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Ferrocenylmethylphosphanes and the Alpha Process for Methoxycarbonylation: The Original Story

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Abstract: The Lucite Alpha process is the predominant technology for the preparation of acrylics. This two-stage process involves the palladium-catalysed formation of methyl propanoate from ethene, CO, and methanol, followed by the oxidative formylation of methyl propanoate into methyl methacrylate. A range of *bis*-1,2-disubstituted aminomethylferrocenes has been prepared and characterised. These complexes serve as precursors to a variety of bulky ferrocenylmethyldiphosphanes that, in turn, function as ligands in the palladium-catalysed process. We describe the crystal structures of five ligand precursors and provide a rationale for their design. In situ catalyst testing on palladium complexes derived from ferrocenylphosphanes demonstrates that these are highly selective (>99.5%) catalysts for the formation of methyl propanoate from ethene, CO, and methanol and have turnover numbers exceeding 50,000. This article credits those researchers who worked on this project in the early days, who received little or no credit for their achievements and endeavours.

Keywords: ferrocene; phosphane; methoxycarbonylation; catalysis; ligand; palladium

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1. Introduction

This paper documents early work between 1996 and 2006 on the synthesis of ferrocene-based ligands for the so-called Alpha process [1–3]. This work remained unpublished because of circumstances prevalent at the time of completion. There have been some work presentations; we published two short communications on ligand synthesis [4,5]. However, this is the story of the ligands' synthetic development and use. This work brings together these reports [1–5] and adds previously unpublished material.

Figure 1 shows commercial routes to produce MMA (methyl methacrylate, methyl-2-methyl-2-propenoate). The first step in the two-step Lucite Alpha process [6] involves the palladium-catalysed production of methyl propanoate (MeP) from methanol, ethene, and carbon monoxide. In the second step, catalytic condensation of methyl propanoate and formaldehyde in a heterogeneous fixed-bed cerium oxide catalyst forms methyl methacrylate under anhydrous conditions [6,7].

Tooze et al. developed the first step of the Lucite Alpha process [8–11]; their scheme is a refinement of a polymerisation process developed by Drent et al. at Shell [12–15]. The Drent process is mechanistically complex, and involves the reaction of ethene and carbon monoxide to furnish alternating polymers (Figure 2).

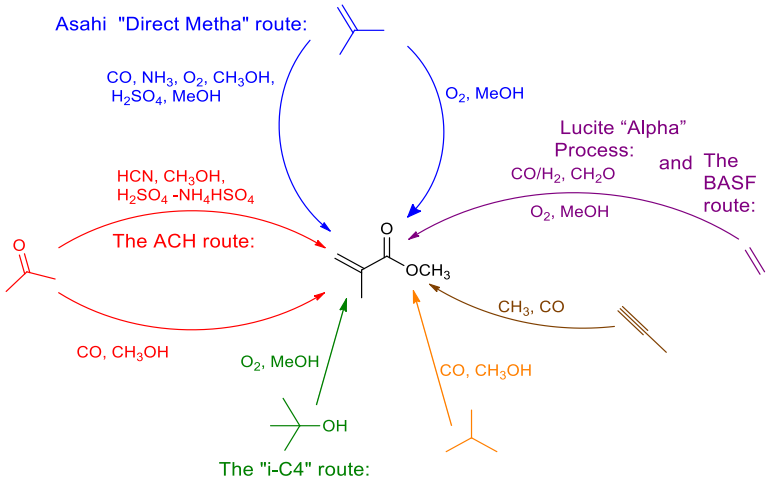


Figure 1. Commercial routes to methyl methacrylate and related acrylics.

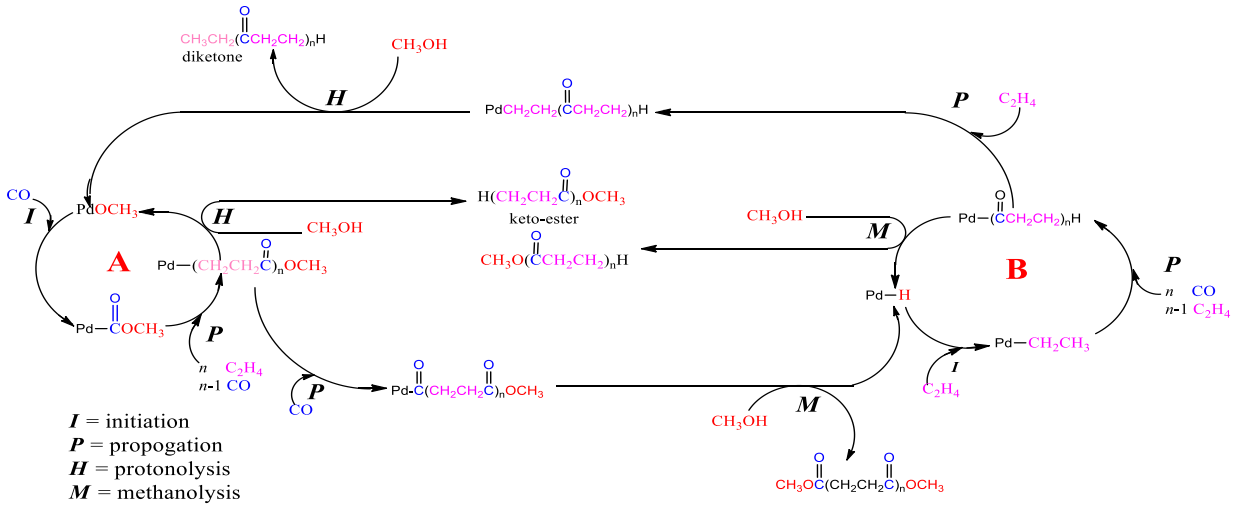


Figure 2. Products obtained from the palladium-catalysed reaction of ethene, carbon monoxide, and methanol according to Drent et al.

Since the initial development work on ethene–CO polymerisation by Drent, the mechanism of this process has been well studied [16–31]. Tooze et al. modified the process to produce methyl propanoate, which is the most straightforward "polymer" obtained after quenching with methanol, i.e., the process operates for one cycle only (Figure 3).

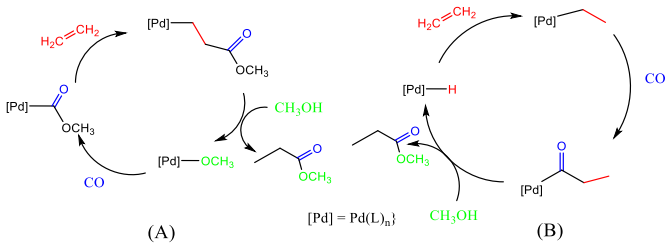


Figure 3. (**A**) Simplified carbomethoxy cycle and (**B**) simplified hydride cycle to methyl propanoate formation [8–10].

Eastham and co-workers [32] performed further mechanistic investigations specific to the Lucite process, and their results support and clarify much of the work by Drent. Their research has led to a complete understanding of the reaction mechanisms of hydroalkoxycarbonylation and carboalkoxycarbonylation reactions under industrial operating conditions [33–47].

Our group pioneered the preparation of ferrocene-based ligands for the methoxycarbonylation reaction of ethene, and we previously described the synthesis of ferrocene-based ligands—such as compound **2**—that are similar in structure to the Alpha ligand, compound **1** [5,6]. Butler and Greenwell developed the ligand synthesis in 1998, and the work was further developed by Fortune in a programme partially funded by INEOS Acrylics/Lucite International. "Traditional" ferrocene-based ligands such as dppf [(1,1′-*bis*-(diphenylphosphino)ferrocene] [48], and its permethylated analogue octamethyl-1,1′-*bis*-(diphenylphosphino)ferrocene (omdppf) [49], have applications in the methoxycarbonylation and polymerisation of ethene and styrene. Subsequently, many studies have used ferrocene-based ligands [50–56]. Comparing the complexes of different metals in catalysis is difficult because of the other possible coordination modes of palladium when the metallocene metal centre is non-innocent. For example, dppf-type complexes feature a dative interaction between the palladium atom and the metallocene metal centre (Figure 4). Given all the accumulated evidence available from mechanistic studies, a bulky and highly basic ligand design should favour the formation of low-molecular-weight esters.

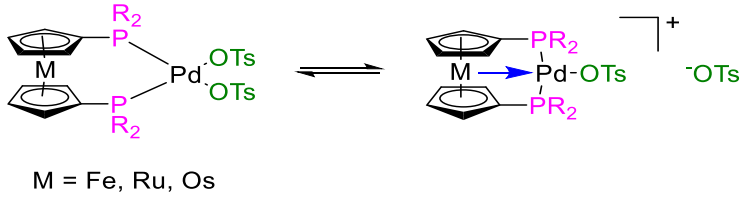
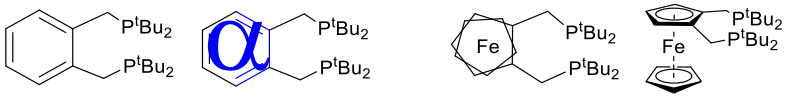


Figure 4. Non-trivial coordination of ferrocenylphosphine ligands with palladium: the dative iron–palladium bond.

The complete mechanism of the Alpha process was unknown when performing this work; since then, there has been a steady flow of research articles on the subject, with key articles by Heaton and Iggo [34–37]. The number of research papers has increased substantially since performing the original work. For this reason, the reader is directed to the large number of articles cited in three key review papers [7,56,57]. The most recent paper [57] brings together much of the academic–industrial work in the research area. In this study, we focus on original work on our ligands, which predates these mechanistic studies.

2. Ferrocene-Derived Alpha Ligands: Results and Discussion

Our original communications highlighted the preparation of a ferrocene ligand for application in the palladium-catalysed reaction of carbon monoxide, ethene, and alcohols. This is essentially the ferrocenyl analogue, **2a**, (*butphos*) of the Alpha ligand, 1,2-bis(di-*tert*-butylphosphinomethyl)benzene, **1** (Figure 5) [4].



1 **2a**

Figure 5. The Alpha ligand, 1,2-bis (di-*tert*-butylphosphinomethyl)benzene (**1**), with a top view of *butphos* (**2a**), its ferrocene-based equivalent.

Figure 6 shows a synthetic route to the formation of the ferrocene ligand, **2a** [2,4]. The 1,2-bis-dimethylaminomethylferrocene intermediate **5** was obtained in yields of approximately 90% and was purified via sublimation to provide a bright orange crystalline compound.

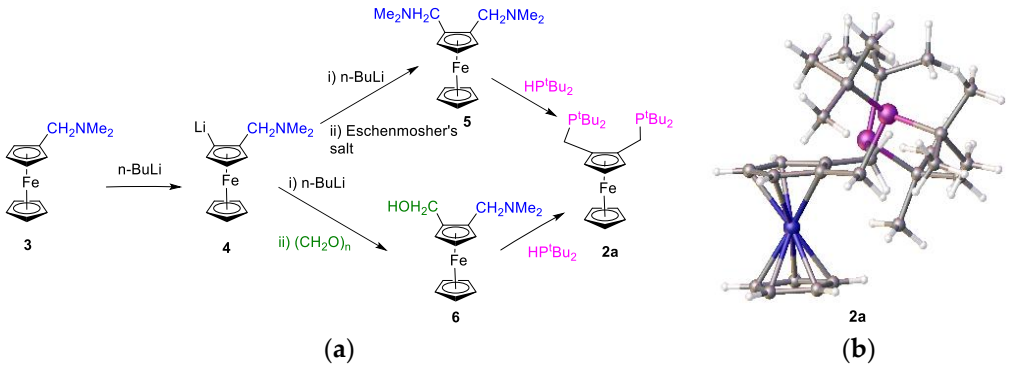


Figure 6. (**a**) Synthetic route to 1,2-bis-[di-(*tert*-butyl)phosphano)] ferrocene, *butphos*, **2a**, and (**b**) a view of the crystal structure of **2a**.

In the ^{1}H NMR spectrum of compound, **5**, there is a characteristic singlet at 2.17 ppm due to the magnetically equivalent N-methyl groups. In the second step of the synthesis, we applied Ugi's method to prepare the bis-phosphane **2a**. In the ^{31}P{^{1}H} NMR spectrum of **2a**, a single resonance at 23.80 ppm confirms that the two phosphane atoms are equivalent and are relatively basic.

In an alternative synthetic route, we used compound **7** as an intermediate to prepare 1,2,3-tris(tri-^{t}butylphosphinomethyl)ferrocene, **8**, (Figure 7) [2,5]. Compound **8** was prepared as the first 1,2,3-trisubstituted ligand for use in the Alpha process; we felt that a third phosphorus donor group might benefit the catalytic lifetime by introducing steric effects below the plane of the substituted cyclopentadienyl ring.

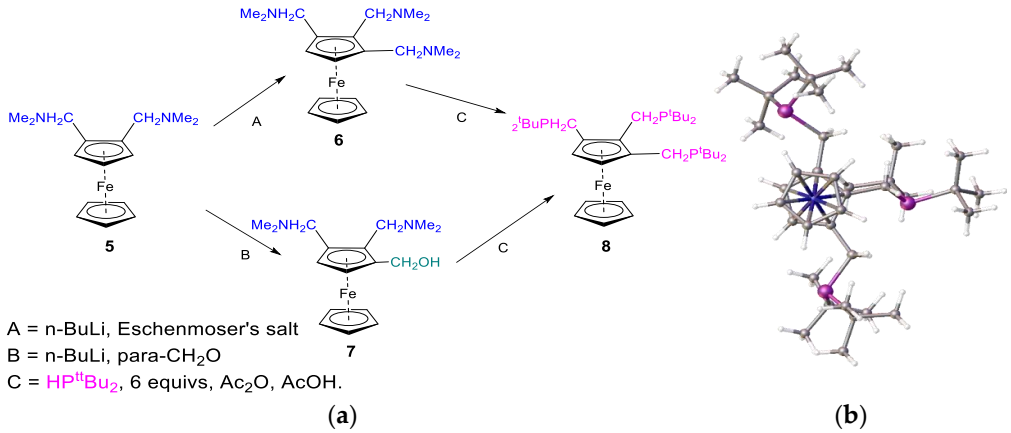


Figure 7. (**a**) Synthetic route to 1,2,3-tris-(tri-^{t}butylphosphino)ferrocene, **8**, and (**b**) crystal structure of compound **8** [4,5].

Compound **7**, an orange oil, was converted to tris-phosphane **8** as analytically pure yellow/orange powder (Figure 7). In the ^{31}P NMR spectrum of **8**, there are two resonances with a 2:1 integration ratio: the two outer phosphanomethyl groups (Figure 8) at 20.58 ppm, and the inner phosphorus slightly more upfield at 21.35 ppm. The crystal structure of compound **8** revealed a high degree of steric crowding due to the proximity of the six tert-butyl groups. The molecular conformation exhibits the outer phosphane groups, with one t-butyl group above the substituted cp-ring plane, while the other is below it. The inner-arm methylenephosphine methyl groups are located above the cp-ring plane, thus minimising steric crowding.

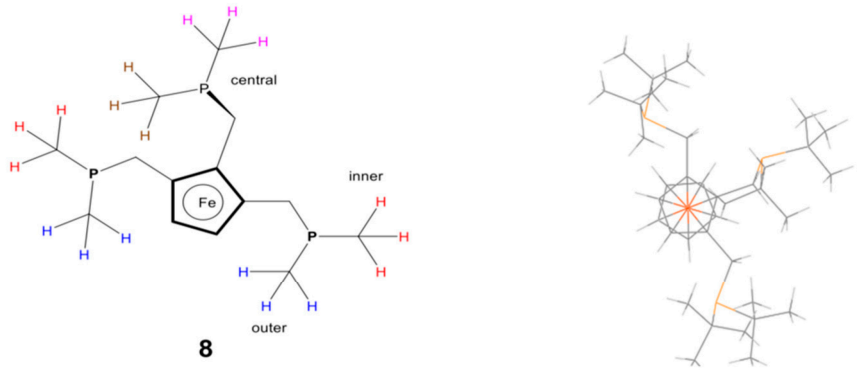


Figure 8. Tris-phosphane **8** from above the cyclopentadienyl ferrocene ring plane: (**a**) schematic and (**b**) stick diagram, obtained from the crystal structure of **8**.

One of the key targets in our ligand design process was the control of substitution of the unsubstituted ferrocenyl cyclopentadienyl ring. Greater control would allow changes in ligand basicity, and it would grant some additional steric control. There are several synthetic methods available to substitute the unsubstituted cyclopentadienyl ring. As reported by Hartwig et al., substitution at all positions on the cp ring is possible for simple mono-phosphino ferrocenes [58,59]. These authors modified some related ligands, including di-tert-butylphosphinoferrocene. We adopted this approach for the one-step synthesis of the less basic 6,7,8,9,10-penta-phenyl(diphenylphosphino)ferrocenyl, **10** (Figure 9); however, the yields were low. We also investigated the possible use of the N, N-dimethylaminomethylferrocene precursors in place of a phosphane, **9**. Still, we could not isolate any product because the ortho-metallated palladium complex does not undergo self-catalysis. Attempts to obtain amine **11** were unsuccessful; on the attempted lithiation of **12** with t-butyllithium, a deep green/blue solution formed, which reverted to starting materials upon attempted quenching.

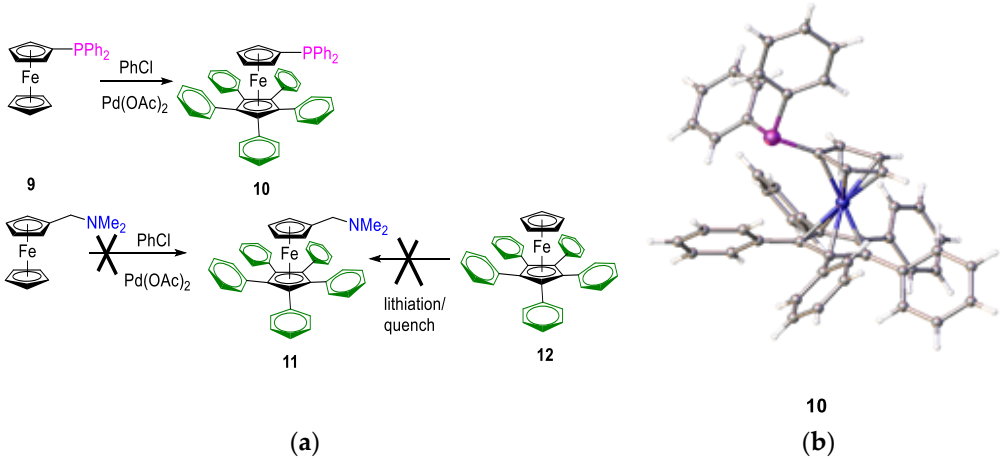


Figure 9. (**a**) Preparation of per-aryl-substituted ferrocenylphosphine **10**, from diphenylphosphino-ferrocene **9**, and the scheme showing the difficulty of preparing analogous ferrocenylethylamine, **11**, from either N,N-dimethylaminomethylferrocene or compound **12** using n-BuLi lithiation followed by quenching with Eschenmoser's salt. (**b**) crystal structure of compound **10**.

Because of these disappointing results, the work moved on to examine the preparation of more easily prepared silyl-substituted ligands. These were chosen based on results obtained from the concurrent catalytic reaction trials using palladium complexes of substituted conventional benzene-based ligands (standard Alpha ligands). The syn-

thetic route is shown in Figure 10, with the target precursors as silyl-substituted bis-(aminomethyl)ferrocenes, such as **17** and **20**.

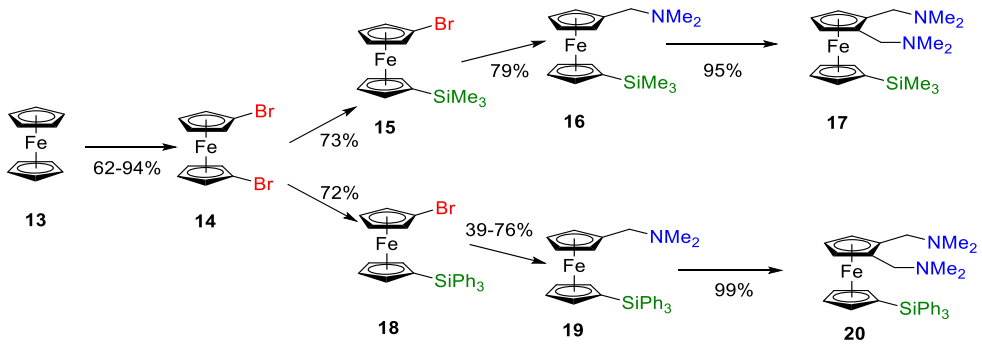


Figure 10. Preparative route to bulky alkyl- or aryl-sily-ferrocenylmethylamine ligands.

The synthetic route uses 1,1′-dibromoferrocene, **14**, as a key intermediate, as it is easy to prepare from ferrocene at high yields [60] Additionally, the tetra-substituted ferrocenes **22** and **24** (Figure 11a) were targeted as key precursors to bis-phosphanes. We had the requisite experience to make low-cost intermediates in this synthetic area [61,62].

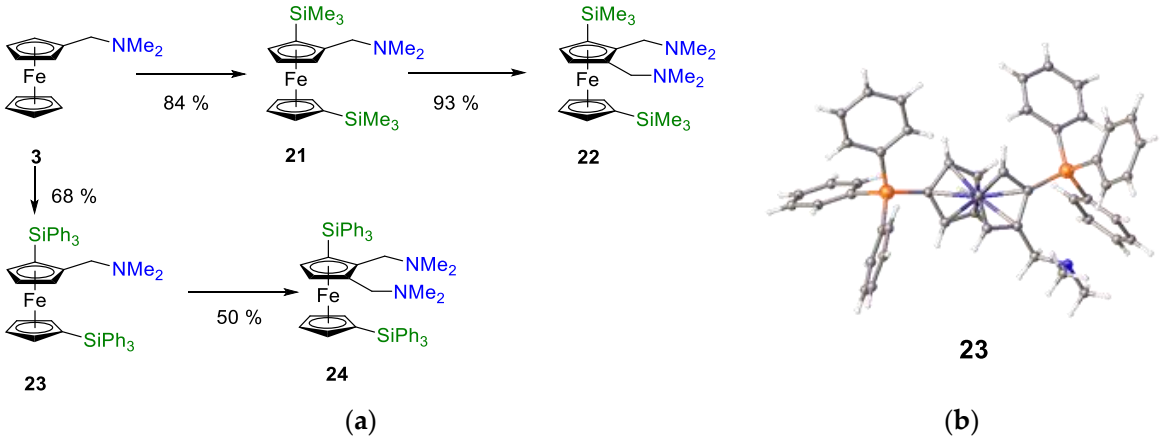


Figure 11. (**a**) Synthetic route to multiply substituted ferrocenyl-alkylamines. Individual reaction steps involve lithiation, followed by quenching with $ClSiPh_3$, $ClSiMe_3$, or Eschenmoser's Salt. (**b**) ORTEP diagram of 2-(N,N′-dimethylaminomethyl)-1,1′-bis-triphenylsilylferrocene, **23**. Ellipsoids are at 50% probability, and hydrogen atoms are removed for clarity.

We characterised compounds **22** and **24** and structurally determined compounds **23** and **24**. These compounds exhibit similar structures to the parent diamine, **5**; the bulky triphenylsilyl groups on the cp rings lay in a staggered geometry (calculated torsion angles Si1-C(cp1)-C(cp2)-Si2 = 148.2° (**23**) and 123.1° (**24**)). Both amine groups lay above the cp plane, with the methyl groups orientating to limit the overall angle that the amine could sweep with respect to the cp ring. The crystal structure of **5** superimposes that of compound **24**. The differences are only a few degrees of rotation of either amine group (Figure 12b) (data in Supplementary Materials).

The amine ligands can be reacted with nickel(II) halide salts at room temperature to produce the corresponding complexes. Thus, for example, the complex of precursor **24** was prepared, and its structure was determined. However, the tetrahedral coordination mode as exemplified by the nickel dibromide complex—**24-NiBr$_2$** (Figure 13)—rules out bis-amine nickel complexes as potential catalysts. Nevertheless, the structural data are important, and crystallographic data are available in the Supplementary Materials.

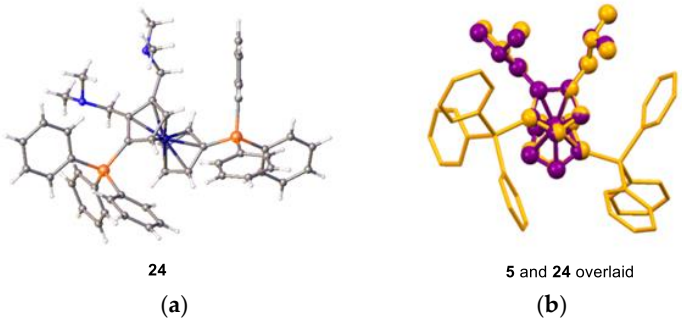


Figure 12. (**a**) ORTEP diagram of bis-2,3-(N,N′-dimethylaminomethyl)-1,6-bis-(triphenylsilyl) ferrocene, **24** (showing ellipsoids at 50% probability and the hydrogen atoms removed for clarity) and (**b**) image showing the close overlap of compounds **5** (purple) and **24** (orange), with the similar areas highlighted by balls.

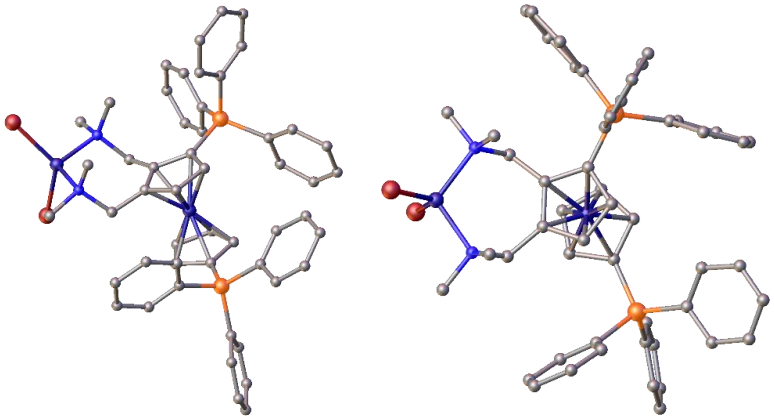


Figure 13. (**a**) Side and (**b**) top views of the tetrahedral $NiBr_2$ complex of the bis-methylamine precursor, **24**. This tetrahedral coordination of nickel is considered disadvantageous for methoxycarbonylation catalysis.

Synthetic data for all ligand precursors including compounds **2a**, **5**, **6**, **7**, and **8** [2–5]—are available in the Supplementary Materials.

Early results from catalytic trial reactions of the palladium complexes derived from the benzene-based standard Alpha ligand, and those of ferrocene ligand complexes, indicated the dynamics of the metal–ligand complex; flipping can occur between conformers A, B, and C (Figure 14). The polymerisation reaction—i.e., alternating ethene and CO insertions—may propagate from intermediate stage B rather than from single ethene insertions at A or C (Figure 15). There is more space around the palladium to accommodate the geometry required by substrate coordination and migratory insertion reactions.

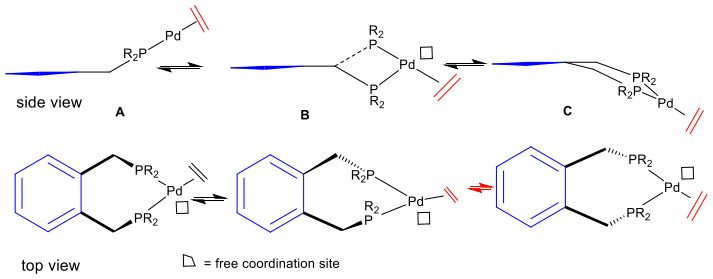


Figure 14. Conformational scheme for the Alpha ligand palladium complex, showing conformational flipping.

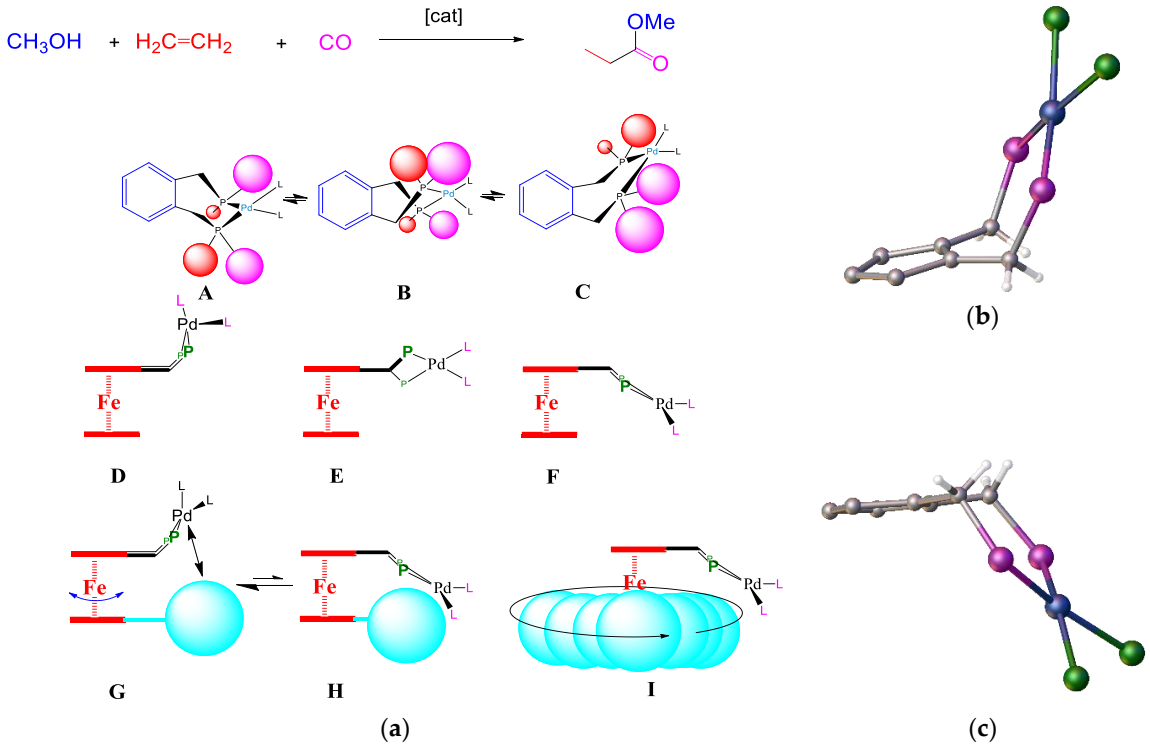


Figure 15. (**a**) Conformational flipping of **A**–**C** with the Alpha catalyst, and **D**–**I** with a ferrocenyl phosphane complex. At conformer **D**, the palladium sits above the cp ring. **E**,**F** show the flipping process. **G**–**I** show the steric blocking effect of a substituent on the bottom non-P ring. (**b**) flipping of Pd centre above Cp plan and (**c**) flipping below cp plane.

Thus, as described in the ligand modification section, the single bulky silyl-substituent attached to the unsubstituted cp ring would increase the lower cp ring's steric bulk. It is then possible to determine whether the rotation of the cyclopentadienyl ring would provide sufficient steric crowding (Figure 15a(G–I)). In summary, the rationale for using tri-alkyl- and tri-aryl-silyl substituents was because the synthesis of such compounds is straightforward and cheap, which is a prerequisite for an industrial-scale process. The silyl-substituted compounds **17** and **20**, prepared according to the schematic (Figure 10), were ideal precursors.

2.1. Catalyst Testing

The structure of the palladium dichloride complex of ligand **2a** was originally determined in 2004 from a crystal obtained via slow diffusion of petrol/ether into chloroform (Supplementary Materials). A more recent structure was crystallised from dichloromethane/petroleum ether (Figure 16, top and side views).

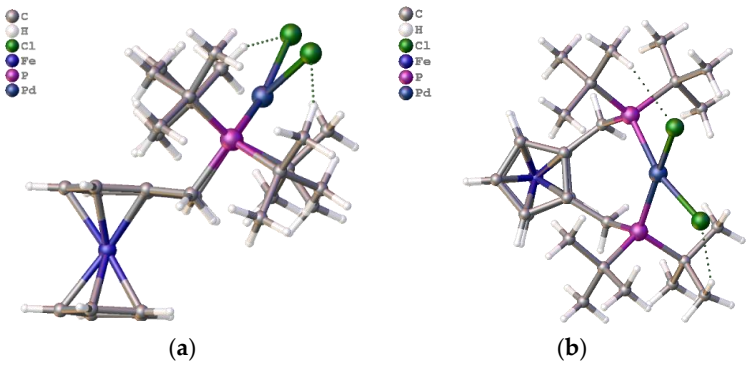


Figure 16. (**a**) Side view and (**b**) top view of palladium dichloride complex of *butphos*, **2a** [Pd(L**2a**)Cl_2].

In addition to our report, a further study was also published later by Claver et al. [63]. These workers reported the preparation of the complex from a sample of the ligand donated without our knowledge. The catalyst testing was performed concurrently with benzene-based ligands at Lucite International Ltd., Cleveland, OH, USA. The synthetic procedure was as follows: reactions of 1,2-bis-(N,N-dimethylaminomethyl)ferrocene, **5**, with a secondary phosphane were performed in acetic acid/acetic anhydride at 70 °C for 60 h. This methodology initially resulted in low (20–30%) yields of the bidentate phosphanes and, therefore, we developed an improved method. The improved method involved the reaction of a secondary phosphane with compound **5** at ca. 130 °C in a mixture of degassed acetic acid and acetic anhydride (9:1). The solvent was removed in vacuo, and the residue was stirred in methanol for 30 min. After removal of the methanol in vacuo, the residue was washed with ethanol. This preparation furnished a free-flowing solid of the adamantylphosphine-substituted derivative, with up to 83% yield. In Figure 17, drawings of bulky ferrocenylphosphanes, prepared in situ, are shown. These complexes were prepared and used under industrial conditions, and so complete characterisation data are unavailable. However, the synthetic methodology is available in the Supplementary Materials. The commercially available phosphane 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-adamantane was also reacted with **5** to provide the corresponding bidentate ferrocenylphosphane ligand, **2i** (Figure 17).

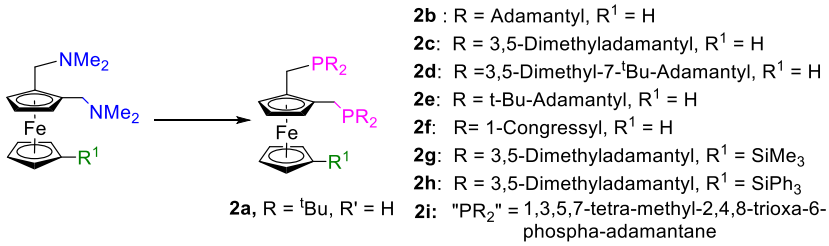
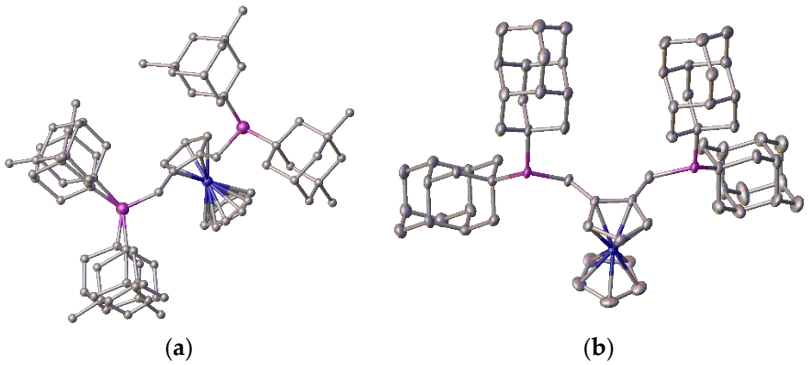


Figure 17. Examples of the bulky ferrocenyldiphosphines obtained from precursor **5** and the secondary phosphanes, HPR_2.

As examples, two of these bulky ligands **2c** and **2f** were characterised by crystallography, and are shown in Figure 18.



(**a**) (**b**)

Figure 18. Ferocenylbisphosphine ligands: (**a**) **2c** (3,5-dimethyladamantyl, local disorder in one pendant arm) and (**b**) **2f** (dicongressyl), showing the steric bulk of the phosphine substituents.

2.2. Catalyst Testing: Initial Evaluation of Ferrocene-Based Ligands vs. Alpha Ligand in the Palladium-Catalysed Formation of Methyl Propanoate from Ethene, CO, and Methanol

We continued catalysis development using the standard Alpha ligand palladium complexes in tandem with this work during the catalytic trials. We altered the experimental conditions throughout the study in order to accommodate improvements. Consequently, it is difficult to make direct comparisons except within individual datasets. The catalyst precursors generally were prepared in situ to reflect industrial conditions. We carried out

the coordination of the ferrocenyl phosphine ligand to palladium to form the active catalyst according to the method reported for diphenylphosphinopropane [64,65].

In a typical run, $[Pd(OAc)_2]$ (1.44×10^{-5} mol) was added to an autoclave, together with ligand 2 (7.61×10^{-5} mol) and 70% *w/w* methyl propanoate/methanol (300 mL) and methanesulphonic acid (140 × Pd equivalent). The autoclave was heated to 100 °C and maintained at this operating temperature for the duration of the experiment. Then, we repeated the procedure for each ligand, **1**, **2a**, and **8**. Table 1 shows the results from these initial trials over the first three hours.

Table 1. First catalysis trials for methyl propanoate formation from ethene, CO, and methanol using palladium(II) complexes of bidentate phosphane ligands (**1**, **2a**, and **8**).

Ligand	Run	Initial Rate (Moles Catalyst/Moles Product/h)	Turnover Number after 3 h
2a	1	31.810	59.941
	2	30.322	63.941
8	1	24.506	50.751
	2	32.884	50.751
1	1	29.106	44.775
	2	30.335	51.997

In all cases, the initial reaction rates for the benzene-based ligand (**1**) complex and the ferrocene-based complex (**2a**) are similar (circa 30,000 (mol cat.) $(\text{mol prod.})^{-1}$ h^{-1}). However, turnover numbers (TONs) for the ferrocene-based complex are significantly higher than those for the benzene-based analogues. The selectivity for the formation of methyl propanoate for the catalyst derived from ligand **2a** was always >99%; thus, these ligands are vastly superior to other ferrocene-based ligands, such as dppf (see [66] for an overview). The high turnover numbers for the ferrocenylphosphane-based catalysts resulted from the greater basicity of the ferrocenyl ligand and the difference in its bite angle. The fall in reaction rate, which occurred after three hours, was attributed to catalyst decomposition, possibly because of de-ligation of one of the phosphines from the metal centre. We used the palladium complex of ligand **8** to counter this; however, the turnover number was reduced, even though the maximum reaction rate was reached more quickly (8–10 min compared to 25 min). More comprehensive tests were carried out following these initial results, again, under the industrial operating conditions. Table 2 provides the results data as average weight gains for the complexes for standard Alpha **1** and *butphos* **2**a. There was no evidence of metal deposition in any of these runs, and all reaction solutions from the autoclave were pale green/yellow.

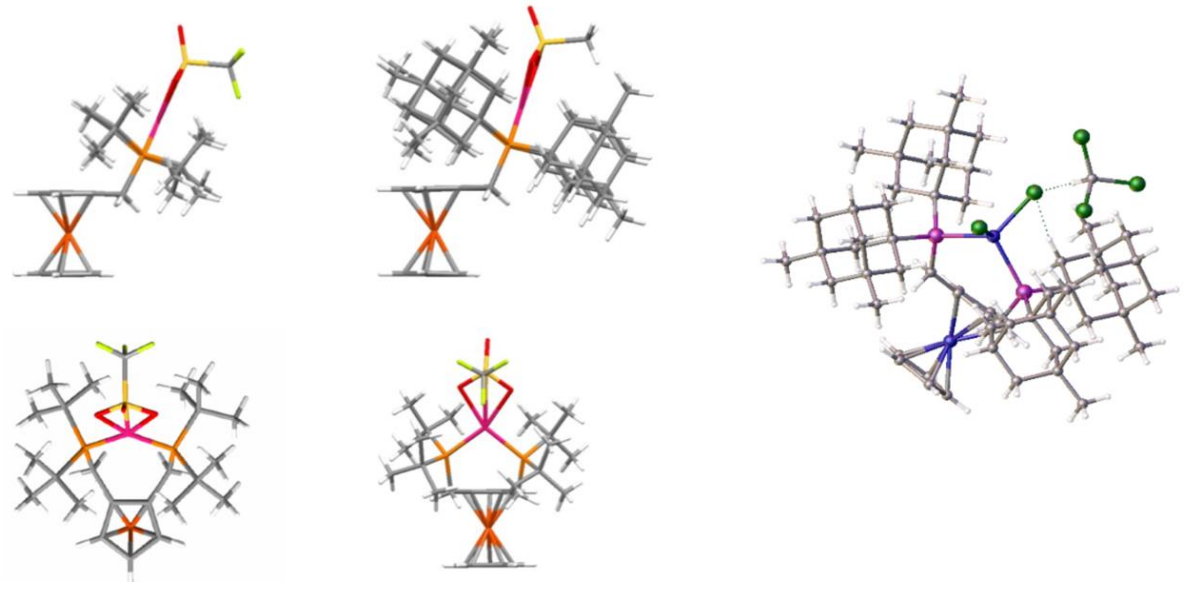
Table 2. The methoxycarbonylation of ethene using the alpha ligand, **1**, and *butphos*, **2a** *.

Ligand	Run	Weight Gain (g)	Average Weight Gain (g)	Turnover Number (TON)	Average (TON)
1	1	268.65	257.304	47,973	45,932
1	2	244.47		43,655	
1	3	258.98		46,173	
1	4	252.13		45,023	
1	5	262.29		46,837	
2a	1	302.64	300.90	54,042	53,731
2a	2	306.84		54,792	
2a	3	293.40		52,392	
2a	4	303.09		54,123	

* $Pd(OAc)_2$ (22 mg, 0.1 mmol) and its respective phosphane ligand (0.5 mmol) were weighed into a 500-mL, 3-neck, round-bottomed flask in an inert atmosphere glove box. On removal, we added 300 mL of degassed MeOH and stirred the mixture for 1 h. To this solution, methanesulphonic acid (140 µL, 2 mmol) was added, and the weight of the catalyst solution was recorded. The autoclave was charged with the solution and heated to 100 °C (3.0 bar vapour pressure), stirring at 1000 rpm. Introducing a gaseous mixture of CO:ethene (1:1) to the autoclave, to a total pressure of 13.0 bar, initiated the reaction. This provided a 1:1 ratio of ethylene to CO, with a total pressure of 10 bar above the solvent vapour pressure. The temperature and pressure were maintained and monitored for 3 h. After venting the gases, we cooled the unit to room temperature. The depressurised unit was emptied, and the final weight of the MeP solution was measured.

In this set of experiments, 0.1mmol of the palladium complex was used in neat methanol. The gas composition was 50:50 CO:ethene for all experiments. The use of neat methanol and relatively high palladium concentrations is generally optimal for high initial rates but accelerated catalyst decay can occur under these conditions. The palladium complex of the Alpha **1** standard gave rise to an average productivity after 3 h of approximately 257.3 g—or an average TON of 45,932. Independent research carried out by Lucite International has shown that average productivity is enhanced when bulky groups, such as tert-butyl, are attached to the 4-position, and increase the steric bulk of alpha ligands [64]. The disadvantage in benzene-derived Alpha ligand design (Figure 10), identified from crystallographic analysis of their palladium complexes, is that the Pd, P, and methylene atoms in the ligands lie approximately in the same plane of a square planar palladium(II) complex [65]. The benzene ring then tilts at 60–80 degrees to this plane, suggesting that the benzene ring can flip between three different positions: up, down, or one up and one down. This ring flipping can, in some cases, lead to ligand dissociation and, hence, catalyst decay. A study of complexes like [(P-P)$PdCl_2$] supports this, and the exchange of the CH_2 proton has been observed [65]. For the Alpha ligand, by adding steric bulk to the benzene ring, it is possible to influence the rate of the ring flipping and, consequently, retard the rate of catalyst decay. In the *butphos* ligand family **2a**, the average productivity after 3 h outperforms the Alpha standard, with an average weight gain of 300.9 g, or an average TON of 53,731.

Additionally, variable-temperature NMR analysis of 1,2-di-tert-butylphosphinomethyl ferrocene palladium complexes shows that the chemical shifts of CH_2 protons are essentially static at room temperature (see supporting information). Thus, the ferrocenyl ring is not flipping on the NMR timescale at room temperature. Finally, the conformation of the complexed ligand is confirmed by crystal structural data obtained from complexes of methanesulphonic acid salts of the ferrocenylphosphines (isolated during catalyst trials), as shown in Figure 19.



(**a**) (**b**)

Figure 19. (**a**) Typical "above the plane" coordination of palladium (there is a methylsulphonate bound to the palladium); (**b**) $NiCl_2$ complex of ligand **2c**. Figures supplied by I.R.Butler and P.N.Horton (data to be published).

The graphics in Figure 19a, which were prepared from crystal structural data, clearly show the palladium atom positioned above the plane of the ferrocene cyclopentadienyl rings. This positioning may be one reason for the improved activity over the standard Alpha ligand system and allows better steric control of the catalyst system. Even in the

nickel complex of ligand **2c**, the nickel lies above the cp plane (Figure 19b). However, in this complex, it was also clear that the steric crowding required for optimal catalytic performance was not present in the tetrahedral coordination mode. Finally, data were collected from the silyl-substituted ligand complexes and run again, compared with the Alpha standard. Table 3 presents the results from these experiments in tabular form.

Table 3. Pd-based catalysis with ferrocenyl phosphine ligand substituted on the lower ring with silyl groups. The graphic shows the palladium dichloride complex, 1′-triphenylsilyl-bis-1,2-(di-^{t}butylphosphinomethyl)ferrocene, and catalyst precursor.

Ligand	Run	Weight Gain (g)	Average Weight Gain (g)	Turn over Number (TON)	Average (TON)
1	1	64.0	60.25	79,365	74,714
1	2	56.5		70,064	
2g	1	59.6	59.6	73,908	73,908
2h	1	74.28	74.28	93,192	93,192

The average weight gains achieved with the trimethylsilyl-substituted ligand **2g** were low and did not significantly improve catalytic performance. However, the triphenyl-substituted ligand, **2h**, did show the expected improvement. In addition, the effect of increasing the steric bulk of the phosphine substituents on the catalysis rate did occur for the diadamantyl-substituted ligand **2b** and the bulky dimethyladamantylphosphinoferrocene **2c** (Table 4).

Table 4. Comparison of the Alpha ligand, **1**, and bulky adamantyl ferrocene ligands—**2b,** and **2c**—in the palladium-catalysed formation of methyl propanoate.

Ligand	Recycle Run	Wt. GAIN (g)	TON	Cumulative (TON)
1	1	246.13	43,952	
1	2	219.35	39,170	83,122
1	3	11.86	2118	85,240
2b	1	347.69	62,088	
2b	2	282.00	50,357	112,445
2b	3	179.80	32,107	144,552
2c	1	325.73	58,166	
2c	2	295.12	52,700	110,866
2c	3	271.50	48,482	159,348
2c	4	264.01	47,145	206,493
2c	5	191.10	34,125	240,618

These data show that the steric bulk on the ferrocenylphosphine increases the reaction rate and turnover numbers. In addition, the catalysts are recyclable, and give highly cumulative turnover numbers. In the case of ligand **2c**, the fall in reaction rate from the initial rate of 52,700 to 34,125 (approx. 58% of original activity) occurred on its fourth run with the same catalyst, making this a very stable catalyst. The palladium catalyst derived from the standard Alpha ligand had lost approximately 95% of its activity after two recycles. The catalyst derived from ligand **2b** also retained about 50% of its activity after two cycles. The adamantylphosphinoferrocene complexes had a much higher TON (approximately 40% increase) when compared to Alpha standards. We also compared some of the more sterically bulky ligands under identical catalytic conditions (Table 5).

From these data, the catalysts prepared from less bulky phosphines show high initial rates; however, the weight gain data show that the metal complexes with more bulky ligands perform better after 3 h. Finally, for completeness, the ruthenocenyl bis-amine analogue of compound **5**—compound **26**—was prepared and crystallographically characterised (Figure 20).

Table 5. Comparison of the lifetimes of catalysts derived from bulky ligands **2b**, **2c**, **2f**, and **2i**, with prototypic palladium dichloride complexes of ligands **1** and **2a**, under optimised conditions.

Ligand Used	Initial Rate (Moles MeP/Mole Pd/h)	Weight Gain (g) (3 h)
2a	73.000	307
2b	51.630	340
2c	61.000	-
2f	56.000	369
2i	50.000	282
1	78.000	307

(**a**) (**b**)

Figure 20. (**a**) Side and (**b**) top views of the crystal structure of the bis-methylamine of ruthenocene, compound **26**.

Although the basic structure of compound **26** is remarkably similar to that of compound **5**, with the amines both sitting above the cp ring, the actual macrostructures of the crystals used had rather different characteristics. Compound **25** was the starting compound [66–69]; it was only possible to obtain crystals of **26** as fine needles, generally clumped together. This clumping made the crystallography difficult, and the structure obtained indicated two molecules—the second with 15% occupancy—at a 53° angle to the first, and the second Ru atom sitting 1.4 Å away from the first (Supplementary Materials). However, the ligand precursor is isomorphic; we would expect similar reactivity of the metal complexes, with any differences caused by the relative stabilities of the complexes and the different electron donation properties of ruthenocene compared to ferrocene. The complex **27.PdCl$_2$** (Figure 21) was prepared in situ, and we compare its performance in the catalytic preparation of methyl propanoate to its ferrocenyl analogue **2a.PdCl$_2$**.

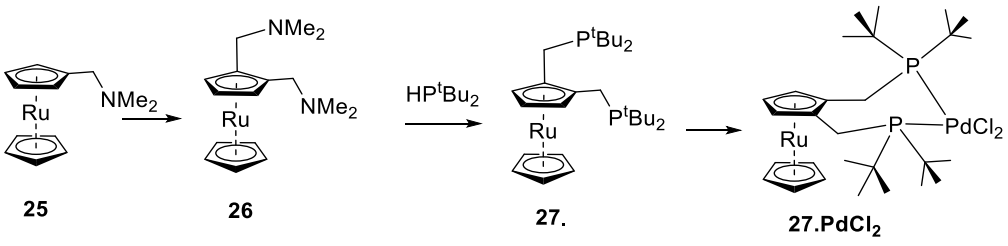


Figure 21. Schematic of the preparation of the 1,2-bis-(N,N-dimethylaminomethyl)ruthenocene, **26**, 1,2-bis-[di-(tert-butyl)phosphano)]ruthenocene, *rubutphos*, **27**, and the complex **27.PdCl$_2$** [69].

These data (Table 6) indicate that the average catalyst activity of the ruthenocene analogue of the catalyst again outperforms both catalysts **1.**PdCl$_2$ and **2a.**PdCl$_2$ under the reaction conditions used. The rationale for this is the improved stability of the ligand and its palladium complex under the operating conditions. These data were all produced pre-2006, and it is necessary to update the reader on more recent progress with ferrocene-based

ligands. We briefly discuss the reaction mechanism studies of the hydride and methoxy routes (Figure 22). Several reversible steps account for the incorporation of deuterium into the methyl propanoate part when d-methanol is a substrate for both cycles. Maintaining a strict square planar coordination leads to a congested environment around palladium when bulky ligands are present. In these mechanisms, there are many intermediates where there is a free coordination site where stabilisation by solvent will play a significant role. It would be interesting to see whether any deuterium ends up in the ligand because of the possible stabilisation of the metal centre by protons on the bulky ligands. The mechanism for our catalyst is more likely to follow the protonation route, given the strongly acidic conditions of our reaction environment.

Table 6. The individual and average weight gains and catalytic testing results for the palladium dichloride complex of 1,2-di-tert-butylphosphinomethyl ruthenocene, **27**. These are the same conditions used for **2aPdCl$_2$** (see Table 2).

Ligand	Run	Weight Gain	Avg Wt. Gain	TON/Pd	Avg. TON/Pd
27	1	54.44	——	67,509	——
27	2	50.38	52.41	62,475	64,992

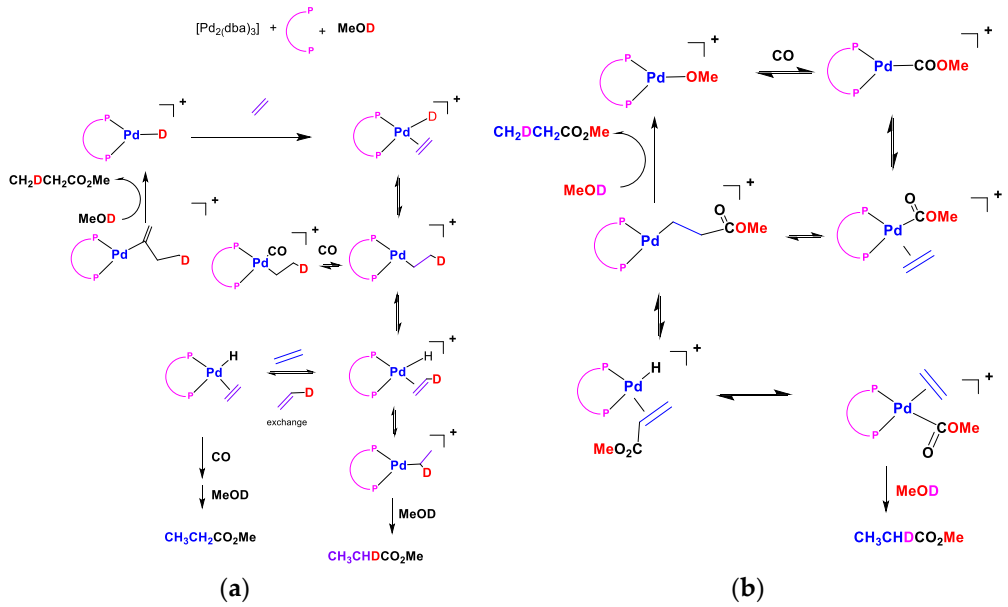


Figure 22. (**a**) The proposed hydride (left) and (**b**) carbomethoxy (right) mechanisms for the formation of methyl propanoate. The palladium complex of ligand 1 catalyses the CO, ethene, and MeOD. (amended from [44,57]).

Finally, it is prudent to update the reader on the work of Beller et al. [70–75] in this field, which is much more recent and detailed. These researchers have examined methoxycarbonylation using metal complexes of several adapted ferrocene-based ligands. These ligands generally contain phosphines substituted with t-butyl groups, such as compound **29** shown in Figure 23. These ligand types are essentially variants of those developed by Cullen et al. [76,77]. We had trialled some of these in early our work but discounted them because of their poorer selectivity. These tend to be sterically less congested around the metal centre in comparison to our ligands; however, they incorporate additional features due to the nature of additional functional groups, such as coordinating and protonation sites. However, clearly Beller et al. have championed these ligands and have reported excellent product yields. They have also incorporated adamantyl groups on the phosphorus similar to those in our ligand family thus adding additional steric bulk.

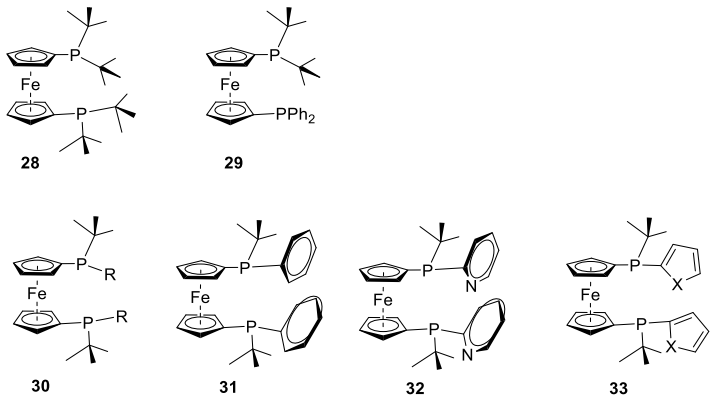


Figure 23. A small selection of the ferrocene-based ligands used in methoxycarbonylation, from the ligands developed by Cullen et al. (**28**: T-J. Kim; **29**: Butler), **30**, general ligand design; and **31**, **32**, **33**, ligands developed by Beller et al.

The inclusion of pyridyl substituents in the ligand design is a useful innovation. However, these would probably become protonated during catalysis, decreasing their solubility. It would be interesting to use the palladium complex of these ligands to isolate critical intermediates. In summary, they have shown that ferrocene-based ligands are extremely valuable in this research area, and numerous patents have come from their work. Thus, we have even more confidence that the ligands described in this paper are worthy of much deeper investigation, as are the new ligands under development within our group. A recent DFT study may help advance the mechanistic insights of this process [78]. Further synthetic details of in situ methods for phosphane preparation can be found in the Supplementary Materials.

3. Conclusions

This review/report covers the historical synthesis of ferrocenylmethylphosphines, which are important ligands in the preparation of methyl propanoate from ethene, CO, and methanol using the palladium-catalysed process, with >99% product selectivity. The research work was internationally leading at the time, but deemed less important in-house. Given that the Lucite Alpha process now dominates the acrylics industry, one can only speculate how this was allowed to happen, and how far this would have progressed in the interim if this had not occurred. This review credits those individuals who worked on the project but have received little or no recognition—in particular, the work of Dr. Kevin Morris, whose Ph.D. work appears in this report. Previously undisclosed catalysis results and structural data are contained in the present work. Further mechanistic work on the ferrocene-based catalysts has been carried out by Dr. Ian Butler (IRB), Professor Brian Heaton, Dr. Jonathan Iggo, and Dr. F. Zacchini; this has yet to be reported.

4. Patents

1. Butler, I.; Eastham, G. EP1554039A2 a catalyst system comprising a 1,2-bis-(phosphino)metallocene ligand1, novel carbonylation ligands, and their use in the carbonylation of ethylenically unsaturated compounds. US2010113255A1 (B2) • 6 May 2010 • Earliest priority: 2 December 2006 • Earliest publication: 5 June 2008;
2. Butler, I.; Eastham, G. a catalyst system comprising a 1,2-bis-(phosphino)metallocene ligand. EP1554039A2 (B1) • 20 July 2005 • LUCITE INT UK LTD [GB] Earliest priority: 12 September 2002 • Earliest publication: 25 March 2004;
3. Butler, I.; Eastham, G.R. Novel carbonylation ligands and their use in the carbonylation of ethylenically unsaturated compounds. ZA200903063B • 28 April 2010 • LUCITE INT UK LTD. Earliest priority: 2 December 2006 • Earliest publication: 7 October 2009;

4. Butler, I.R.; Eastham, G.; Fortune, K. a catalyst system comprising a 1,2-bis-(phosphinoalkyl) ferrocene ligand. CA2498293A1 (C) • 25 March 2004 • LUCITE INT UK LTD [GB]Earliest priority: 12 September 2002 • Earliest publication: 25 March 2004.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/inorganics9070057/s1: Crystal structural data for compounds included with deposition codes; experimental data for ligand preparation including previously reported compounds, and details of catalyst preparation (57 pages).

Author Contributions: The following lists the contributions made by each of the authors**:** K.M.F., performing synthetic experiments, data analysis, proofreading, and editing; C.M.R., crystallographic investigation; C.C. (nee Bünzli), ligand synthesis work; P.N.H., multiple crystallographic investigations, proofreading and data write-ups, depositions; M.E.L., crystallographic investigations; S.J.C., crystallographic investigation; M.W., catalyst formation and testing; W.C., crystallographic investigations and proofreading; R.W.H., crystallographic investigations; I.R.B., project conception, supervision, and planning, performing synthetic experiments, data analysis, manuscript writing, and proofing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Partial data is available in the thesis work reported as refs [2,3].

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Conflicts of Interest: The authors declare no conflict of interest.

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