catalysts modified with perfluoroalkylated phosphine ligands can be carried out in perfluorocarbon solvents with high regioselectivities and rates of reaction. Studies of the electronic and solubility properties of such phosphines have shown that direct attachment of the perfluoroalkyl groups result in highly electron deficient phosphines together with better fluorous phase compatibilities. However, in the hydroformylation of long chain alkenes, it is clear that the actual factors leading to high regioselectivity and catalyst retention in the fluorous phase cannot be directly correlated with the measured properties of the free ligands.

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