NEW REACTIONS OF ALKENES

by

ALAN STEPHEN FRANK BOYD, B. Sc.

Thesis presented for the degree of
DOCTOR of PHILOSOPHY

University of Edinburgh

June 1974

Abstract

Part One describes a study of the palladium-assisted arylation of alkenes. After a historical introduction there is a review of the work of Moritani and other contributors in this field in investigating the synthetic and mechanistic behaviour of this reaction.

Experiments were performed in an attempt to determine the most useful oxidant for the regeneration in situ of Pd^{II} from Pd^{O} precipitated during the reaction. The criteria for choosing an oxidant are examined. Sodium dichromate was found to be the most efficient oxidant, but its efficiency was observed to be reduced at high concentrations. Some success was obtained from a reaction in which the oxidant was added dropwise to the mixture.

A brief series of experiments was carried out in an attempt to extend the synthetic scope of the reaction, but with limited success.

Mechanistic investigations were pursued and a series of reactions are described in which benzene and a substituted benzene competed for reaction with a limited quantity of styrene. Also a series of kinetic experiments is described in which an attempt was made to determine the absolute rates of reaction of various ring-substituted styrenes in reaction with benzene. Results from these indicate that the reaction bears a close similarity to electrophilic aromatic substitution but the reaction was thought to have complex kinetics. The kinetic behaviour of a suggested mechanism was then simulated with an analogue computer and the results were found to be in good agreement with observations made on the real system. This new evidence, together with the published results of other workers, tends to support an arylpalladium salt intermediate, and a review of the history and chemistry of this species is given.

Part Two describes free-radical induced addition of caprolactam to alkenes. The work was an attempt to devise a

short synthetic route to alkylated caprolactam and to investigate the likelihood of its polymerisation. However, although the reaction was moderately successful with 1-octene this proved not to be the case with other alkenes. The reaction gave almost invariably complex product mixtures from which the desired 1:1 adducts could not be easily separated. A pure sample of one such adduct was obtained but could not be induced to polymerise.

After reaction with cis, cis-1, 5-cyclooctadiene there was evidence that the product mixture contained a small amount of a cyclooctenyl adduct in addition to the expected bicyclooctyl adduct. This was unexpected and is believed to be the first time such an observation has been made.

Acknowledgements

I would like to record my thanks to various members of Edinburgh University Chemistry Department: to Professor J. I. G. Cadogan and Dr. I. H. Sadler for their encouragement and guidance throughout the research work; to Dr. A. J. Bellamy for advice and assistance with analogue computing; to Dr. T. A. Stephenson for palladium acetate and palladium chloride, and advice on organometallic chemistry; to Dr. J. T. Sharp for instruction in the operation of the MS 20 spectrometer; to Mrs. Madelaine Groves for instruction in the operation of the R-10 and HA-100 spectrometers and, together with Mr. John Millar, for n. m. r. spectra; to Mr. David Thomas for mass spectra and Mr. Brian Clarke for elemental analyses. I would also like to thank my other colleagues in the Chemistry Department for valuable and stimulating discussions on various practical and theoretical aspects of the work described in this thesis. I thank Mrs. C. G. Ranken for her skill and patience in typing the manuscript and Mr. Colin Baxter for the photographs.

I would also like to thank Dr. R. H. Hall of the British Petroleum Company's Epsom Research Centre for his interest and for samples of n-eicosane, 1, 5-hexadiene and caprolactam. I thank the British Petroleum Company Ltd. for the generous award of a Studentship during the tenure of which this work was carried out.

FOR MY FAMILY

CONTENTS

Page

PART ONE

PART TWO

PART ONE

Palladium-Assisted Arylation of Alkenes

INTRODUCTION : CONTENTS

INTRODUCTION

1. HISTORICAL DEVELOPMENT

In March 1894 Francis C. Phillips presented a dissertation[1] concerning methods of analysis of the natural gas from Western Pennsylvania. Among his observations was: "The reaction between palladium chloride and ethylene leads to the production of aldehyde." He also noted the precipitation of the metal as a black powder during this reaction.

In 1933 Ogburn and Brastow published a short account[2] of a method of estimating and separating palladium from a mixture of the other platinum metals. The separation was specific and quantitative, and achieved by passing ethylene through an aqueous solution of the mixed chlorides, upon which the palladium precipitated as a black powder.

These two independent reports went unremembered until 1956 when work was started by a group led by Jurgen Smidt, of the Consortium für Electrochemische Industrie G. m. b. H., which culminated in the Wacker Process,[3,4,5] (Wacker-Chemie being the parent company). This produced acetaldehyde continuously from ethylene and air using Phillips' reaction, with the vital addition of a recycling, oxidation step for the palladium. It may be described by the following sequence of reactions:

$$C_2H_4 + PdCl_2 + H_2O \longrightarrow CH_3CHO + Pd + 2HCl$$

$$Pd + 2CuCl_2 \longrightarrow PdCl_2 + 2CuCl$$

$$2CuCl + \tfrac{1}{2}O_2 + 2HCl \longrightarrow 2CuCl_2 + H_2O$$

Scheme 1-1

This gives a net reaction thus:

$$C_2H_4 + \tfrac{1}{2}O_2 \xrightarrow{PdCl_2,\ CuCl_2} CH_3CHO$$

Hitherto, the stoichiometric consumption of the rare and expensive palladium compounds to produce the commonplace and cheap acetaldehyde was not even considered worthy of a mention in 'Beilstein'[3]. The realisation that by adjusting the conditions enabled the palladium salts to be used catalytically instead of stoichiometrically promoted an explosive growth in the study of the interaction of olefins and other unsaturated compounds, with transition metals, notably palladium.[6]

It was suggested that nucleophilic attack on an ethylene-palladium chloride complex[4] might be the essential step in the Wacker Process, and this prompted van Helden to investigate the possibility of nucleophilic attack on palladium-complexed aromatic compounds.[7] To his surprise, biaryls were found in the reaction mixture. He also noted the need for acetate in the reaction. Davidson and Triggs also reported this reaction[8, 9] and, by analogy with work on other metal-aryl interactions, suggested the intermediacy of a σ-bonded palladium-aryl complex.

Then, in a series of short communications,[10-15] Moritani and his colleagues published details of a reaction apparently combining the essential features of the two types already mentioned. After boiling a solution of benzene, styrene and palladium acetate in acetic acid for eight hours they obtained a high yield of stilbene,[11] the addition product of benzene and styrene. They went on to show the broader applicability of the method[14-18, 21, 26, 27] and how it was possible to obtain some measure of palladium recycling by the addition of cupric or silver acetate, and oxygen or air.[13, 15]

Almost at the same time R. F. Heck published a series of papers[28-34] in which he described a reaction, apparently similar, in which the aryl part was in the form of an aryl-mercury salt. He also described palladium recycling procedures. More recently, Shue,[35-37] Norman[38] and Selke[39] have reported significant results in this field, details of which may be found in Sections 3 and 5, (pages 4 and 14).

2. THE PALLADIUM ASSISTED ARYLATION OF ALKENES

The direct, one step attachment of an aryl group to an alkene is a reaction that has obvious attractions for the organic chemist. If it can be carried out using a catalytic quantity of the essential palladium salt, and be tolerant of a wide range of chemical structure and reactivity in the starting materials, then an important and useful new synthetic method will have been developed.

The reaction reported by Moritani[15] may be written in its most concise form thus:

$$\mathrm{ArH + RCH{=}CH_2 + Pd(AcO)_2 \xrightarrow{AcOH} RCH{=}CHAr + Pd + 2AcOH}$$

It represents oxidative coupling of the two reacting organic species and concurrent reduction of the metal from $\mathrm{Pd^{II}}$ to $\mathrm{Pd^{o}}$. It represents a new type of reaction, clearly related to earlier organopalladium reactions but significantly different, as a consideration of the reacting species will show.

From the same reaction mixture, less the alkene, it has already been noted that van Helden obtained biaryls.[7] He favoured the use of a palladium chloride - sodium acetate mixture instead of palladium acetate but Davidson successfully used the latter in a similar aryl coupling reaction.[8] Moritani found that the salt mixture used by van Helden was also effective in alkene arylation.[11, 12, 15]

From the same reaction mixture, less the aryl compound, Kharasch reported that no reaction occurred. He was the first to successfully prepare an alkene-palladium salt complex and his method, which is still used, involves the prior preparation of a benzonitrile-palladium salt complex,[40] (Scheme 2-1):

$$\mathrm{PdCl_2 + Ph\,CN \longrightarrow (PhCN)_2{\cdot}PdCl_2}$$

$$\mathrm{2(PhCN)_2PdCl_2 + 2RCH{=}CH_2 \longrightarrow (RCH{=}CH_2{\cdot}PdCl_2)_2 + 4PhCN}$$

Scheme 2-1

The $PdCl_2$-alkene complexes are only moderately stable. They readily decompose on heating, or in solution, and slowly decompose in the solid state at room temperature liberating the alkene. Although the chloride complexes mentioned above are well known, an acetate complex of similar constitution has not been isolated.[41]

Despite these observations, the arylation of alkenes in the presence of palladium acetate, as reported by Moritani does occur. Apart from arylated alkenes the only by-products reported were a few per cent of acetoxylated alkenes. No biaryl was detected.[15] Palladium acetate was found to be the most useful salt for this reaction, although a mixture of potassium acetate and palladium chloride, in a molar ratio of 20 to 1, was also used but with less success.[11, 15] The alkene was present in equivalent quantity to the palladium salt, and the aromatic species present in one hundred-fold excess. Acetic acid was also present in similar quantity, and found to be essential for the reaction to occur. The product was always formed by the aryl substitution of a hydrogen on the least substituted carbon atom of the double bond.[12, 15] Yields of the order of 60% to 90%, based on alkene, were observed but could be much lower depending on the state of crowding of the double bond. Examples of this are shown in Table 2-1.

Table 2-1. Reaction of phenyl substituted ethylenes with benzene, in the presence of palladium acetate.[14, 15]

Alkene	Product	Yield %
Styrene	trans-stilbene	90
1, 1-diphenylethylene	triphenyl ethylene	72
trans-stilbene	triphenylethylene	28
triphenylethylene	tetraphenylethylene	13

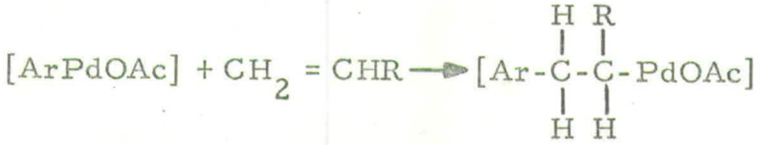
3. RELATED ARYLATION REACTIONS

In addition to the reaction first noted by Moritani,[15] several other alkene arylation procedures using palladium salts have been reported. While products and palladium salts have generally been similar to those used by Moritani, the aryl reactant has in each case been modified.

The most investigated of these reactions is that reported by Heck.[28-34,42-44] In this, an aryl-mercury salt is mixed with the alkene and the palladium salt in a suitable solvent. After a reaction time, ranging from a few minutes to several hours, a yield, ranging from a few percent to quantitative, of arylated alkene is obtained. Apart from hydrocarbon alkenes[28, 33] many other unsaturated systems have been arylated, including unsaturated esters, allylic alcohols[29] and halides,[30] enol esters, vinyl ethers and halides,[31] and even carbon monoxide.[34] The important step in this reaction is said to be a metal exchange reaction.[28] The arylmercury salt reacts with the palladium salt to form a reactive arylpalladium salt:

$$\mathrm{ArHgOAc} + \mathrm{Pd(OAc)_2} \longrightarrow [\mathrm{ArPdOAc}] + \mathrm{Hg(OAc)_2}$$

(Aryl lead and aryltin compounds have also been used in place of aryl mercury salts, but with less success[32, 33]). This then reacts directly with the alkene giving an aryl alkylpalladium salt:



$$[\mathrm{ArPdOAc}] + \mathrm{CH_2} = \mathrm{CHR} \longrightarrow [\mathrm{Ar}-\overset{\mathrm{H}}{\underset{\mathrm{H}}{\mathrm{C}}}-\overset{\mathrm{R}}{\underset{\mathrm{H}}{\mathrm{C}}}-\mathrm{PdOAc}]$$

which loses the elements of acetic acid, and palladium to give products:

$$[\mathrm{Ar}-\overset{\mathrm{H}}{\underset{\mathrm{H}}{\mathrm{C}}}-\overset{\mathrm{R}}{\underset{\mathrm{H}}{\mathrm{C}}}-\mathrm{PdOAc}] \longrightarrow \mathrm{ArCH{=}CHR} + \mathrm{Pd} + \mathrm{HOAc}.$$

Precipitated palladium has been recycled by using cupric salts as oxidants.[28]

The predominant product is the one which is formed with the least steric interaction, though other expected products have been detected, depending on reactants and conditions. No kinetic studies have been published but much work has been done on determining minor products, investigating electronic, steric, and solvent effects,[42,43] and extending the scope of the reaction.[28-34,44] It has been found that steric factors predominate in determining the products formed, with electronic and solvent effects of much less importance. No investigation into the nature of the vital aryl-palladium salt intermediate has been published.

Selke[39] and, independently, Garves[45] have described reactions in which arylsulfinic acids are treated with palladium salts. In a suitable solvent and in the presence of alkenes, arylation takes place. Again, the formation of an aryl palladium salt is postulated:

$$\mathrm{Ar\,SO_2Na + Na_2PdCl_4 \longrightarrow [ArPdCl] + SO_2 + 3NaCl}$$

As before, it reacts with the alkene giving the arylation product:

$$\mathrm{[Ar\,PdCl] + CH_2 = CHR \longrightarrow ArCH{=}CHR + Pd + HCl}$$

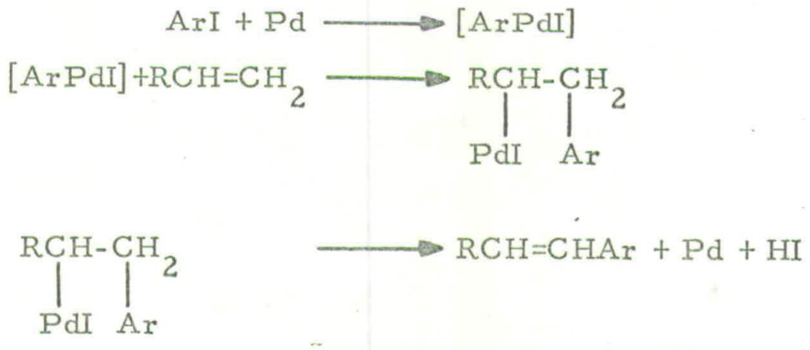
Addition of mercuric chloride to the reaction mixture was found to improve the yield, implying a close relationship to the reaction reported by Heck. Again, the palladium was recycled by cupric chloride.

More recently Kikukawa[46,47] has described an arylation reaction using bis(triphenylphosphine)palladium acetate. If this complex is heated in a suitable solvent with an alkene a mixture of arylated alkenes is obtained.

$$\mathrm{[P(Ar)_3]_2\,Pd(OAc)_2 + CH_2{=}CHR \longrightarrow Pd + ArCH{=}CHR}$$

It was found that the triarylphosphine need not be bonded to the palladium salt before reaction, as a mixture of alkene, phosphine and palladium acetate also gave the arylation products. Although mechanistic details are vague it seems as if an aryl palladium salt is yet again involved. The fate of the dearylated phosphine is undetermined. A most significant common factor to all the reactions described above is the formation of biaryls in the absence of alkene, and the almost complete absence of biaryls in the presence of alkene. This is also the case in the reactions described by Moritani.[15]

Heck,[48] and independently Mizoroki,[49] have recently reported a further variation on the palladium assisted arylation of alkenes. An aryl halide, typically an iodide, was caused to react with an alkene (e. g. styrene) in the presence of a catalytic quantity of palladium acetate. In the simplest case a 75% yield of stilbene was obtained from iodobenzene and styrene after two hours at 100° in the presence of only 0. 01 equivalents of palladium acetate. The reaction is said to proceed thus, (Scheme 3-1):



$$ArI + Pd \longrightarrow [ArPdI]$$

$$[ArPdI] + RCH{=}CH_2 \longrightarrow \underset{PdI}{RCH}-\underset{Ar}{CH_2}$$

$$\underset{PdI}{RCH}-\underset{Ar}{CH_2} \longrightarrow RCH{=}CHAr + Pd + HI$$

Scheme 3-1

As can be seen, an aryl palladium salt is again invoked as an intermediate. It is, however, more important to note that the initial palladium species is the metal, Pd^0, said to be produced by in situ reduction of the acetate by the alkene. Since palladium metal is produced at the end of the reaction, no oxidants are necessary for recycling and the reaction is truly catalytic in palladium. Phenyl, benzyl and styryl halides all undergo this reaction, but in all cases use of the more labile halogens, bromine, or usually, iodine is necessary. A possible limitation of the reaction is the necessity for a base to neutralise hydrogen halide formed by the final step of the reaction. Potassium acetate and tri-n-butylamine have been used for this purpose.

Further work on these last two reactions has been reported by Heck[100], and by Julia[101] who have used palladium supported on carbon as the source of the metal.

4. MECHANISTIC INVESTIGATIONS

The very rapid development of organo-palladium chemistry, particularly for industrial use, has led to the creation of a large gap between the successful application of the reactions and the understanding of the basic chemical steps involved. Various methods and processes have been devised and conditions optimised, largely empirically. Theoretical considerations on the other hand have floundered in a morass of confusing and often contradictory kinetic and other data. In particular, the choice of reaction medium, i. e. aqueous or non-aqueous, low pH or neutral solution, presence or absence of chloride or acetate etc., seems to lead to quite large differences in what products are formed and their yields.[6,50] Largely due to all this the theoretical foundation of the palladium assisted arylation of alkenes is somewhat uncertain.

Moritani and his colleagues were the first to perform mechanistic studies[14,16-18,20,22-25] on the palladium assisted arylation of alkenes, though latterly Shue[35-37] and Norman[38] have made valuable observations, which are described later on.

Much information can often be obtained by studying the effect on a reaction of the incorporation of various substituents into the same basic starting materials. Moritani has studied the effect of various substituents on both the alkene[16,18,20,22-24] and the aromatic[14,17] compound. More recently Shue has studied the effect of deuterium substitution on the two reacting species.[36]

4A REACTIONS OF STYRENE WITH SUBSTITUTED BENZENES

Styrene was chosen by Mortani because of its previously noted[15] high reactivity in this reaction. It was caused to react with various monosubstituted benzenes.[17] The most important results from this work were obtained from a series of competition reactions. In these, a limited quantity of styrene was allowed to react with a large excess of an equimolar mixture of benzene and

Table 4-1. Competition reaction of Styrene with Benzene and Monosubstituted Benzenes.[17]

$$PhCH{=}CH_2 + PhH + C_6H_5X \xrightarrow{Pd(OAc)_2} PhCH{=}CHPh + PhCH{=}CH\ C_6H_4X$$

X	Yield (%) stilbene	Yield (%) subs. stilbene	Isomer distribution (%)			Partial Rate Factors			Overall Reactivity Ratio $^{kX}/_{kH}$
			o	m	p	f_o	f_m	f_p	
CH_3	36	26	4	0	96	0.08	0.	4.2	0.72
C_2H_5	35	23	0	0	100	0	0	3.9	0.66
Cl	34	20	5	25	70	0.09	0.4	2.5	0.59
NO_2	38	19	0	100	0	0	1.5	0	0.50

All reactions were carried out at 90°. All yields are based on starting styrene. In Moritani's report[17] some of the partial rate factors were erroneously calculated.

a substituted benzene. The product mixture from such a reaction gives the following information: firstly, the overall reactivity ratio of the two aromatic compounds (from the ratio of the quantities of substituted products to unsubstituted product); and secondly, the reactivity of the various sites on the substituted benzene. The latter information is obtained by considering the isomer distribution of the substituted products in conjunction with the overall reactivity ratio, and is expressed as a partial rate factor, f_{ortho}, f_{meta} and f_{para}. (A partial rate factor is defined as the ratio of the reactivity of the site on the substituted benzene to the reactivity of a single site on unsubstituted benzene).[51] Moritani's results are shown in table 4-1, opposite.

From these results Moritani drew the surprising conclusion that, since the presence and nature of substituents on benzene "had no effect on reactivity,"[17] bond formation to this species could not be the rate determining step. This was despite the fact that in the same paper appear results of the addition of styrene to chlorobenzene which show a quite striking variation of isomer distribution and yield with apparently small changes in reaction conditions. These results are summarised in Table 4-2.

Table 4-2. Reaction of chlorobenzene with styrene.[17]

$$PhCl + PhCH{=}CH_2 \longrightarrow PhCH{=}CH\ C_6H_4Cl$$

Chlorostilbene Isomer Distribution (%)			Chlorostilbene Yield (%)	Palladium Salt	Temperature
o	m	p			
5	25	70	20	$Pd(OAc)_2$	90° *
19.4	32.3	48.4	62	$Pd(OAc)_2$	110°
28.6	34.3	37.1	35	$PdCl_2$+NaOAc	110°

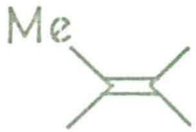
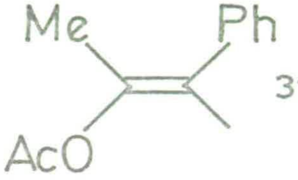
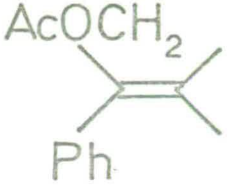
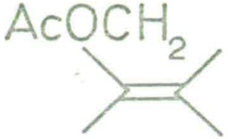
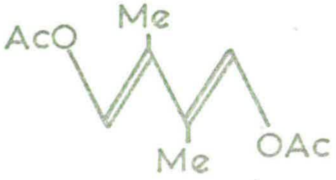
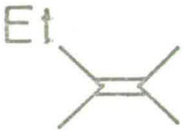
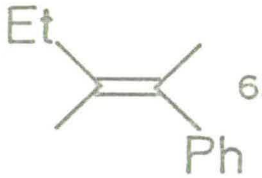
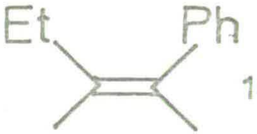
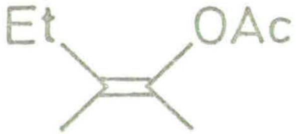
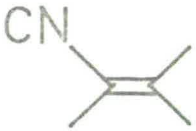
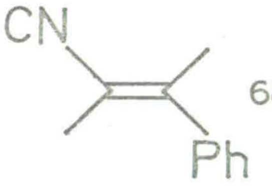
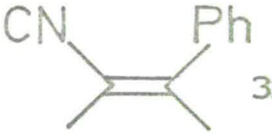
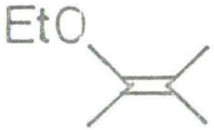
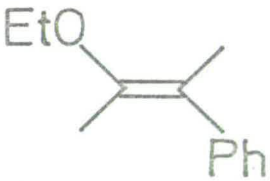
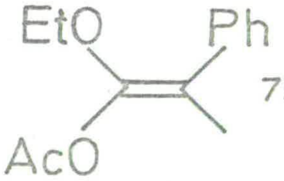
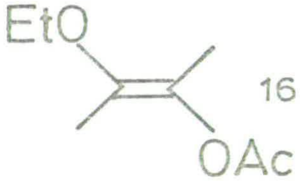
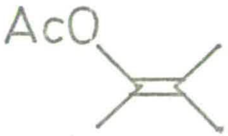
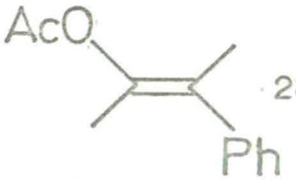
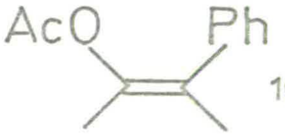
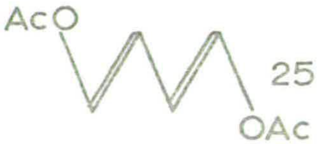
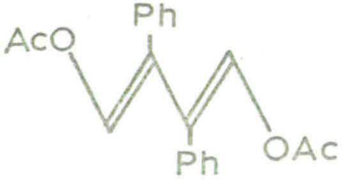
* Equimolar PhH/PhCl

Moritani does not comment on these results. Apart from the differences as noted in the table, the reaction conditions and quantities, and analytical procedure are similar for all three reactions. It is likely that the discrepancies arose through the use of column chromatography as the analytical technique, and that some of the components of the fairly complex mixture were imperfectly eluted.

Shue has also studied the phenylation of styrene[35-37] and has found a significant kinetic isotope effect following competitive reaction of benzene and hexadeuterobenzene.[36] Thus, from a reaction mixture containing styrene and an excess of an equimolar mixture of benzene and hexadeuterobenzene, a mixture of stilbene and pentadeuterostilbene was obtained in the ratio of 5.3 to 1. A similar value was obtained for the rate ratio from independent absolute rate determinations. These findings thus tend to contradict those of Moritani,[17] since an isotope effect of this size indicates that the aromatic species is indeed involved in the rate determining step of the reaction.[52]

4B REACTIONS OF BENZENE WITH SUBSTITUTED ALKENES

A varied assortment of substituted alkenes were selected for investigation by Moritani.[16, 18] The results he obtained are shown in Table 4-3. In each case the products mentioned were derived from reaction with excess benzene in acetic acid using an equimolar quantity of palladium acetate to alkene. Gaseous alkenes were bubbled into the mixture at atmospheric pressure. Evidently, in many cases side reactions predominated. In fact only three of the eight alkenes studied underwent phenylation as the major reaction pathway. In the case of propene and 1,3-butadiene, formation of π-allyl complexes with the palladium is possible. Such complexes are known to be stable and their formation might possibly inhibit reaction with the aromatic compound. Moritani found[16] that under the same reaction conditions a complex of this type, μ-dichloro-bis (π-1-acetoxy methyl allyl) palladium-(II), (4-1), gave rise to products

Alkene	Product Distribution %								Total Yield %
		31		11		20		36	32
		63		16		15		3	21
		68		32					25
		9		75		16			13
		28		16		25		31	

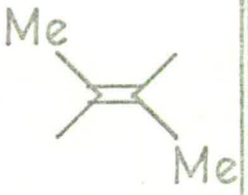
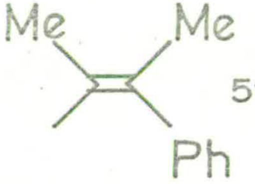
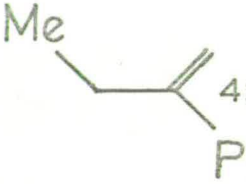
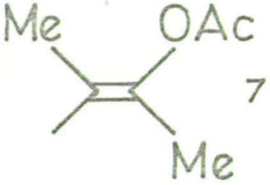
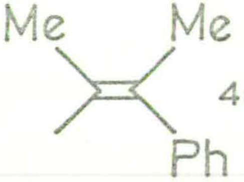
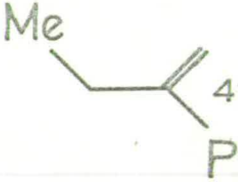
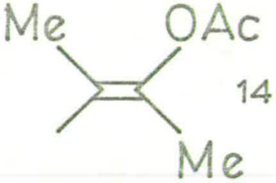
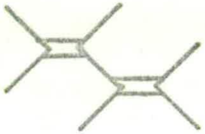
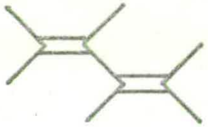
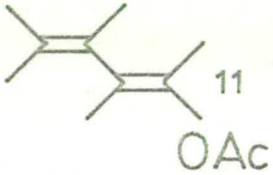
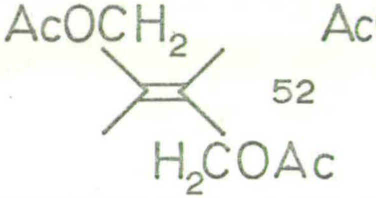
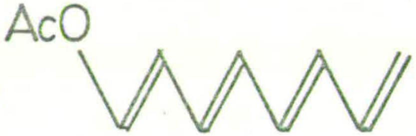
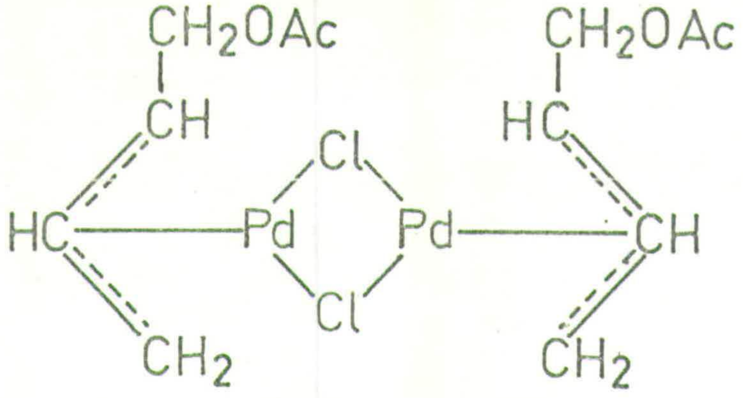
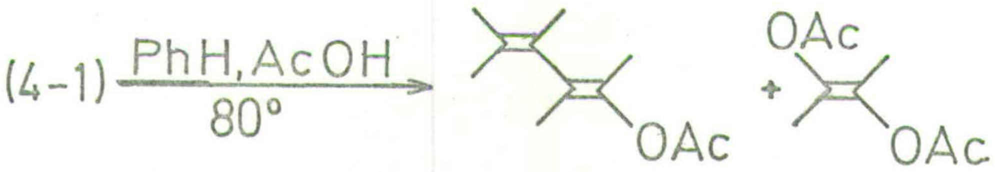
	 51  42  7	26
	 45  41  14	26
	 25  11  52  12	100

Table 4-3. Reaction of various Alkenes with Benzene (after Moritani[16, 18])

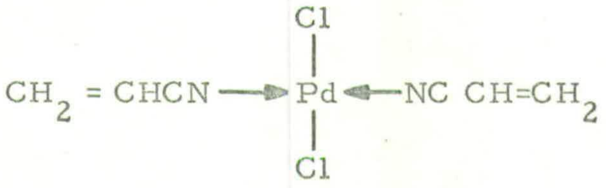


4-1

formed by acetoxylation and coupling of the ligands, and decomposition of the complex:



Alkenes which contained polar groups, such as acrylonitrile, vinyl acetate and ethyl vinyl ether, also gave rise to product mixtures.[18] In these cases it was suggested that the formation of fairly stable complexes with palladium through the involvement of the lone pair of electrons on oxygen or nitrogen occurred. This would again inhibit the arylation reaction by blocking the reactive site, i. e. the palladium atom. Acrylonitrile is in fact known to form a complex of this type,[18, 53] (4-2):

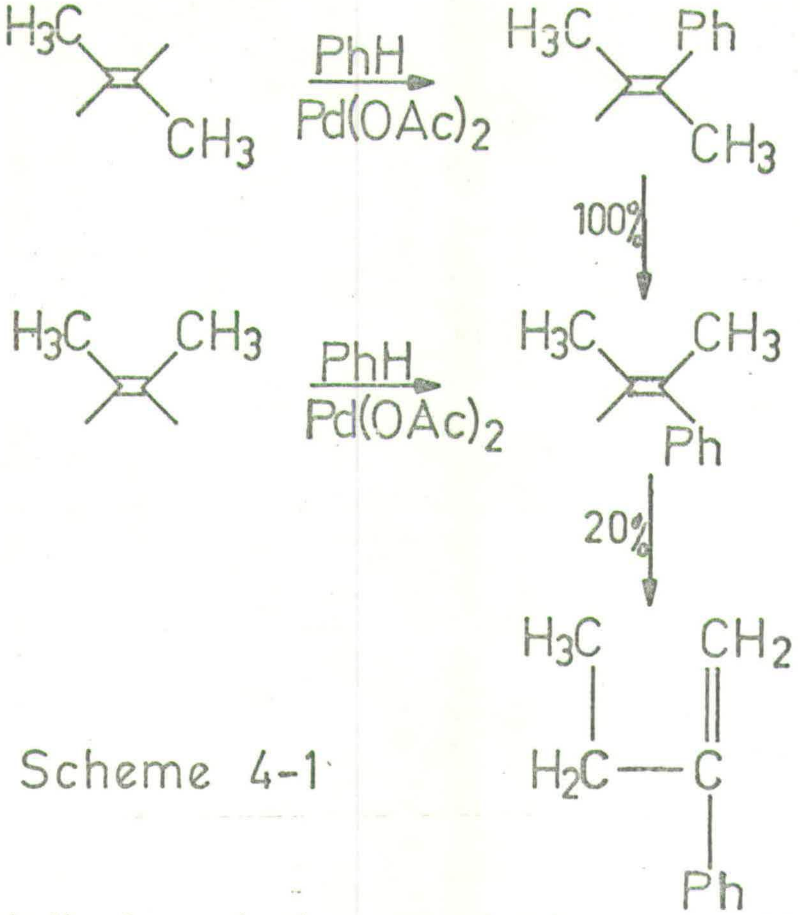


$$CH_2 = CHCN \longrightarrow \overset{\displaystyle Cl}{\underset{\displaystyle Cl}{Pd}} \longleftarrow NC\ CH{=}CH_2$$

(4-2)

dichloro-bis(acrylonitrile) palladium II

A certain similarity may be noticed in the products obtained from cis- and trans-2-butene. This was explained[16] when the expected product from trans-2-butene, 2-phenyl trans-2-butene (4-3) was found to isomerise quantitatively to the cis isomer (4-4) under the reaction conditions. Furthermore, 4-4 was found to isomerise in 20% yield to the other product formed 2-phenyl-1-butene (4-5), (Scheme 4-1):



4-3

4-4

Scheme 4-1

4-5

A similar isomerisation system has been reported by Yamamura[54] during investigation of the palladium assisted phenylation of β-methyl-β-nitrostyrene.

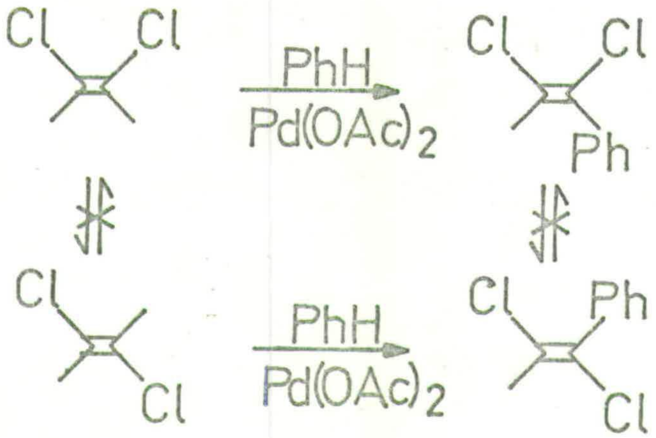
Despite these complexities, Moritani drew the following conclusions:

(a) The reactivity of the lower alkenes decreases in the order propylene > 2-butene > 1-butene, but alkenes which can easily form π-allyl complexes give rise to acetates and dimers as major products.[16]

(b) An electron withdrawing group enhances the reactivity of the alkene but this may be modified by the ease with which a stable complex may be formed with the palladium.[18]

Shue has reported work on only one substituted alkene, namely β,β'-dideuterostyrene.[36] From both competitive reactions and independent absolute rate determinations with it and non-deuterated styrene in reaction with benzene, rate ratios of approximately 1:1 and 1. 25:1 respectively, were found. This is too low a figure to indicate a primary kinetic isotope effect, so cleavage of the styrene-β-hydrogen bond is probably not involved in the rate determining step of the reaction.

The arylation was also carried out by Moritani with benzene and isomeric 1, 2-dichloroethylenes.[24] Complete retention of configuration was found, the stereochemistry of the products, isomeric cis and trans 1-phenyl-1, 2-dichloroethylene being the same as that of the respective starting materials. Starting materials and products were found not to isomerise under the reaction conditions, (Scheme 4-2):



Scheme 4-2

This result implies either retention of the double bond throughout the reaction, or the existence of a bridged, rigid or hindered intermediate in which no rotation can occur.

4C OTHER OBSERVATIONS

A reaction pathway, rejected early on, was a stepwise addition-dehydrogenation process. The reaction could be envisaged thus, (Scheme 4-3):

$$PhH + PhCH = CH_2 \longrightarrow PhCH_2\text{-}CH_2Ph \quad \text{bibenzyl}$$

$$PhCH_2\text{-}CH_2Ph \longrightarrow PhCH = CHPh + 2H,$$

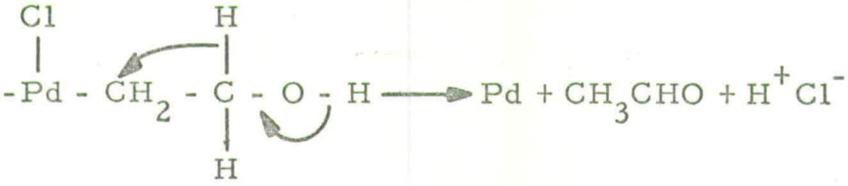
Scheme 4-3

the second step being analagous to other palladium catalysed dehydrogenations. However, it was found that bibenzyl failed to dehydrogenate under the reaction conditions.[12]

In the Wacker reaction, a hydride shift is known to occur.[4] Thus, if tetradeuteroethylene is oxidised by the Wacker process, all four deuterium atoms are found in the product.

$$D_2C = CD_2 \xrightarrow{PdCl_2} CD_3CDO$$

This is accounted for by a hydride shift step,[55, 56] in which a hydroxylated ethylene molecule, σ-bonded to palladium, decomposes to products, thus:



$$-\underset{}{\overset{Cl}{Pd}} - CH_2 - \underset{H}{\overset{H}{C}} - O - H \longrightarrow Pd + CH_3CHO + H^+Cl^-$$

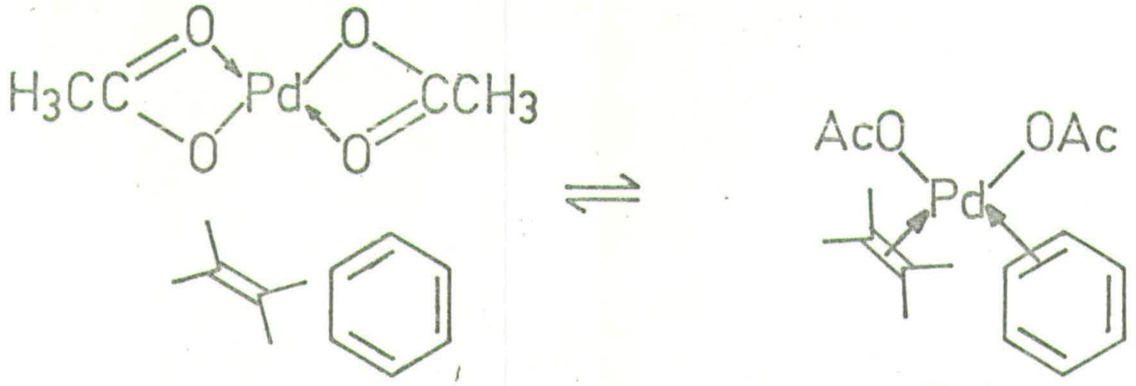
However, in the Moritani reaction it was found that if β,β'-dideuterostyrene was arylated with benzene the product contained only one deuterium atom:[20, 22]

$$PhCH = CD_2 + PhH \xrightarrow[AcOH]{Pd(AcO)_2} PhCH = CDPh$$

Thus, in this respect at least, the mechanism is different from that of the Wacker reaction.

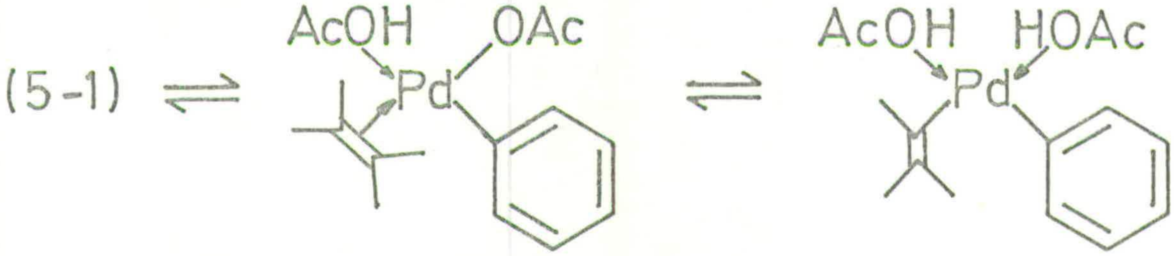
5. THE MECHANISM OF ALKENE ARYLATION

Moritani has proposed the following scheme for the reaction mechanism.[18] The alkene and the aromatic compound both co-ordinate with the palladium acetate to form π-complex 5-1:



5-1

This transforms in two steps to a palladium-alkene-aryl σ-complex, with proton transfer to the acetate ligands, (Scheme 5-1):

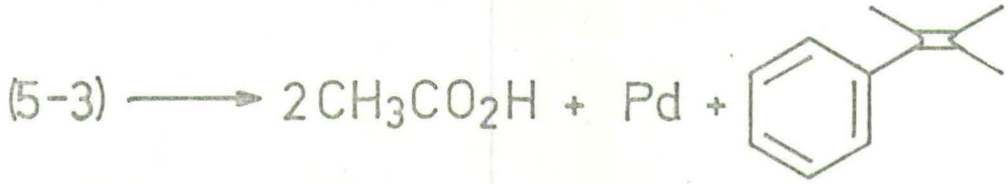


5-2

5-3

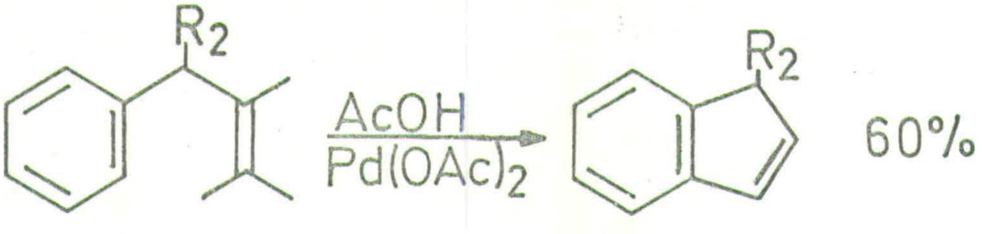
Scheme 5-1

The double σ-complex, 5-3, then decomposes to give products.



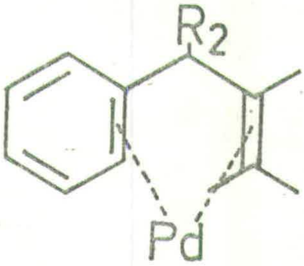
The step where a σ-bond is formed between palladium and alkene to give 5-3 is suggested as the slow, rate-determining step. This suggestion is made on the basis of the variation of reactivity shown by the various substituted alkenes,[16, 18] and the lack of variation shown by the aromatic compounds.[17] Shue's work,[36] however, tends to refute this idea. His determination of kinetic isotope effects eliminates hydrogen loss from the alkene as the slow step and implicates hydrogen loss from the aromatic compound as rate determining. His work also rules out reversible σ-bond formation between the palladium and the aromatic compound, since after reaction with a mixture of hexadeuterobenzene and benzene, no pentadeuterobenzene was found. If a reversible reaction had taken place some degree of isotopic scrambling would have been expected.

Norman has reported an intramolecular variant of the reaction:[38]



R = Me, Ph

However, despite a superficial similarity to the alkene arylation as reported by Moritani, a similar mechanism to that proposed[18] is said not to be possible, since it would involve complex 5-4, (cf. 5-1):

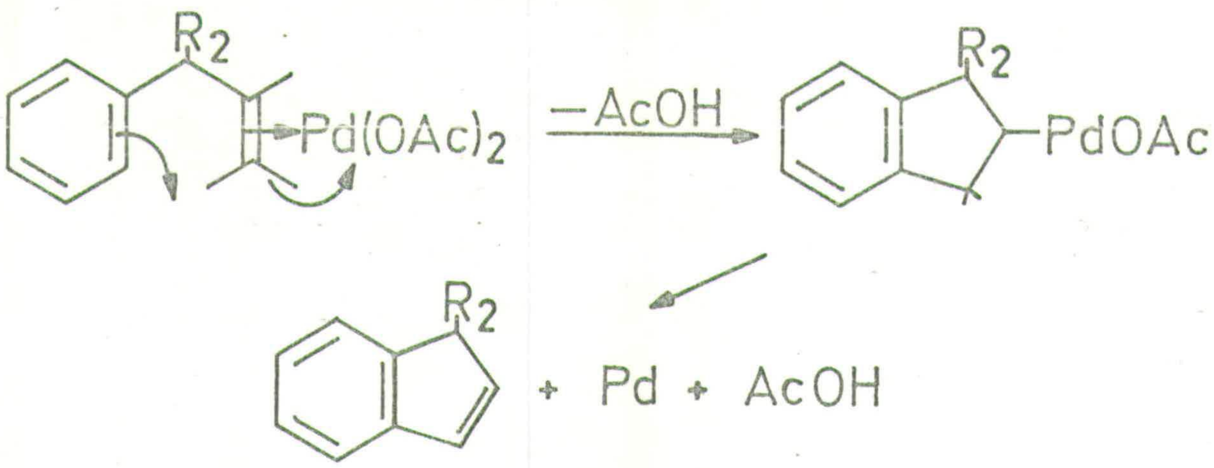


5-4

which is discounted on steric grounds. In 5-4 the hydrogen atom ortho to the side chain would interact with one of the terminal alkene hydrogen atoms and prevent the two unsaturated systems assuming the parallel configuration said to be required[38] for bond formation with the palladium.

Norman suggests that the alkene double bond alone is complexed to the palladium, and that this bond then becomes subject to nucleophilic attack from the ring, (Scheme 5-2, see over).

The existence of some form of palladium-starting material complex is undeniable in this case. While following a reaction, such as that above, by taking samples and analysing by g. c., it was



Scheme 5-2

noted, quite soon after the beginning of the reaction, that much of the starting material could not be accounted for. This was explicable if it is assumed that a complex is irreversibly formed with the starting material quite quickly, which then slowly decomposes to give the products. By adding a ligand with a known high affinity for palladium to the samples before analysis, the complex was decomposed and the starting material accounted for. This observation,[38] of course, suggests an entirely different rate determining step, intermediate complex decomposition.

6 OXIDATIVE RECYCLING PROCEDURES

During almost all palladium assisted organic reactions palladium metal is precipitated at the step where the products are formed.[1, 2] The cost of palladium, as the metal sponge or the chloride is around £1.00 per gram[57] so palladium assisted synthesis is superficially a most uneconomic procedure. However, the metal is easily oxidised to the stable +2 state and this property is made use of in oxidative recycling processes in which an oxidising agent, present in the reaction mixture, returns the precipitated metal to the active Pd^{II} state. This effectively makes the reaction catalytic in palladium. The oxidant is consumed but it is preferably chosen to be much cheaper than the palladium salt. In the Wacker reaction[3, 4, 5] the oxidant itself is subject to recycling, being readily oxidised by atmospheric oxygen (see Section 1, page 1).

Following the example set by the Wacker reaction the most commonly used oxidant is copper-II chloride, $CuCl_2$. The recycling steps in the Wacker reaction are summarised thus, (Scheme 6-1):

$$Pd^{o} + 2Cu^{++} \longrightarrow Pd^{++} + 2Cu^{+}$$

$$2Cu^{+} + \tfrac{1}{2}O_2 + 2H^{+} \longrightarrow 2Cu^{++} + H_2O$$

Scheme 6-1

This two step, double recycling system effectively oxidises the palladium with atmospheric oxygen (in fact, the Wacker reaction consumes only ethylene and air). Direct oxidation of palladium metal with air is possible but too slow to be of any use in organopalladium synthesis.[6c] The majority of recycling systems investigated have been used for industrial processes and precise details are not available. However the use of ferric ion, hydrogen peroxide, benzoquinone, potassium persulphate, potassium dichromate, potassium bromate and lead dioxide has been reported,[6c] and two patents describe electrochemical methods.[58, 59]

Moritani reported successful recycling of palladium in the arylation of alkenes using silver acetate or cupric acetate.[13, 15] He also reported that in the presence of such oxidants the reaction could be effected by palladium metal itself. Later it was reported[16] that a double recycling system could be used by either bubbling air or oxygen through the reaction mixture, or doing the reaction in an autoclave in the presence of air or oxygen. More recently Shue has reported[35, 37] the use of 'mild' oxygen pressure (20 Atmospheres) with no need for metal salt intermediates. Acetic acid was also omitted, with consequent elimination of acetoxylated by-products. Heck has reported[28] the use of recycling procedures in the related arylmercury-salt arylation reaction. He used Cu^{II}, Fe^{III} and Hg^{II} salts; oxygen pressure has also been used by Itatami,[60] in an aryl coupling reaction similar to that reported by van Helden.[7]

The catalytic efficiency of the palladium salt used in a reaction involving a recycling procedure is commonly expressed as the yield of desired product based on starting palladium salt, quoted as a percentage. Though this may be satisfactory in describing the efficiency of the recycling procedure it tells little of the overall usefulness of the reaction. This is better measured by the percentage conversion of starting material. If both figures are reported a proper judgement of the synthetic value of the reaction can be made. Typical results from both Shue's and Moritani's work are presented in this way in Table 6-1.

Table 6-1: Palladium assisted phenylation of styrene in the presence of various oxidants.[15, 35]

Styrene	Equiv. $Pd(OAc)_2$	Equiv. oxidant	Equiv/atm	Yield % on: styrene	$Pd(OAc)_2$
1.0[a]	0.4	$Ag(OAc)+O_2$	2.0/1	55.2	138
1.0[a]	0.1	$Ag(OAc)+O_2$	0.1/50	24.5	245
1.0[a]	0.1	$Cu(AcO)_2 \cdot H_2O+O_2$	0.1/50	44.6	446
1.0[b]	0.1	O_2	20	24.8	248
1.0[b]	0.011	O_2	20	12.2	1100
1.0[b]	0.039	O_2	20	23.9	613

a) Acetic acid present.[15]

b) Acetic acid absent.[35]

7. PROGRAMME OF WORK

It is clear from the foregoing that much remains to be explained about the palladium assisted arylation of alkenes. The work of Moritani can hardly be said to have been systematic. Substituent effect studies can frequently reveal or imply mechanistic pathways, but little can be determined from Moritani's results, due to the host of complicating factors which arose from a poor choice of alkenes. The conclusions he drew from that work, and the work on substituted benzenes, can hardly be justified, and have been brought into some doubt by Shue's experiments with deuterated reactants. Consequently, part of the aim of the present work has been to eliminate some of the confusion created by Moritani and provide more reliable data.

Various ring substituted styrenes were used as the reacting alkenes. These systems were chosen for the following reasons: firstly, the known high reactivity of styrene in this reaction;[15] secondly, ring substituents can be expected to exert an electronic influence at the reaction site (the β-carbon atom) but are sufficiently distant not to have more than a slight steric effect; thirdly, they are rather more easily handled quantitatively, being solids or liquids, than the gases used by Moritani.[15, 16] As reacting aromatic compounds, monosubstituted benzenes were used, the substituents chosen being the same as those used in the styrenes.

In common with most workers in the field of organo-palladium chemistry Moritani chose cupric salts[13, 15] for oxidative recycling apparently for no better reason than that they work for the Wacker reaction. However, as will be shown there is good reason to believe that cupric and silver acetate, as used by him are not the most efficient oxidants. A more thorough search for an efficient oxidant has been carried out, testing many compounds all under substantially similar conditions, in an attempt to find the most useful one.

Some experiments were carried out in an attempt to extend the synthetic scope of the reaction.

In order to maintain close control over the system under study nearly all the experiments were variations on one basic reaction. In nearly all cases only one reaction parameter (e. g. substituent, quantity of one reactant, or oxidant) was changed at a time. For a similar reason, gases and very reactive reagents were also avoided, wherever possible.

EXPERIMENTAL AND RESULTS SECTION: CONTENTS

EXPERIMENTAL AND RESULTS SECTION

1 INSTRUMENTATION AND TECHNIQUES

1A Gas Chromatography

Four instruments were used for g. c. analysis. A Pye 104, model 54, fitted with a Pye Wide Range amplifier was used for quantitative and qualitative analysis. Columns used were 7ft (2. 1 m) x 0. 25 in (6mm) i. d. glass, or 5 ft (1. 5m) x 0. 25 in (6 mm) i. d. stainless steel. Stationary phases, coated on 80-100 mesh Chromosorb W, were apiezon L grease, 10% loading (10%APL), neopentyl glycol succinate, 2% loading, on acid-washed silanised support (2% NPGS), and silicone elastomer E301, 5% loading (5% SE30). Nitrogen carrier gas was used at 50 ml $min.^{-1}$ Gas supplies to the flame ionisation detector (f. i. d.) were hydrogen (50 ml min^{-1}) and air (750 ml min^{-1}). For quantitative work gas flows were carefully checked and the detector maintained at 280° by the detector oven. Integration of the chromatograms was carried out using a Kent Chromalog II semi-automatic electronic integrator with the appropriate settings for each case.

A Pye 105 model 15 automatic preparative chromatograph was used when samples of separated components were required. Columns used were 7 ft (2. 1 m) x 3/8 in (9. 5 mm) i. d., and 15 ft (4. 6 m) x 3/8 in (9. 5 mm) i. d., glass. Stationary phases used were similar to those already described, but coated on 60-80 mesh support at loadings of 10% or 20%. Nitrogen carrier gas flow was 200 ml min^{-1} and the column effluent was split, 1% being fed to the f. i. d. and 99% to a trap for collection.

A modified Griffin and George D6 chromatograph was used for some quantitative work. The detector of this instrument was a Martin gas-density balance[61] which had a response proportional to the number of moles of compound flowing through it. Thus, no calibration is necessary when using an internal standard, and molar ratios can be obtained directly from peak area ratios by a simple calculation.[62] Integration of the chromatograms was carried out by direct peak area measurement, (peak height x width at half height, and peak height x retention time). Columns were 2 m x 4 mm i. d. glass or stainless steel with similar packings to those already described for the Pye 104. Nitrogen carrier and reference gas flow was 50 ml $min.^{-1}$

A Perkin-Elmer F11 chromatograph fitted with capillary columns was also used. Columns were 50 m x 0. 02 mm i. d. and coated with APL, polyethyleneglycol m. w. 20000 (CAR20M) or fluorosilicone oil (QF1). Nitrogen carrier gas flow was 4 ml min^{-1} and an inlet split system was used.

1B Quantitative Methods and Data Treatment

Due to the unique response of the f. i. d., calibration was necessary for the Pye 104 instrument, except when isomer ratios were being measured. When absolute quantities were required an internal standard technique was used. The peak integral ratio of the standard to the compound to be measured was calculated from the integrator print-out, and the molar ratio corresponding to this was obtained from a calibration graph. This graph, of peak integral ratio versus molar ratio, had been obtained from the analysis of standard mixtures of the two pure compounds concerned. In all cases the graph was found to be a straight line passing through, or very close to, the origin.

All calculations were done using a Wang 360K electronic calculator and CP-2M programme card reader. This latter accessory allowed lengthy operations, such as straight-line fitting by the method of least squares, to be carried out quickly and thus routinely. All calibration graph data were treated in this way. Molar ratios were thus available by calculation eliminating graph-reading inconsistencies. For much-used systems the slope and intercept figures obtained from the least squares calculation were transferred onto a card along with any subsidiary calculations that were required. The calculation for obtaining molar ratios from D6 chromatograms was also carried out in this way.

The reproducibility of the peak integral ratios obtained under optimum conditions from the chromatogram-integrator combination was found to be within the manufacturers' specification of 0.2%. However, conditions were not always at the optimum[63] and for this reason a pair of peak integral ratios were said to be concordant if the difference between them was less than 3% of the smaller figure. The reasons for the discrepancies that arose were twofold. Firstly, small quantities of involatile materials with long retention times arising from previous injections, were added into peaks of interest by the integrator. This problem could be eliminated either by careful timing of injections or by purging the column after each injection or after every few injections. Both these procedures were costly in terms of time and this factor had to be balanced against the likely improvement in reproducibility which would be obtained. It was justified in a few cases. Secondly, the integrator had a limited capability to deal with grossly distorted peaks and even with perfectly Gaussian-shaped ones gave erroneous integrals in cases of severe overlapping produced as a result of imperfect separations. By adjusting g. c. conditions these errors could be minimised, but in one case a different column had to be used, and in another direct peak area measurement was necessary.

Usually, measurements on reaction mixtures produced ratios that were reproducible within the instrument specification. Those measurements that were disregarded were those that were dubious from the point of view of either the recorder trace or the integrator printout or both. Two satisfactory ratios within the 3% concordance limit were averaged for use in each case.

1C Nuclear Magnetic Resonance Spectroscopy

Proton n. m. r. spectra were obtained from two instruments, a Perkin-Elmer R10 operating at 60MHz and a Varian HA-100 operating at 100MHz. The latter was operated in the field sweep mode with the signal from internal tetramethyl silane (TMS) used for field-frequency lock. TMS was also used as the reference signal and chemical shifts are recorded as τ parts per million downfield from TMS at 10τ.

1D Infra Red Spectroscopy

Two instruments were used for recording i. r. spectra, a Perkin-Elmer 337 and 157G. Samples were examined either as liquid films or Nujol mulls between sodium chloride plates, or as solutions contained in 0. 1 mm path-length cells with sodium chloride windows.

1E Mass Spectrometry

High resolution mass spectra were obtained from an AEI MS902 instrument. Mass spectra were also obtained from an AEI MS20 instrument coupled to a Pye 104 chromatograph. By means of a silicone membrane separator, compounds eluted from the column could be fed into the source region of this spectrometer and the spectrum thus obtained.

1F Melting Points

Melting points were obtained on a Reichert hot-stage microscope and are uncorrected.

1G Column Chromatography

Laporte Industries Type H Alumina 100-120 mesh was used for column chromatography. It was found to be of activity I (Brockmann scale[65]).

1H Thin Layer Chromatography

T. l. c. was carried out using 0. 25 mm layers of either alumina (Merck Alumina G, Type E) or occasionally silica (Merck Silica gel G). Separated components were detected either by their own fluorescence in u. v. light, or by their quenching of the fluorescence of added indicator (Woelm Fluorescent Indicator Green, added to the adsorbent, 0.5%), and in any case by their reaction with iodine.

1J Dry-Column Chromatography

This relatively new technique, developed by Loev,[64] was found to be very useful. Alumina was used exclusively and made suitable for d. c. c. by equilibration of activity I adsorbent with sufficient water (7%) to obtain activity III[65] which was the same as t. l. c. plates. Fluorescent indicator (0.5%) was usually added also. Columns were packed in nylon tubing and developed with solvent preferably from the same batch or container as had been used for preliminary t. l. c. analysis. Separated components were located on the column either by their own fluorescence or by their quenching of the fluorescence of the indicator, or by slicing the column into several (usually 20) evenly-sized fractions, extraction, and g. c. analysis of material extracted. The extraction of material from the sliced column portions was generally carried out on a Buchner funnel, washing the material out with ether. If ether had been used to develop the column a more polar solvent such as chloroform or methanol was used for this purpose.

1K Solvents and Reagents

Chromatographic solvents were dried before use, hydrocarbons and ether with sodium, chlorinated solvents firstly with magnesium sulphate and then molecular sieves. Ethanol, often found in chlorinated solvents as a stabiliser, was removed by washing with water. Light petroleum (fraction of boiling range 40-60° unless otherwise stated) was always distilled before drying. The purity of all reagents was estimated before use, generally by g. c. (but also by t.l.c., m.p., refractive index, etc.). If necessary they were recrystallised or fractionally distilled. Reagents for competition reactions and kinetic experiments were distilled and stored over molecular sieve. Toluene was treated with concentrated sulphuric acid and distilled as described by Vogel.[66] Molecular sieve, type 4A, was dried at 310° and stored in a desiccator. Solutions were dried with anhydrous magnesium sulphate. Benzene was distilled, sodium dried and then distilled again from calcium hydride under an atmosphere of nitrogen, and stored over molecular sieve. Fresh reagent-grade glacial acetic acid was stored over molecular sieve. All oxidants used were SLR grade. Anhydrous sodium dichromate was made by heating the hydrated salt at 120° for 3 hours at 0.05 mm pressure.

1L Analogue Computing

Analogue computing was carried out using a Solartron 247 system computer and the results recorded on an X-Y plotter. Details of programming can be found in Section 5, p.43.

2 PREPARATION OF COMPOUNDS

2A Palladium Acetate

This was prepared from palladium chloride by the method of Stephenson.[67] Palladium chloride (5 g, 28.2 mmoles, 1 equiv.) was added slowly to hydrazine hydrate (15 g, 300 mmoles, 10 equiv) stirred in a one litre beaker. Fumes of hydrogen chloride etc. were vigorously evolved and the mixture became warm. After addition was complete the mixture was allowed to cool and palladium sponge (3.0 g, 28.2 mmoles 100% yield) filtered off and dried. After drying, the palladium sponge (2.6 g, 24.4 mmoles, 0.86 equiv.) was added to a mixture of glacial acetic acid (175 ml, excess) and nitric acid (1.8 ml) and the mixture boiled under reflux until no more brown fumes were evolved. The remainder of the palladium sponge (400 mg, 3.8mmoles, 0.14 equiv.) was then added and the mixture boiled again until no more brown fumes were evolved. The solution was filtered hot to remove unreacted palladium and then cooled. Palladium acetate crystallised from the cooling mixture and was filtered off. The remaining solution was evaporated (rotary evaporator/oil pump) to obtain the remainder of the acetate. After being dried in a desiccator at room temperature for 3 hours at 0.05 mmHg pressure, palladium acetate (5.3 g, 23.6mmoles, 84%) was obtained. About 500 mg of palladium sponge was recovered.

2B 3-Trifluoromethyl Benzaldehyde

Styrenes required for kinetic runs were prepared by the method of Wiley and Smith.[68] This method was chosen after consideration of the most readily available starting materials, namely substituted benzaldehydes. Only in the case of the 3-trifluoromethyl substituent was the benzaldehyde not available, and its preparation from 3-trifluoromethylaniline was by the Beech reaction.[69]

A solution of formaldoxime was prepared by mixing paraformaldehyde (6.9 g, 230 mmoles, 1.5 equiv.) and hydroxylamine hydrochloride (16.0 g, 230 mmoles, 1.5 equiv.) in water at about 40°. The mixture was stirred at this temperature until a clear solution was obtained. Anhydrous sodium acetate (18.9 g, 230 mmoles, 1.5 equiv.) was then added and the solution boiled under reflux for 15 minutes.

Meanwhile, a solution of 3-trifluoromethylaniline hydrochloride was formed by adding the amine (25.0 g, 155 mmoles, 1 equiv.) with a dropper to a stirred solution of concentrated hydrochloric acid, (31 ml, 310 mmoles, 2 equiv.) in water (<u>ca</u>. 250 ml) in 2 litre flask. More water was added to effect complete dissolution of the rather insoluble salt. The solution thus formed was diazotised with sodium nitrite (10.7 g, 155 mmoles, 1 equiv.) in water, (<u>ca.</u> 15 ml). The diazonium salt is also fairly insoluble and to obtain a clear solution more water was added, the mixture was stirred and allowed to warm to +5°. Anhydrous sodium acetate was then added to the stirred solution until it gave a neutral reaction to Congo red paper (purple).

Cupric sulphate (2. 2 g, 15 mmoles, 0. 1 equiv.) sodium sulphite (6 00 mg, 5 mmoles, 0. 03 equiv.) and anhydrous sodium acetate (64 g, 789 mmoles, 5 equiv.) were all dissolved in water (ca. 150 ml) and added to the solution of formaldoxime, by now cold, contained in a 5-litre, 3-necked flask. The stirred mixture turned black. The solution of 3-trifluoromethyl benzene diazonium chloride was then slowly added through a funnel, the outlet of which was below the surface of the liquid. The temperature was kept around 20° and the solution stirred for 20 minutes after addition was complete. The colour changed from black through red to brown. Concentrated hydrochloric acid (160 ml, 1. 6 moles, 10 equiv.) was then added and the mixture boiled under reflux for two hours.

The mixture was steam distilled and approximately 1. 5 litres of distillate obtained. After extraction with ether, 25 g of a pungent smelling red oil were obtained. This crude 3-trifluoromethyl benzaldehyde was purified by making the bisulphite compound, which was washed with ether and decomposed with concentrated sulphuric acid. A yellow oil with the same pungent smell was obtained and examined spectroscopically. The n. m. r. spectrum, (CCl_4, 100 MHz) showed a 4-proton multiplet between 2. 5τ - 1. 8τ and a one-proton singlet at 0. 0τ. No impurities were detected by this method. The i. r. spectrum showed a strong absorption centred on 1705 cm^{-1} consistent with an aromatic aldehyde, and a complex band between 1100 cm^{-1} and 1200 cm^{-1} also found in other 3-trifluoromethyl substituted compounds. The oil decomposed in air to give a crystalline compound, m. p. 104° (sharp). This is consistent with the previous observation that 3-trifluoromethylbenzaldehyde oxidises spontaneously in air to give the benzoic acid, m. p. 103-104°.[70]

Because of its instability it was used immediately without further purification. The yield was 10.1 g (58mmoles, 37%).

2C Substituted Cinnamic Acids

These were formed from the benzaldehyde and malonic acid, in ethanol and pyridine as described by Wiley and Smith.[68] The work-up was, however, modified. It was found that the acids were much too soluble in ethanol to be simply filtered from the reaction mixture. The solvent was therefore removed (rotary evaporator) and the impure acid added to an aqueous solution of sodium carbonate (2 equiv.) using a very small amount of ether for transfer, if necessary. The mixture was stirred until a clear solution of the sodium cinnamate was obtained, and then washed with ether to remove organic impurities (i. e. unreacted aldehyde, pyridine etc.) The water-insoluble cinnamic acid was then regenerated using concentrated hydrochloric acid, filtered off and dried as a solution in ether. It was then evaporated into a weighed 100 ml flask and used without further treatment. This method improved yields of the acids from 65-75% to the following (Table 2-1):

Table 2-1 Yields of Substituted Cinnamic Acids

Substituent	Yield
3-CF_3	86%
3-NO_2	97%
4-NO_2	76%*
3-OCH_3	96%

* Unmodified work-up

2D Substituted Styrenes

The cinnamic acid was carefully dried at 50°/0.05mmHg. This was found to be a necessary requirement for decarboxylation.

Table 2-2. Substituted Styrenes

Substituent	Yield %	B. p. °/mmHg	Lit. b. p. °/mmHg	N. m. r. spectra (τ)	I. r. spectra cm^{-1}
4-NO_2	25	125-130/12	87/2[70]	4.5(1H, d); 4.1(1H, d); 3.25(1H, dd); 1.7-2.5(4H, m)	1375(s), 1420 (s) (C-N stretch, aromatic
3-NO_2	43	124/14	120-1/11[71]	4.5(1H, d); 4.15(1H, d); 3.25(1H, dd); 1.7-2.8(4H, m)	1375 (s), 1420 (s) (C-N stretch, aromatic N
3-OCH_3	18	90-92/12	89-90/14[72]	6.2(3H, s); 4.75(1H, d); 4.3(1H, d); 2.2-3.5(5H, m)	1230(m) (aromatic ether C-O stretch)
3-CF_3	22	61/20	55/17[73]	4.7(1H, d); 4.25(1H, d); 3.3(1H, dd); 2.35-2.8(6H, m)	1100-1200 (b, s) (C-F stretch)

The reaction was carried out by heating the acid in freshly distilled quinoline (ca. 2 equiv.) with copper powder and copper chromite (ca. 1 g of each) at 195-200°. Heating was continued until no more carbon dioxide was evolved, (ca. 4h). The mixture was then poured into ice, the quinoline neutralised by addition of concentrated hydrochloric acid and the mixture steam distilled. The styrene was obtained by extraction of the distillate with ether. Alternatively the styrene was co-distilled from the reaction mixture with quinoline, and then purified by further distillation. Although this decarboxylation procedure was the most convenient for obtaining styrenes, it was far from being efficient. Thus, if carbon dioxide loss was followed during the reaction a yield of 60% or more of the styrene might be anticipated but generally, only about a third of this yield was attained after work-up. Yields and boiling points of the styrenes are contained in Table 2-2 (opposite).

2E Substituted Stilbenes

Two authentic stilbenes were required, for g.c. calibration and comparison. They were both prepared by the same method, a Wittig reaction.[75, 76]

Benzyltriphenylphosphonium chloride was prepared by boiling equimolar quantities of benzyl chloride and triphenylphosphine under reflux in dimethylformamide for three hours. After filtering washing and drying, the yield of 99.2% was obtained.

An ethanolic solution of sodium ethoxide was prepared by adding sodium (1 g, 44mmoles, 1.45 equiv.) to 'AnalaR' ethanol (150 ml) contained in a 250 ml dropping funnel. When all the sodium had dissolved the solution of sodium ethoxide was added over a few minutes to a solution of the substituted benzaldehyde (30 mmoles, 1 equiv.) and the benzyltriphenylphosphonium chloride (11.7 g, 30mmoles, 1 equiv.) in solution in 'AnalaR' ethanol in a 500 ml flask. The mixture was then boiled overnight under reflux. After removal of solvent the solid residue was digested with chloroform and water. The chloroform layer was separated, washed with water, dried and the solvent removed. The resulting solid mixture contained triphenylphosphine oxide and _cis_- and _trans_-stilbenes. The latter were separated from the mixture by d. c. c. using carbon tetrachloride as eluant, and then converted wholly to the _trans_ isomer by boiling for 2.5 hours in nitrobenzene with a crystal of iodine. (Alternatively, the triphenylphosphine oxide could be left in the mixture and separated after isomerisation). The major part of the nitrobenzene was removed by distillation and the remainder by d. c. c. using light petrol as eluant.

The stilbenes were recrystallised from aqueous methanol, and yields, m. p. s and spectroscopic data are given in Table 2-3.

Table 2-3 Substituted Stilbenes

Substituent	Yield %	m. p.°	Lit. m. p.°	N. m. r. Spectra (τ)
3-CH_3	80	49-49.5	48[77]	7.68(3H, s); 3.05(1H, s); 2.9-2.5(9H, m)
3-CF_3	55	64-66	66.6-67[78]	2.96(1H, s); 2.9-2.2 (9H, m)

I. r. spectra, cm^{-1}
3020(s, m) (aromatic C-H stretch); 2910 (s, m) (aliphatic C-H stretch)
3040(s, m) (aromatic C-H stretch); 1100-1200 (b, s) (C-F stretch)

3 INVESTIGATION OF OXIDATIVE PALLADIUM RECYCLING PROCEDURES

A number of experiments were carried out aimed at determining the most useful oxidant for the system under study and obtaining the maximum yield from the reaction by its use.

3A Reactions with Various Oxidants

A series of palladium assisted phenylations of styrene were carried out under standard conditions each with a different oxidant in the reaction mixture. A control experiment using no added oxidant was also performed. Styrene was chosen as the alkene as a result of its known high reactivity in this reaction, further, the product, stilbene was easily analysed by g. c. Benzene was used, purified as already described and styrene was distilled under reduced pressure. No significant difference was observed when using undistilled styrene containing a polymerisation inhibitor, or between experiments carried out in air and nitrogen.

The procedure used was as follows. Styrene (1 equiv.), benzene (100 equiv.), acetic acid (50 equiv.), palladium acetate (0. 05 equiv.) and oxidant (sufficient to convert all the styrene to stilbene) were mixed in a 25 ml flask, placed in an oil bath, stirred and maintained at 120^{o} by a magnetic stirrer - hotplate, and allowed to boil under reflux for eight hours, with stirring. No improvement in yield was observed with longer reaction times. The balance used to weigh those reactants present in small quantities was reproducible to within 0. 2 mg. This means that the smallest weight (22. 4 mg, palladium acetate) was subject to this error, which was ca. 1%.

After reaction the mixture was poured into sufficient dilute potassium hydroxide to neutralise all the acetic acid present, and extracted with ether. The ether was evaporated in a current of nitrogen and the organic products kept in a stoppered flask until analysed by g. c. The internal standard for these analyses was either a non-reacting material (eicosane) added before the reaction, or anthracene added just prior to analysis. The results are summarised in Table 3-1, overleaf. This work is the subject of a patent application by the British Petroleum Co. Ltd.

Table 3-1 Palladium-assisted Phenylation of Styrene: Use of Oxidants

Oxidant	Equiv. used	Yields %	
		a	b
$Fe(OAc)_2OH$	2	1.8	37
Anthraquinone	1	1.9	37
$Cu(OAc)_2 \cdot H_2O + O_2$	1	5.7	114
$K_2S_2O_8$	1	5.9	118
O_2 gas	-	6.4	152
$Cu(OAc)_2 \cdot H_2O$	1	7.6	127
$NaClO_3$	1	8.8	176
AgOAc	2	9.8	196
$NaBO_3 \cdot 4H_2O$	1	10.6	212
Chloranil	1	15.5	310
$Na_2CrO_4 \cdot 10H_2O$ *	1	18.1	362
Quinone	1	18.3	366
$Na_2Cr_2O_7$	1	21.0	421
$Na_2Cr_2O_7$	1	27.3	546
$Na_2Cr_2O_7 \cdot 2H_2O$	1	28.2	564
None	-	1.46	20

Yields in col. (a) are based on starting styrene.

Yields in col. (b) are based on palladium acetate.

* This experiment was carried out by Mr. J. A. M. Bayne.

3B Yield Maximisation

A number of experiments were carried out in order to find the optimum combination of quantities of oxidant, palladium acetate and alkene, (i. e. styrene) to obtain the maximum yield of product, (i. e. stilbene) after reaction with benzene. Each reaction was a variation on the type described in Section 3A, page 33 and consisted of styrene (1. 0 equiv.), benzene (100 equiv.), acetic acid (50 equiv.) palladium acetate and oxidant (various quantities). The procedure was identical to that described before (Section 3A, page 33). In the first two series of experiments the quantity of palladium acetate was held at 0. 05 equivalents and various quantities of the two most efficient oxidants, hydrated and anhydrous sodium dichromate, used. The results obtained are shown in Figures 3-1 and 3-2.

A third series of experiments was carried out in which the quantity of hydrated sodium dichromate (the best oxidant) was held at 0. 85 equivalents (the optimum quantity) and the quantity of palladium acetate varied. The results from this series are shown in Figures 3-3 and 3-4.

3C Batch Effects

It can be seen from Figures 3-1 to 3-4 that different batches of the same reaction mixture often gave different results on duplicate reaction. In an attempt to eliminate these differences it was normal practice to make up and carry out a set of five reactions simultaneously, or, in the case of longer runs, to make up the whole set and carry them out five at a time with the remainder stored at -20° until they were used. However, even these measures did not altogether eliminate discrepancies, and it was suspected that the presence of varying quantities of water in the reaction mixture might be the cause. Therefore, a series of reactions made up in a single batch was carried out, into which various quantities of distilled water were introduced. The results are shown in Table 3-2.

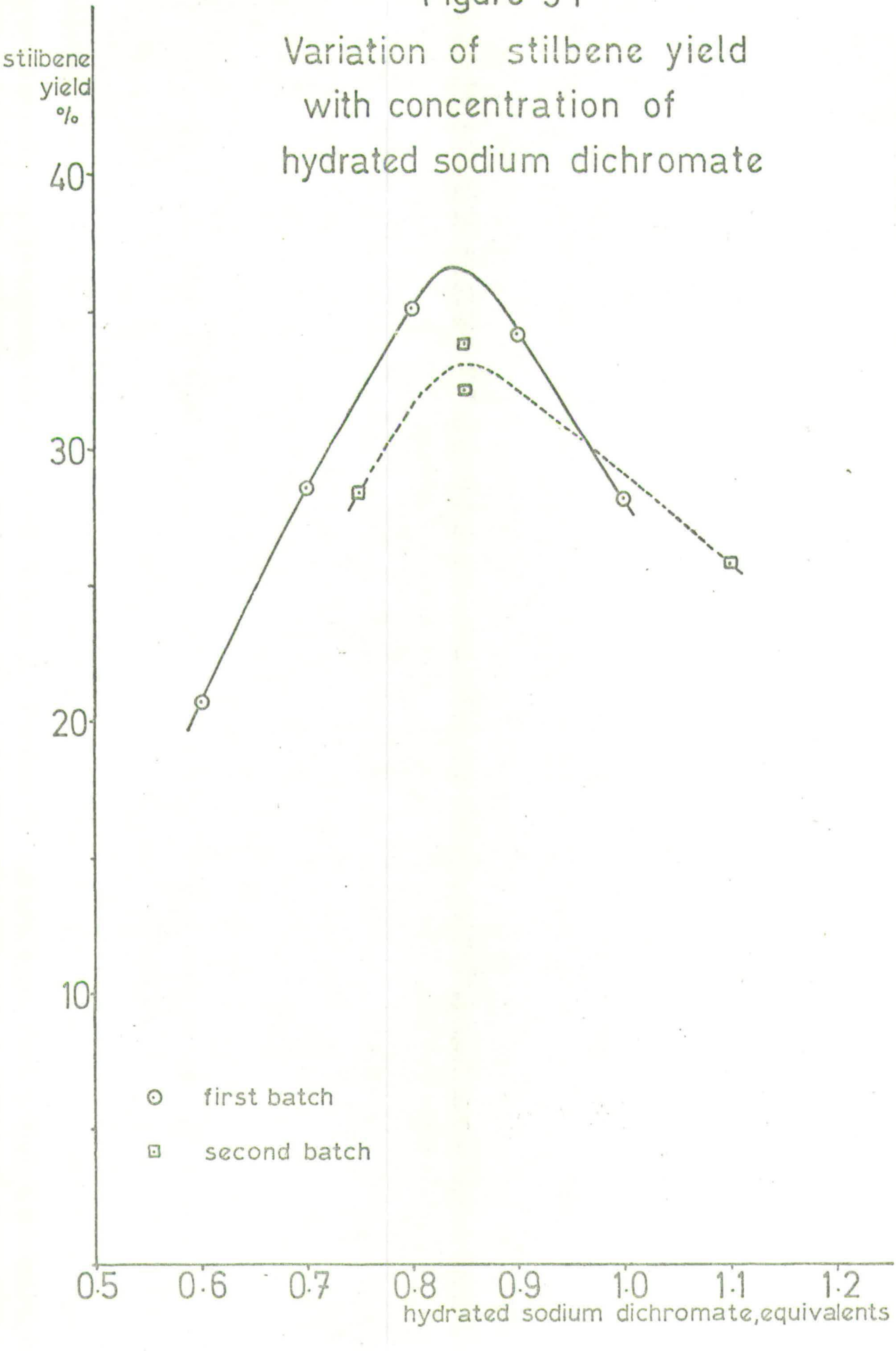


Figure 3-1

Variation of stilbene yield with concentration of hydrated sodium dichromate

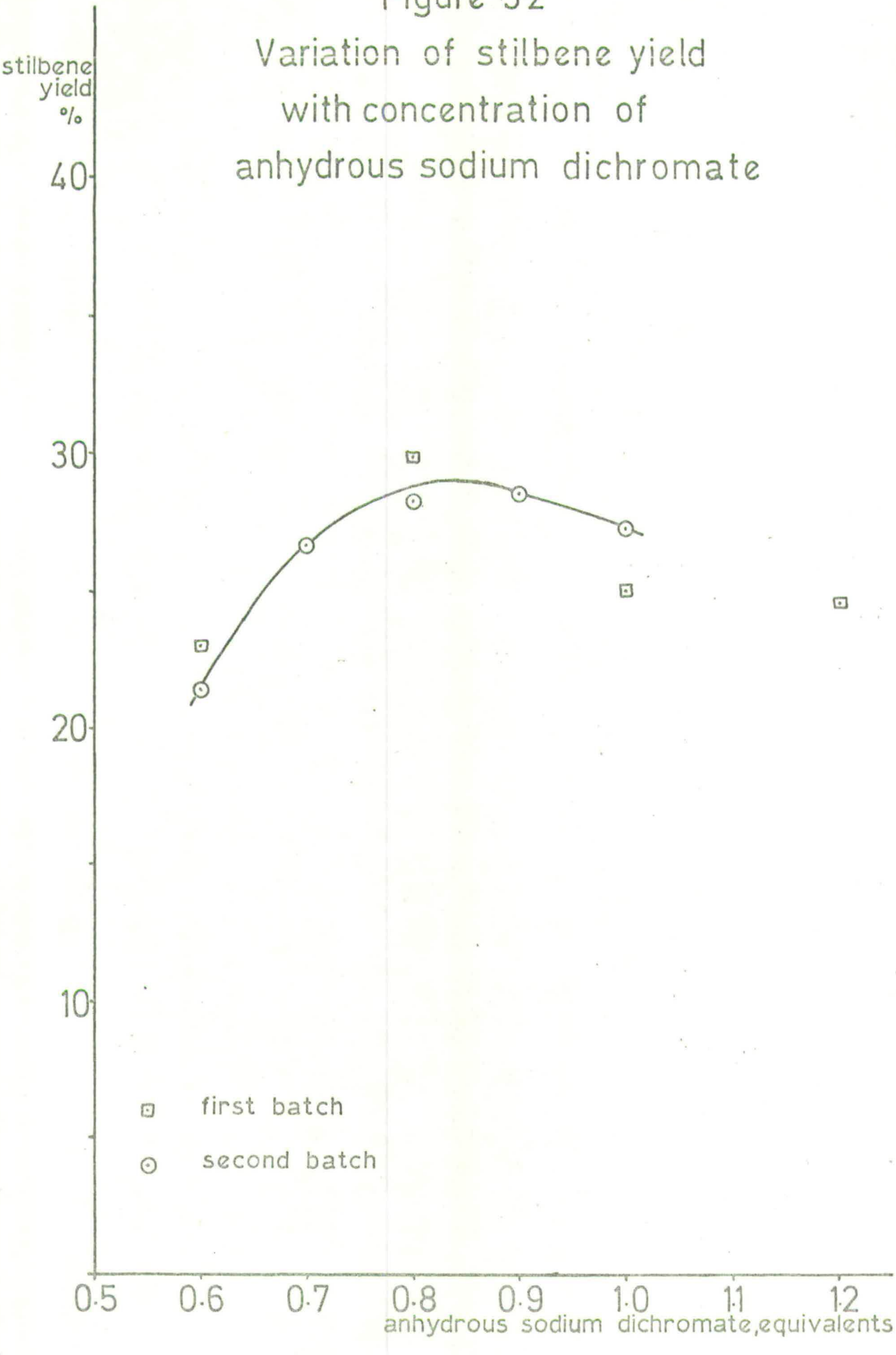


Figure 3-2
Variation of stilbene yield with concentration of anhydrous sodium dichromate

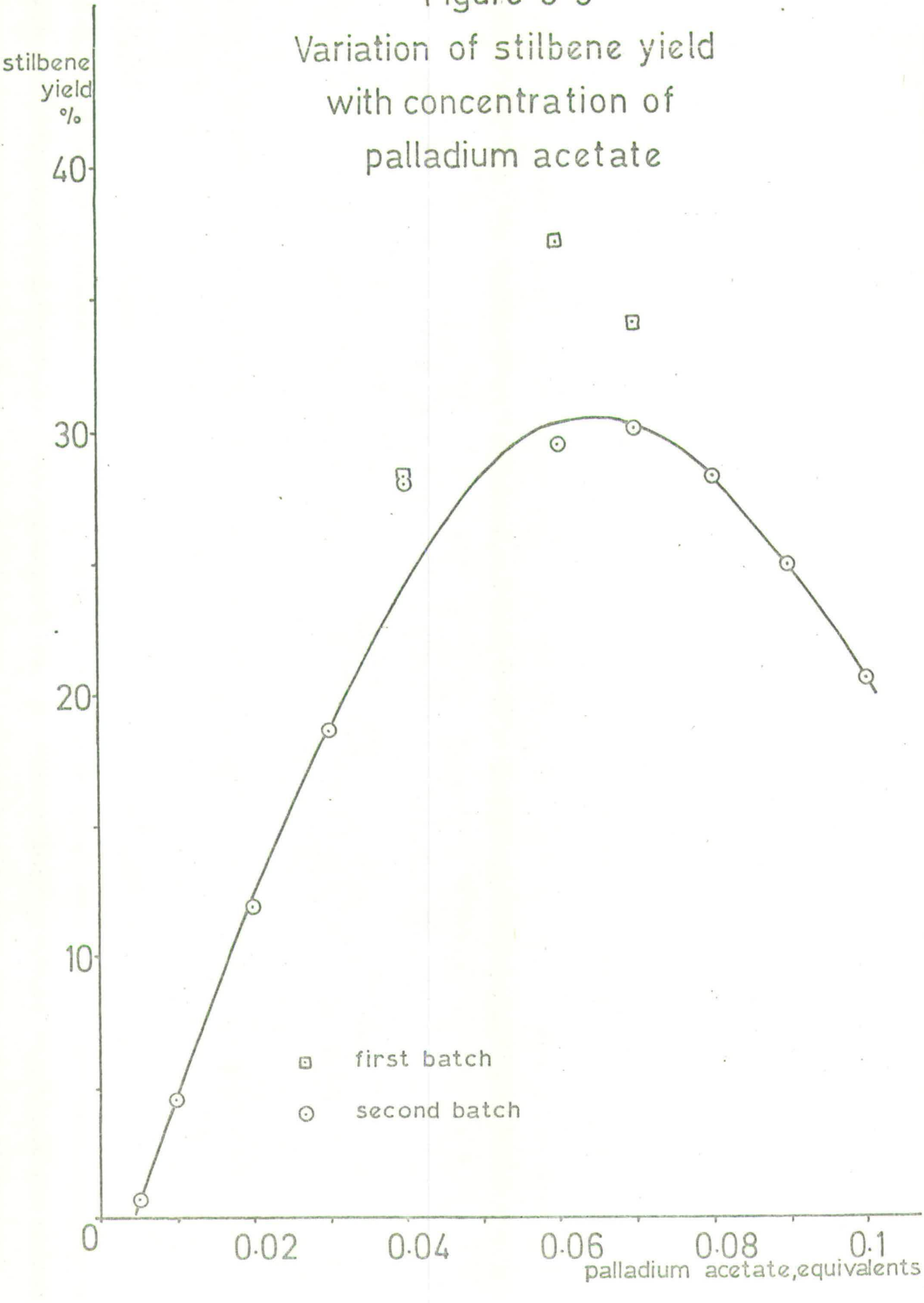


Figure 3-3
Variation of stilbene yield with concentration of palladium acetate

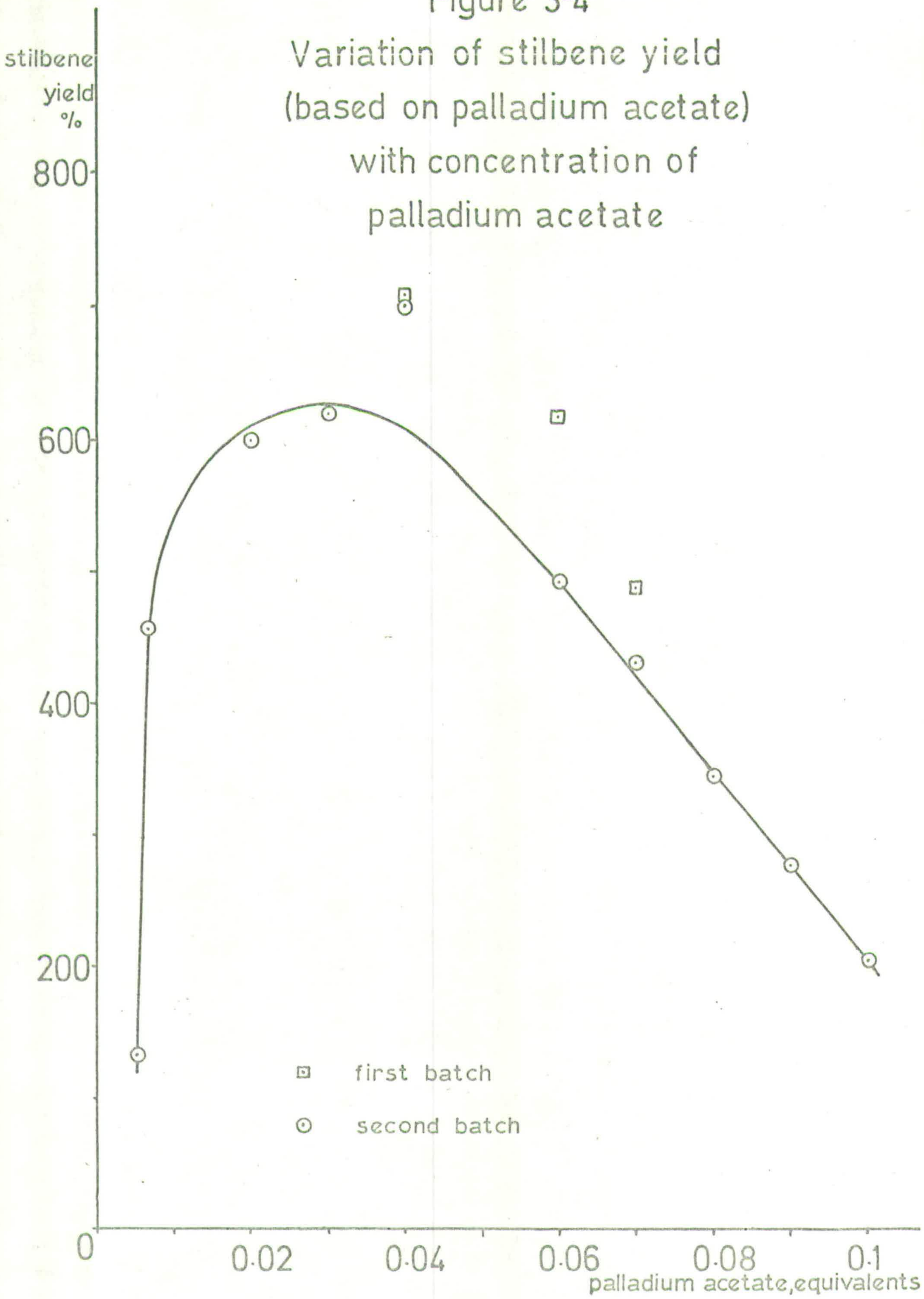


Figure 3-4
Variation of stilbene yield (based on palladium acetate) with concentration of palladium acetate

Table 3-2: Effect of added water on the palladium-catalysed phenylation of styrene.*

Added water (equiv.)	Yield %	
	a	b
0	17.8	357
1.9	21	420
3.4	22	440
5.0	21.4	427
6.7	19.5	389

Yields in column: (a) based on styrene
(b) based on palladium acetate.

* Reaction mixture and procedure was as described on page 33 with 0.85 equiv. of sodium dichromate present. The quantity of acetic acid was increased to 100 equiv. to maintain a homogeneous mixture.

A variation in yield is apparent but further investigations were not considered worthwhile. Because of this effect, experiments using anhydrous sodium dichromate which often had an uncertain state of dehydration were not pursued.

3D Dropwise Addition of Oxidant to the Reaction Mixture

From the results shown in Figures 3-1 and 3-2, it was suspected that a high concentration (>0.85 equiv.) of oxidant led to the greater importance of the destruction of organic materials over the recycling of palladium. Therefore an experiment was carried out in which the oxidant was added dropwise throughout the course of the reaction. It was hoped that while this would provide sufficient oxidant to recycle the palladium, it would diminish the importance of oxidative degradation of the organic materials. In order to obtain a solution of sodium dichromate suitable for addition from a dropping funnel, a reaction mixture relatively rich in water and acetic acid had to be used. Therefore a control reaction was carried out in which the quantities of materials were the same but all the oxidant was placed in the reaction flask. The results are contained in Table 3-3 and tend to confirm expectations.

Table 3-3 Effect of dropwise addition of oxidant on yield of stilbene

	Yields %	
	a	b
Dropwise addition	44	880
Control reaction	26.9	519

Procedures for the reactions were as follows: sodium dichromate (596 mg, 2mmoles, 1 equiv.) dissolved in water (1.0 g, 55.6mmoles, 28 equiv.) and glacial acetic acid (4 g, 67 mmoles, 34 equiv.) were added from a dropping funnel, over six hours, to a mixture of palladium acetate (22.4 mg, 0.1mmoles, 0.05 equiv.), benzene (15.6 g, 200mmoles, 100 equiv.), styrene (208.2 mg, 2.0 mmoles, 1 equiv.), and acetic acid (2 g, 33 mmoles, 66 equiv.), boiling under reflux. After the addition was complete boiling was continued for a further two hours and the mixture worked up and analysed as described in Section 3A, page 33. The control reaction was carried out with identical quantities of reactants all contained in the reaction flask from the start, and boiled under reflux for eight hours. Work-up and analysis were otherwise identical to the dropwise addition reaction.

4 SUBSTITUENT EFFECTS

4A Competition Reactions

A series of reactions was carried out in which styrene was allowed to react with a large excess of an equimolar mixture of benzene and a monosubstituted benzene. The composition of the reaction mixtures is given below in Table 4-1. They were all made up in one batch from dried and purified materials. Reactions were carried out on flasks heated in an oil bath stirred and maintained at 120°. The mixtures were allowed to boil under reflux and the exact temperature noted.

Table 4-1 Composition of competition reaction mixtures

Palladium acetate	1 equiv.*
Styrene	1 equiv.
Acetic acid	50 equiv.
Benzene	50 equiv.
Substituted benzene	50 equiv.

* The standard quantity of palladium acetate used was 1 mmole or 224.4 mg.

Reaction temperatures were measured by immersing the bulb of a thermometer suspended through the condenser in the boiling mixture, and are shown in Table 4-2.

Table 4-2 Temperatures of competition reaction mixtures

Substituted Benzene	Reaction Temperature, °C
Toluene	94
Anisole	100
Bromobenzene	100
Nitrobenzene	99
Trifluoromethylbenzene	93

After boiling under reflux for eight hours, the mixtures were worked up as described in section 3A, page 33. They were then analysed by g. c. for the isomer distribution of substituted stilbenes, and the absolute yields of stilbene and substituted stilbenes.

The isomer distribution of substituted stilbenes was obtained directly as the peak integral ratios of the peaks identified as these compounds. Identification was by retention time comparison with authentic materials and comparison of m. s. cracking pattern obtained from the MS. 20 instrument. It was noted that there was no significant difference between the cracking patterns of ring substitution isomers of stilbenes. The absolute yield of unsubstituted stilbene was obtained by the use of added eicosane as an internal standard. Molar ratios were obtained from a predetermined calibration of the chromatograph. The absolute yields of substituted stilbenes were obtained from the peak integral ratio of either the largest or best separated peak corresponding to one of them, to the peak corresponding to stilbene. As the quantity of stilbene was known, the quantity of substituted stilbene could thus be determined after construction of a calibration graph for stilbene and the monosubstituted stilbene. The figure obtained for just one monosubstituted stilbene could be extended to the others in the reaction by application of the previously found isomer ratio. The results obtained are shown in Table 4-3, overleaf.

Because of analytical difficulties encountered with the mixtures from some of these reactions, the isomer distributions of the bromo- and trifluoromethyl stilbenes were obtained from separate experiments in which no benzene was present. The analysis given for the 3-and 4-methyl stilbenes is for the sum of the two isomers. Only two peaks in the g. c. analysis of this reaction mixture could be assigned to methylstilbenes, but it was later found that 3- and 4-methyl stilbenes were not separable by g. c., even using a capillary column. No way was found of determining the proportion of each in a mixture, but after experiments with synthetic mixtures, the

Table 4-3 Competition Reactions

$$\mathrm{PhX + PhH + PhCH{:}CH_2 \xrightarrow{Pd(OAc)_2} \underset{(4-1)}{PhCH{:}CHPh} + \underset{(4-2)}{PhCH{:}CH\,C_6H_4X}}$$

X	Product isomer distrib. % o	m	p	Total Yield of 4-2, %	Total Yield of 4-1, %	Accountancy of Styrene, %
CH_3	27.9	72.1*		35.3	22.1	57.4
OCH_3	35.8	5.75	58.5	51.4	20.1	71.5
Br	18.8	17.7	63.6	17.3	34.3	51.6
NO_2	14.9	77.7	7.40	3.50	36.7	40.2
CF_3	1.40	80.4	18.2	6.90	38.2	45.1

* Total meta- plus para-isomers.

amount of 3-methyl stilbene is believed to be small, probably less than 20%. A larger quantity than this would have been detectable by the analytical methods used.

From the foregoing information, partial rate factors (see Introduction, Section 4A, p. 9) and overall reactivity ratios were calculated. These are shown in Table 4-4.

Table 4-4 Partial rate factors and reactivity ratios for Competition Reactions

$$\mathrm{PhX + PhH + PhCH{=}CH_2 \xrightarrow{Pd(OAc)_2} PhCH{:}CHPh + PhCH{:}CH\,C_6H_4X}$$

X	Partial Rate Factors f_o	f_m	f_p	Reactivity Ratio k_X/k_H
CH_3	1.30	2.4*		1.60
OCH_3	2.75	0.44	9.00	2.56
Br	0.28	0.27	1.90	0.50
NO_2	0.04	0.22	0.04	0.095
CF_3	0.0076	0.44	0.20	0.18

*Combined value

4B Reaction Rate Measurements

To complement the effects observed in the reactions with substituted benzenes, reported above, a study of the effects on the reaction rate of ring-substituted styrenes was made. The reasons for choosing these compounds have already been stated in the Introduction, Section 7.

Competition reactions were not possible in this case because in order to maintain consistency of reaction conditions the styrene had to remain a minority component of the reaction mixture. The composition of the reaction mixtures is given in Table 4-5.

Table 4-5 Composition of Reaction Mixtures used for Rate Measurements

Palladium acetate	1 equiv.*
Substituted styrene	1 equiv.
Benzene	100 equiv.
Acetic acid	50 equiv.

* The standard quantity of palladium acetate used was 1 mmole or 224.4 mg.

The disappearance of the styrene from the reaction mixture was followed by the g. c. analysis of small samples taken from the reaction mixture from time to time. Approximately 0. 1 ml, or less, of the reaction mixture, boiling under reflux, was removed using a 1 ml calibrated syringe. This sample was placed in a small, stoppered tube, containing approximately 1 ml of 2M potassium hydroxide and 1 ml of ether, and shaken. It was labelled and either analysed immediately or stored at -20° for analysis later. Each reaction mixture contained an inert standard against which the styrene was measured. Standards used were decane or dodecane, depending on the separation of their g. c. peak from that of the styrene to be measured.

Peak integral ratios (standard/styrene) were obtained for each sample taken. The first sample was taken just before reaction commenced, (i. e. before heating the mixture), and all other ratios obtained during the run were divided into, or normalised with respect to, this first sample.

These records of relative concentration against time were tried for fit against 1st order and 2nd order straight line plots, by plotting the natural logarithm and reciprocal, respectively, of the concentrations against time. In all cases the results fitted the 1st order, or log. plot better. However, it was not felt justifiable to call the slope of this line the reaction rate (see Section 3D, Discussion p. 69) due to a probable mixed reaction order, and the possibility of interference from side reactions. The results are shown in Table 4-6, and the graphs are shown in Figs. 4-1 and 4-2.

Table 4-6 Reaction Rate Measurements: Loss of substituted Styrene in Reaction with Benzene

$$\mathrm{X\,C_6H_4\,CH{:}CH_2 + PhH + AcOH \xrightarrow{Pd(OAc)_2} Ph\,CH{:}CH\,C_6H_4X}$$

X	Half Life, min.	Slope of Log plot x 10^{-2} *
H	21.6	3.82
4-CH_3	15.8	5.05
3-CF_3	34.1	2.64
4-Br	22.1	3.10
3-NO_2	22.0	4.30
4-NO_2	35.8	1.98

* Slope of longest straight section.

The temperature of reaction was 84°. Experiments were

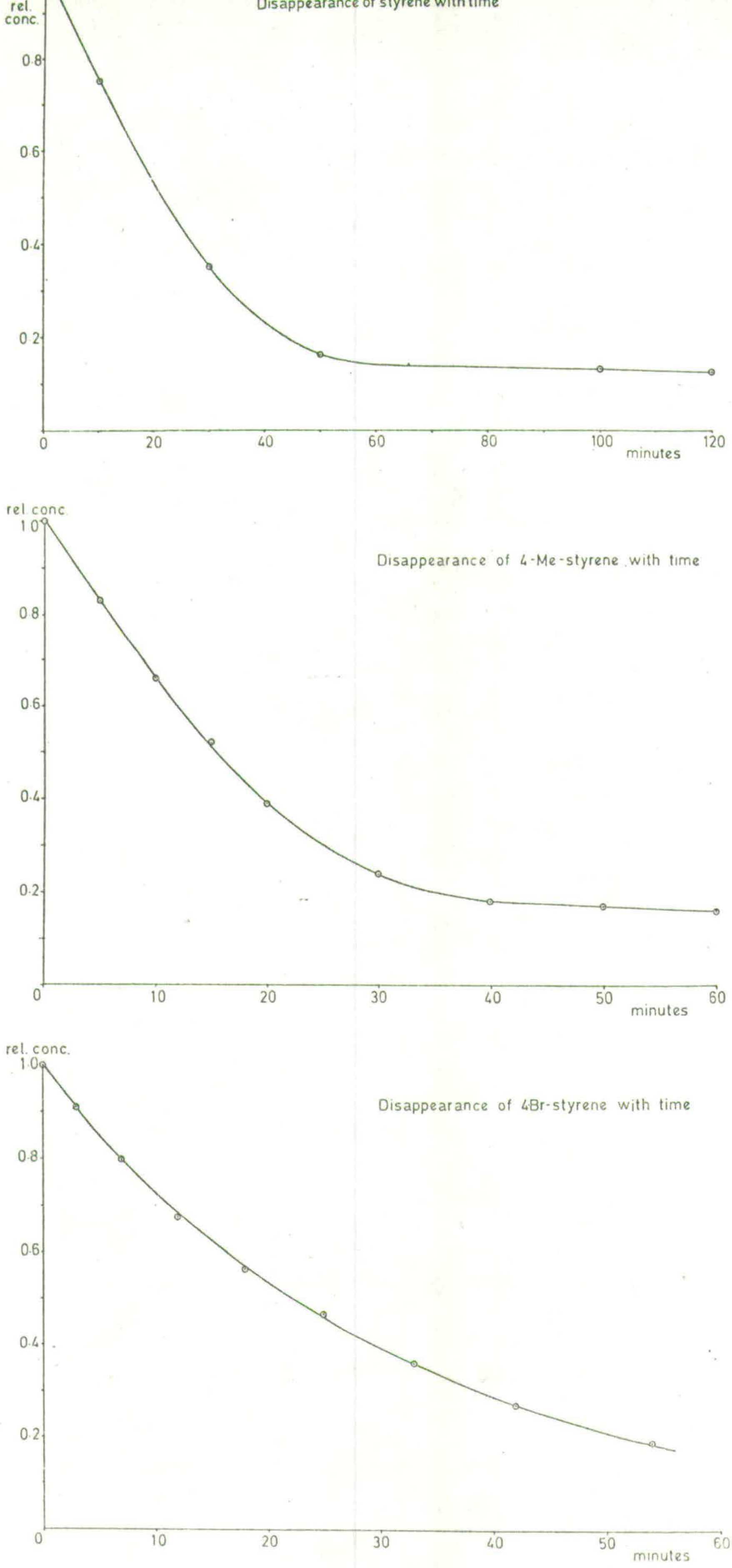


Figure 4-1. Reactant Plots

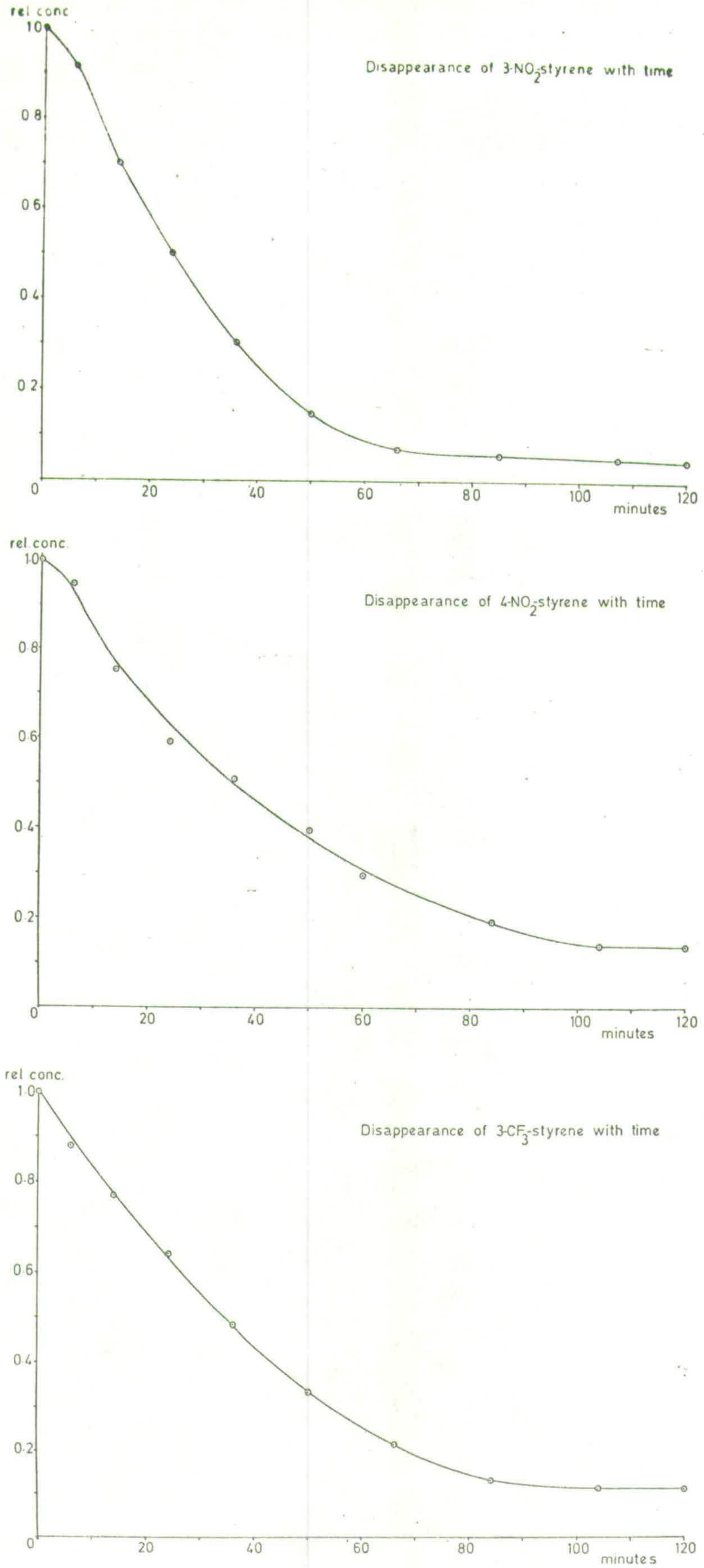


Figure 4-1 (continued). Reactant Plots

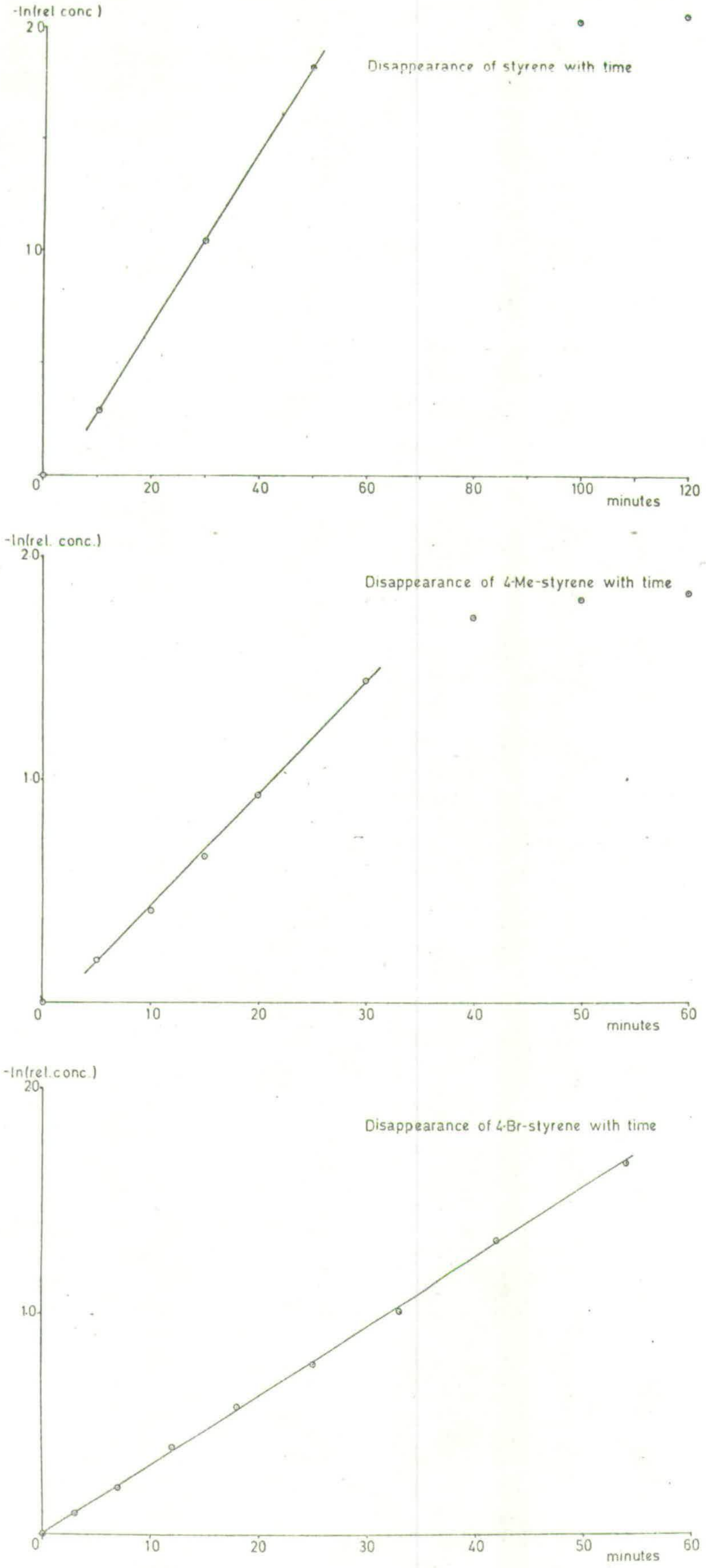


Figure 4-2. Log. Plots

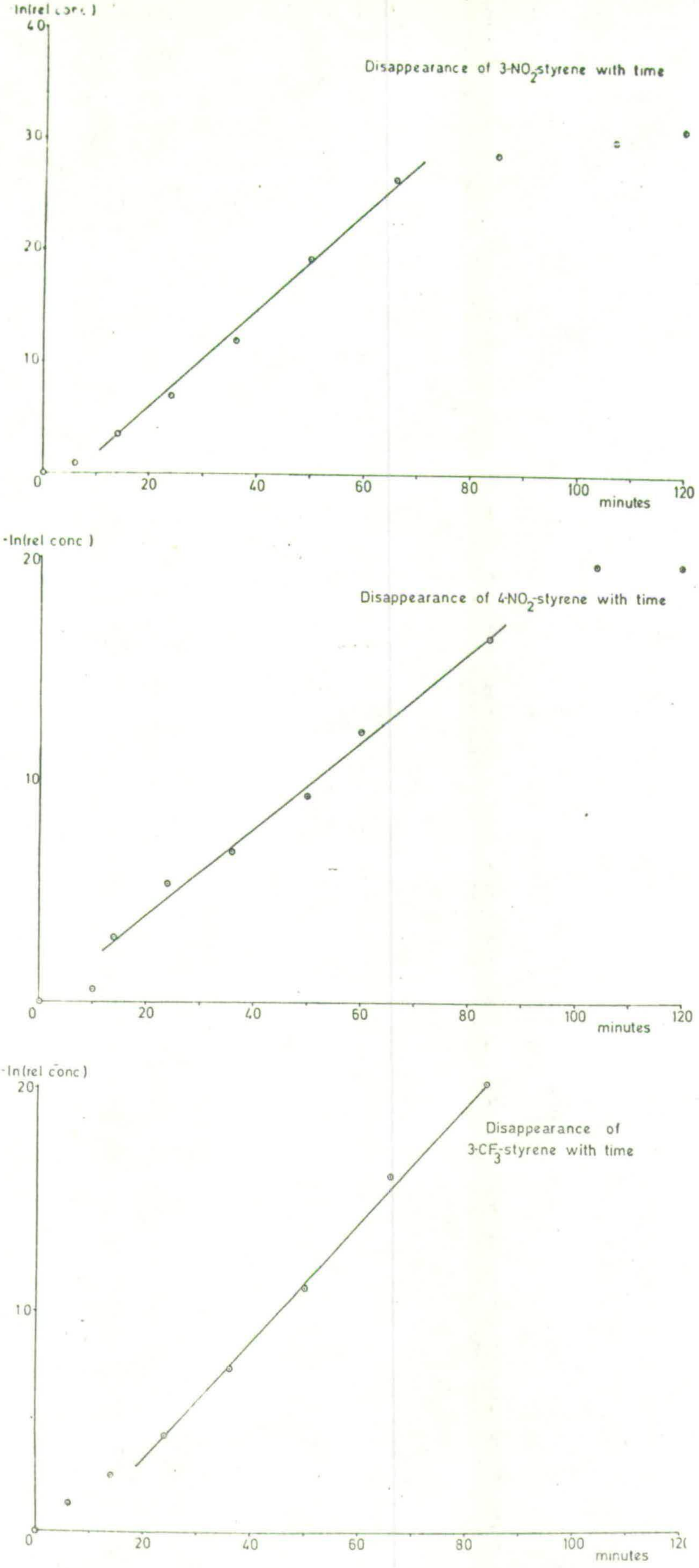


Figure 4-2 (continued). Log. Plots

also carried out using 3-OMe and 4-OMe styrene, but due to analytical difficulties no meaningful results were obtained.

5 ANALOGUE COMPUTER SIMULATION OF REACTION KINETICS

Due to the complexity of the probable reaction sequence, the plots obtained from following the reaction in progress were not immediately useful in mechanistic analysis. For this reason the kinetic behaviour of a reaction scheme derived from other evidence was simulated for comparison with the aid of an analogue computer.[79] A full examination of this evidence will be found in the Discussion, Section 3D, p. 69.

The likely steps in the reaction were assumed to be; (Scheme 5-1):

$$Pd(OAc)_2 + PhH \longrightarrow PhPdOAc + HOAc$$
$$Ph\,Pd\,OAc + ArCH{:}CH_2 \longrightarrow ArCH{:}CHPh + Pd + HOAc$$

Scheme 5-1

Benzene and acetic acid were both present in the reaction mixture in large excess and palladium metal was precipitated during the reaction. These species are thus kinetically insignificant.

The reaction sequence can thus be reduced to a non-reversible (pseudo-) first-order step followed by a non-reversible second-order step, or, symbolically, (Scheme 5-2):

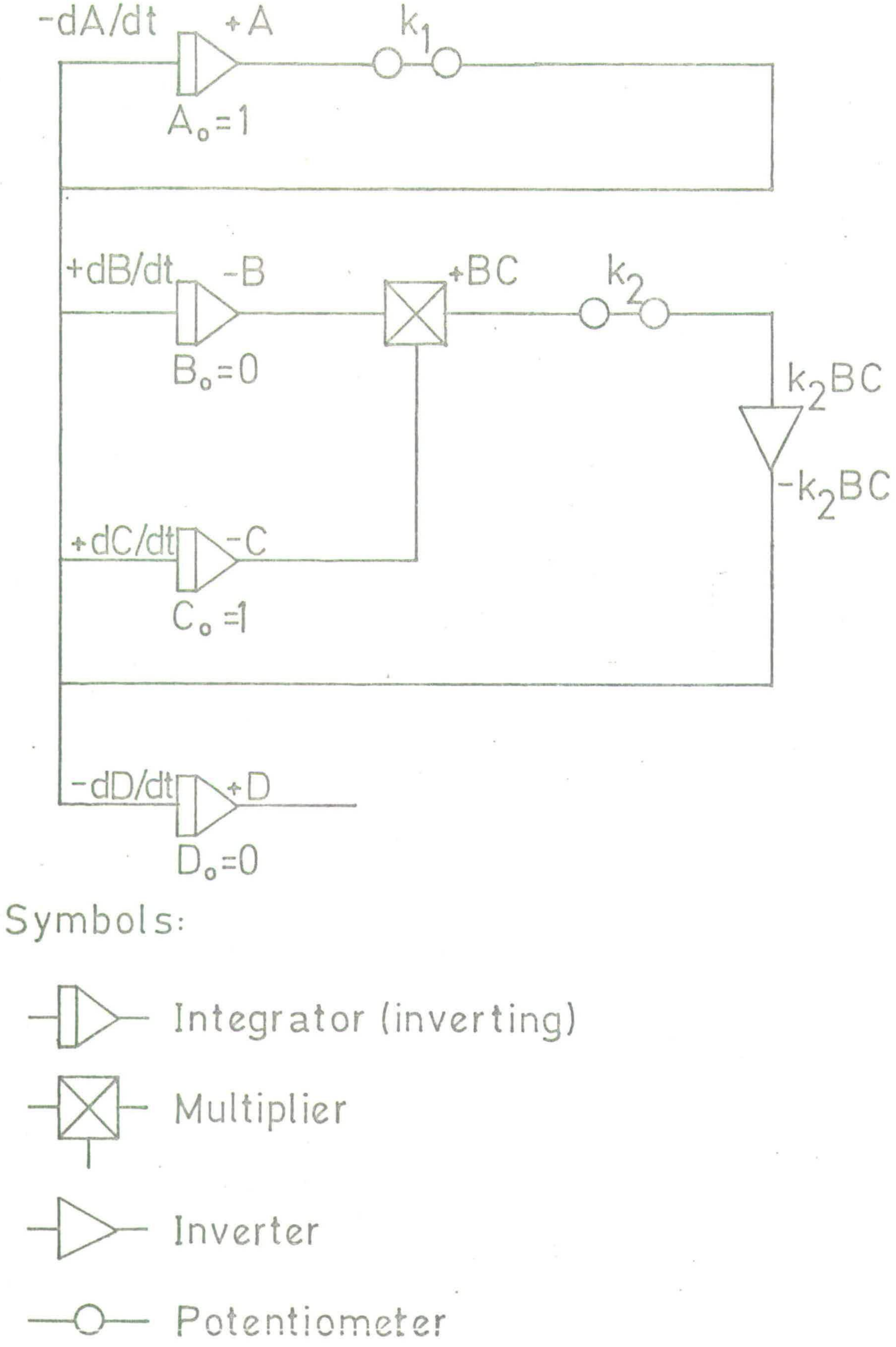
$$A \xrightarrow{k_1} B$$
$$B + C \xrightarrow{k_2} D$$

where

$A = Pd(OAc)_2$ $\qquad$ k_1 = first order rate constant
$B = PhPd(OAc)$
$C = Ar\,CH{=}CH_2$ $\qquad$ k_2 = second order rate constant
$D = Ar\,CH{=}CHPh$

Scheme 5-2

Figure 5-1. Analogue Computer Circuit



The differential equations representing this sequence are shown in Scheme 5-3.

$$-dA/dt = k_1 A$$

$$dB/dt = k_1 A - k_2 BC$$

$$dC/dt = -k_2 BC$$

$$-dD/dt = -k_2 BC$$

Scheme 5-3

The signs in these equations have been altered, where necessary so that like terms have like signs.

An analogue computer programme, or circuit, was then derived from these equations, and is illustrated opposite, Figure 5-1. Each equation has been formed into a closed loop around the circuit components representing the mathematical operators in the equation. Each variable in the equation then appears as a voltage at some point in the circuit. Initially these voltages are held constant by the computer's power supply, but when this is disconnected they change in the manner dictated by the mathematical formulae represented by the circuit until an equilibrium condition is obtained.

The initial condition can be restored immediately at any time by reconnecting the computer's power supply and the entire process repeated *ad infinitum*. The results were plotted on an X-Y recorder which had a constant speed drive applied to the X-axis. The variables, A, B, C and D were each set to the initial values found in the reaction mixture they represented, $A_o = C_o = 1$; $B_o = D_o = O$. The computation was carried out four times and each time a different variable was monitored. Various values of k_1/k_2 were used and the computer generated the plots shown in Figure 5-2.

The assistance of Dr. A. J. Bellamy in programming and operating the computer is gratefully acknowledged.

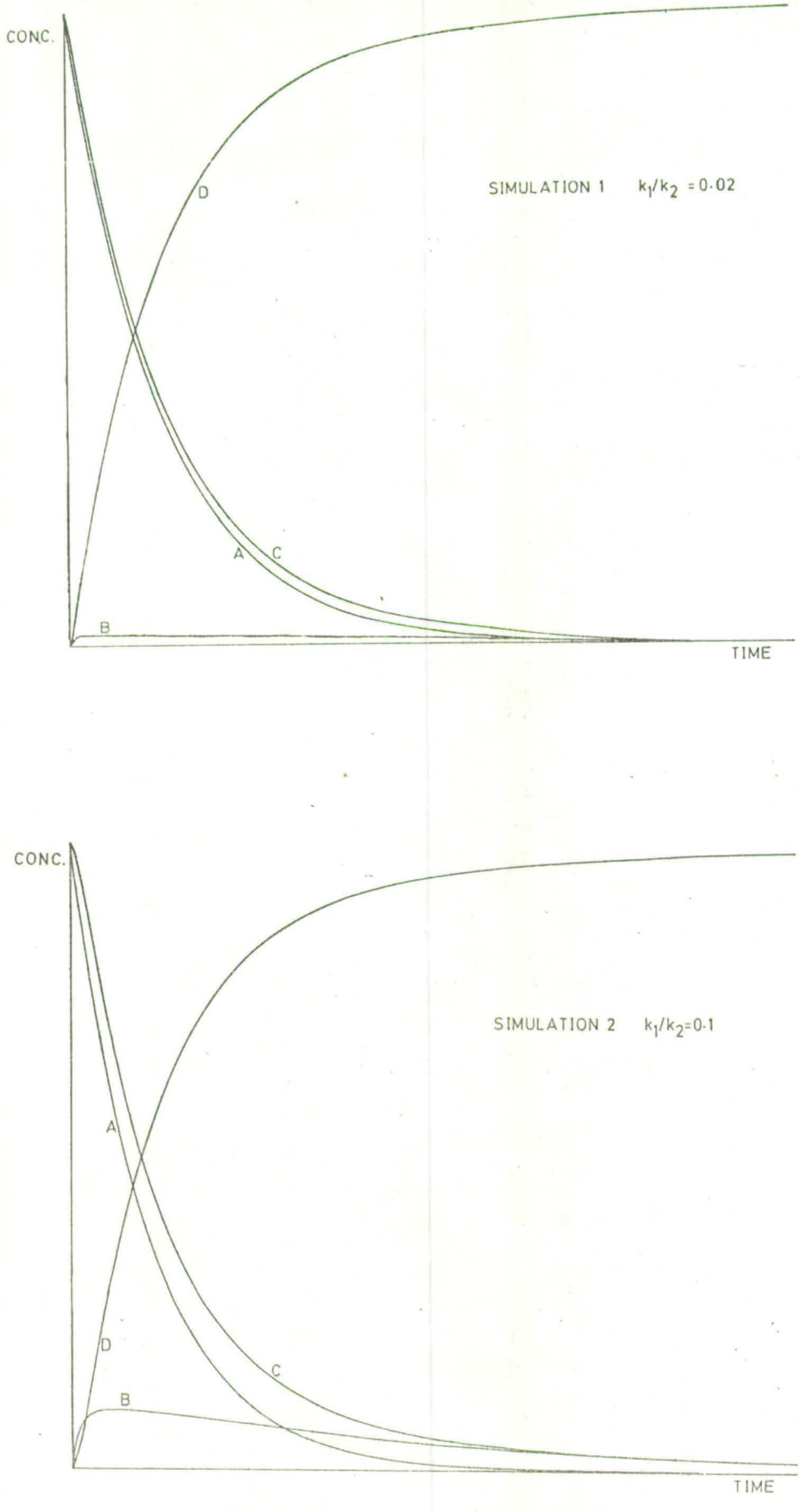


Figure 5-2. Analogue Computer Simulations.

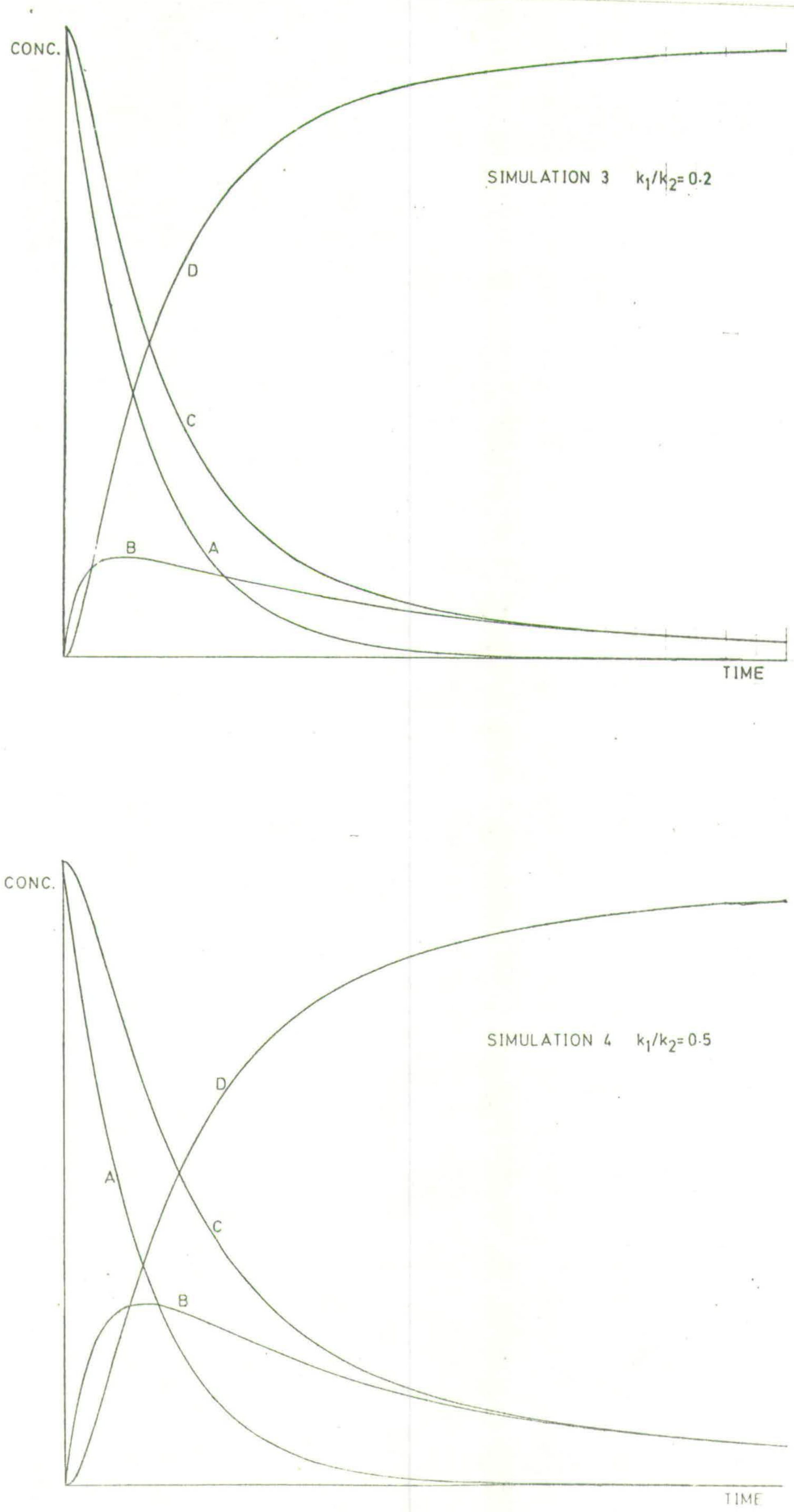


Figure 5-2 (continued). Analogue Computer Simulations

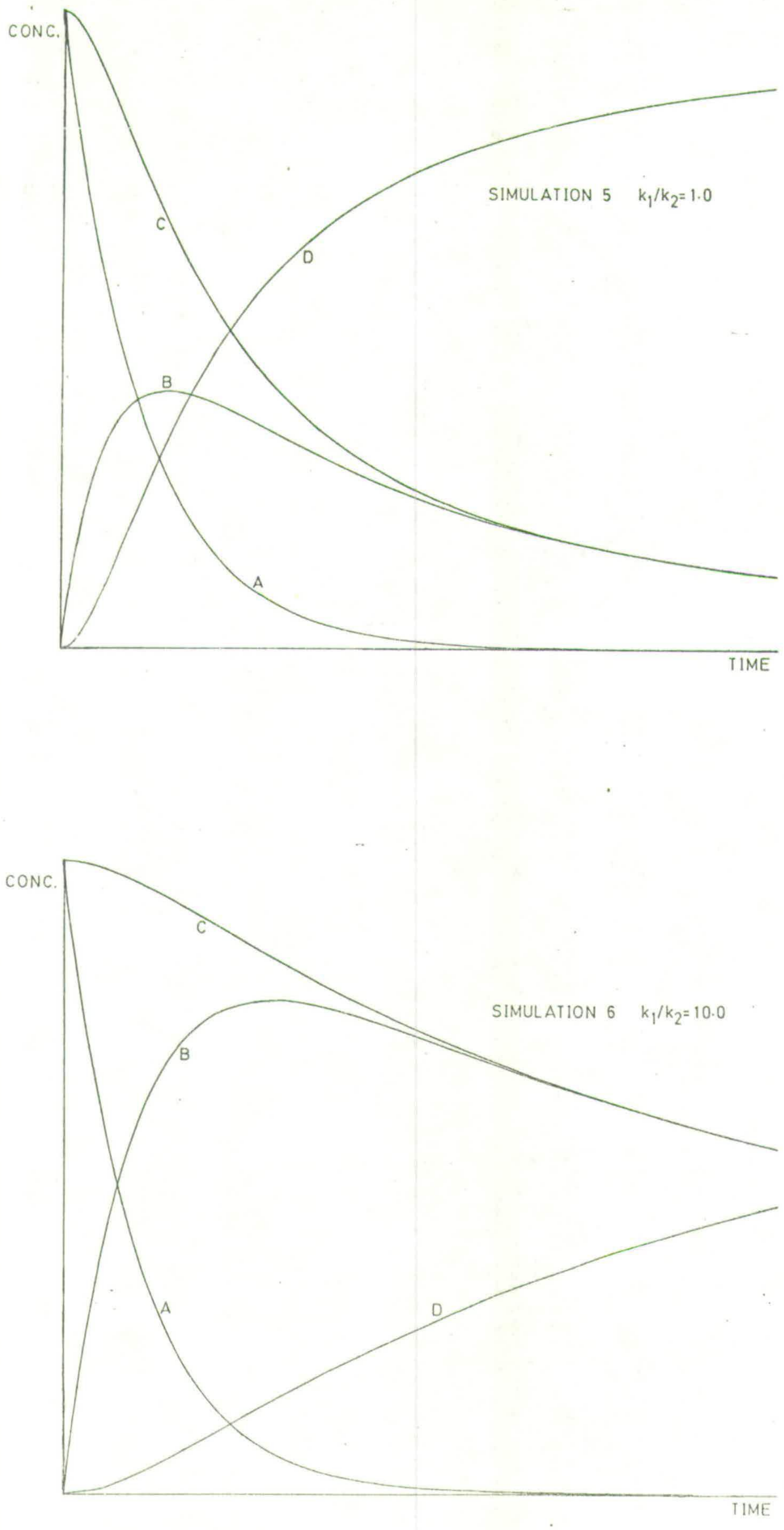


Figure 5-2 (continued). Analogue Computer Simulations

6 ATTEMPTED EXTENSION OF THE SYNTHETIC SCOPE OF PALLADIUM-ASSISTED ALKENYLATION.

A few reactions were carried out in an attempt to determine the extent of the usefulness of the palladium alkenylation reaction. The results were variable, and are described below. All the reactions were performed prior to the investigation of the usefulness of various oxidants in regenerating palladium-II in the reaction medium, and thus oxygen and/or cupric acetate were used, as described by Moritani.[13, 15]

6A Attempted Phenylation of Phenylacetylene

Oxygen (ca. 40 ml/min) was bubbled through a porosity 1 glass sinter into a mixture of benzene (37 g, 500 mmoles, 1000 equiv.), palladium acetate (112.2 mg, 0.5 mmole, 1 equiv.), phenylacetylene (0.51 g, 5 mmoles, 10 equiv.), acetic acid (60 ml, 1 mol, 2000 equiv.) and cupric acetate (1 g, 5 mmoles, 10 equiv.), stirring and boiling under reflux, overnight. The mixture was worked up in the manner described previously except that saturated sodium bicarbonate solution was used to neutralise the acetic acid instead of dilute potassium hydroxide. G.c. analysis (5% SE30, 100-250°) of the red oil obtained after drying and evaporation of solvent, showed no trace of the expected product, diphenylacetylene, and, indeed, very little volatile material. D.c.c. analysis of the mixture, using chloroform, produced only involatile tars that were not further investigated.

6B Vinylation of Biphenyl

Ethylene and air were bubbled (ca. 40 ml/min) into a mixture of biphenyl (77 g, 500 mmole, 1000 equiv.), palladium acetate (112.2 mg, 0.5 mmoles, 1 equiv.), acetic acid (110 g, 1.8 mmoles, 3600 equiv.) and cupric acetate (3.0 g, 15 mmoles, 30 equiv.) which was stirred and maintained at 90° in a stirred oil bath. After reaction overnight the mixture was worked up as previously described. Excess biphenyl

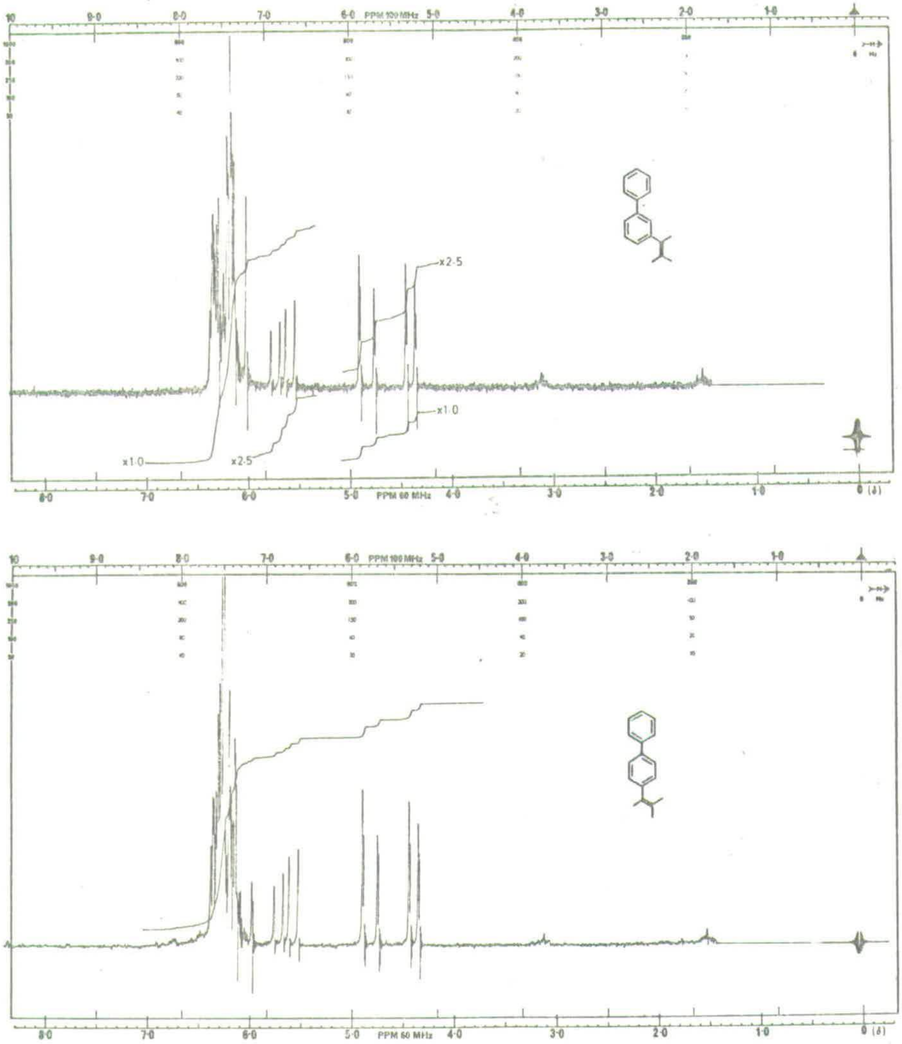
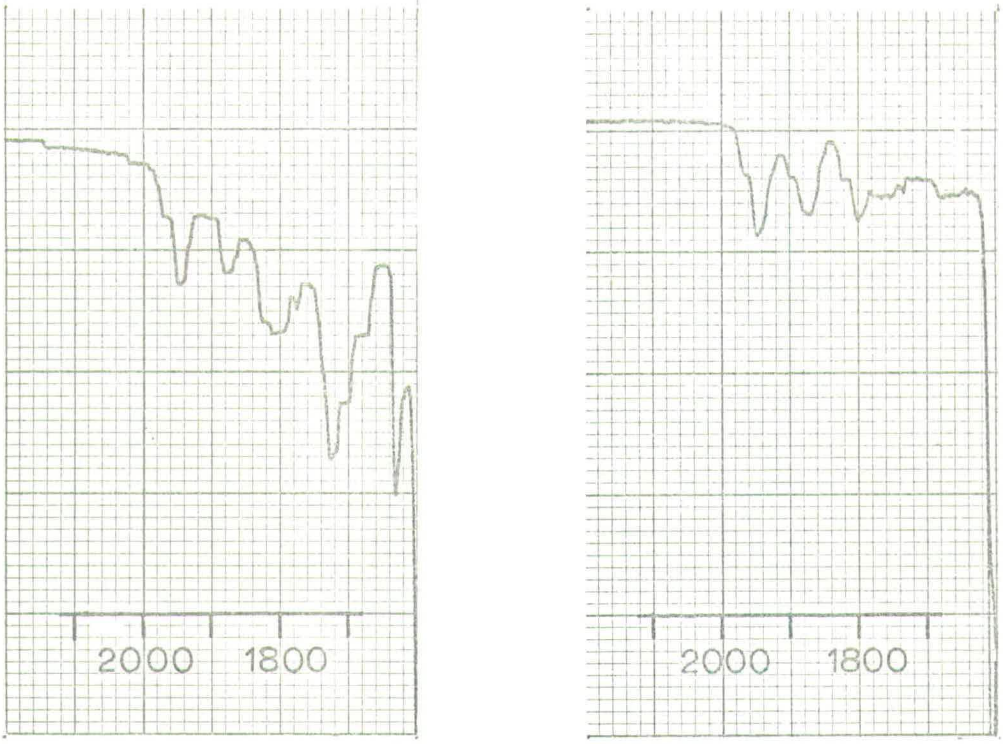


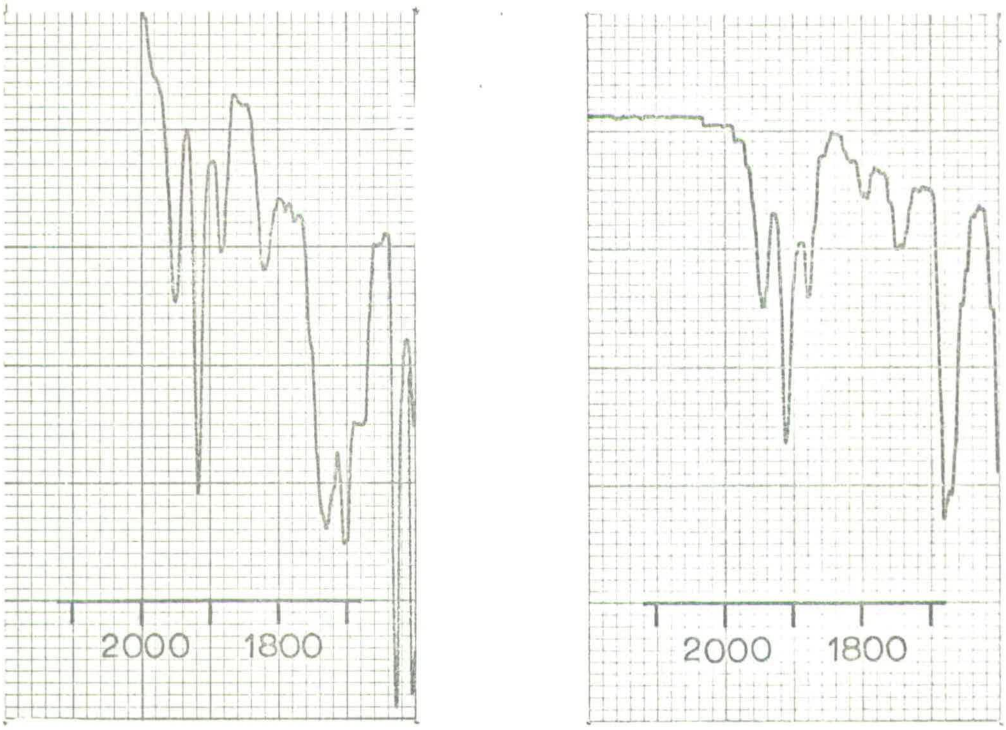
Figure 6-1. N. m. r. Spectra of Vinyl Biphenyls



3-Vinylbiphenyl

3-Ethylbiphenyl

Figure 6-2. I. r. spectra of 3-substituted biphenyls (scale in cm^{-1})



4-Vinylbiphenyl

4-Ethylbiphenyl

Figure 6-3. I. r. spectra of 4-substituted biphenyls (scale in cm^{-1})

was removed by distillation under reduced pressure leaving a red oil as residue. G.c. analysis (5% SE30 200-250^{o}) indicated two major products, designated A and B in order of retention time. There was also a considerable residue of biphenyl. D.c.c. separation of the mixture using cyclohexane gave a mixture of biphenyl with the two products, and a semicrystalline brown solid. The mixture of A, B and biphenyl was separated by preparative g.c. using a 15 ft (5m) 20% APL column at 220^{o}. Automatic processing for 72 hrs gave A (36.9 mg) and B (63.4 mg), the former as an oil and the latter as a solid at room temperature. N.m.r. spectra, Fig. 6-1 (100MHz, CCl_4), showed the characteristic vinyl pattern together with a multiplet in the aromatic region. The integral was correct for an isomeric mixture of vinyl biphenyls $Ph{\cdot}C_6H_4{\cdot}CH{:}CH_2$.

Specific assignment of substitution position was not possible, however, from the n.m.r. spectra. Structural assignment was made after examination of the i.r. spectra of the compounds in the region 1700 cm^{-1} - 2000 cm^{-1}. This region contains absorptions that are frequently characteristic of the aromatic substitution pattern.[80] Comparison of the i.r. spectra of authentic samples of 3- and 4-ethyl biphenyl with the spectra obtained from A and B allowed the assignment of the former to 3-vinyl biphenyl and the latter to 4-vinyl biphenyl (Figs 6-2 and 6-3). In addition the spectrum of B matched, peak for peak, with a published spectrum of 4-vinyl biphenyl.[81] Due to the high temperature required for separation on the preparative g.c., both compounds were contaminated with APL stationary phase, so meaningful m.p.s were not obtained.

The semicrystalline brown residue remaining after d.c.c. separation of the mixture appeared after g.c. analysis to contain only non-volatile components. Conventional column chromatography on alumina, using linear gradient elution[82] (light petroleum to ether) resulted in the separation of 38.5 mg of a white powder, C. This appeared to be pure by g.c., as only one peak was observed, with a retention time of 80 minutes (5% SE30, 250^{o}). It had a sharp m.p.

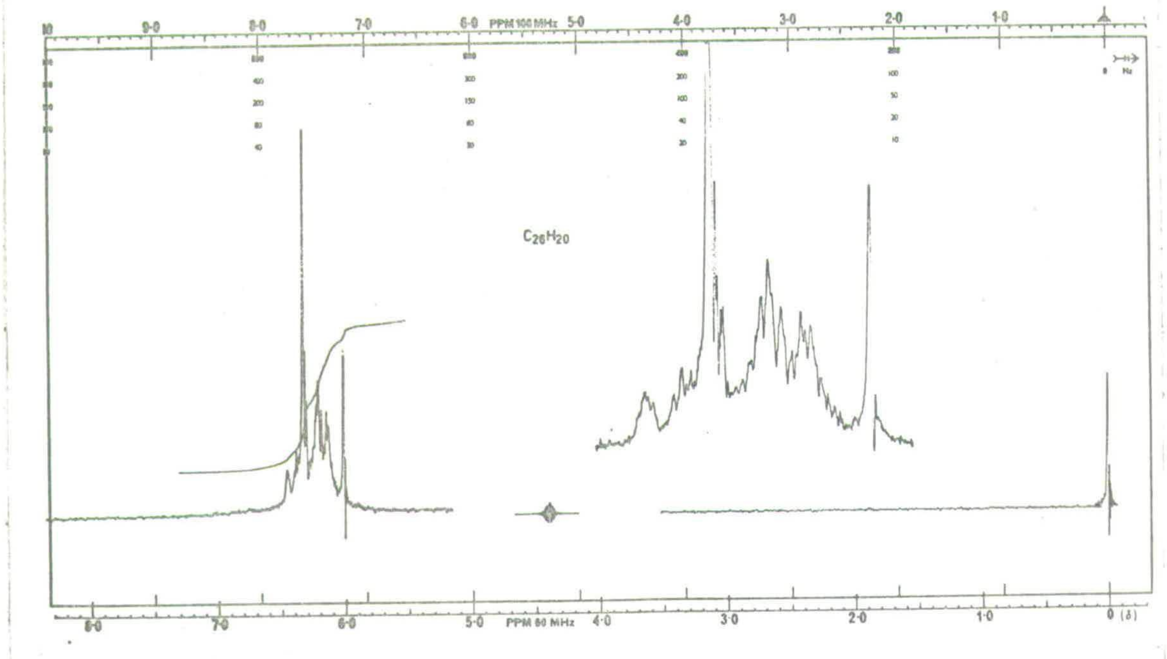
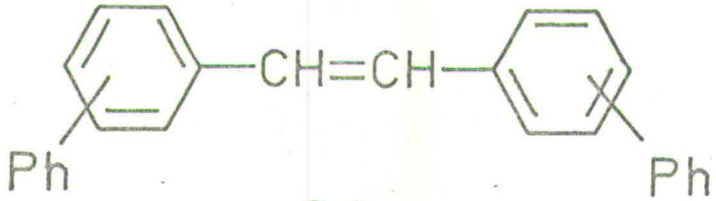


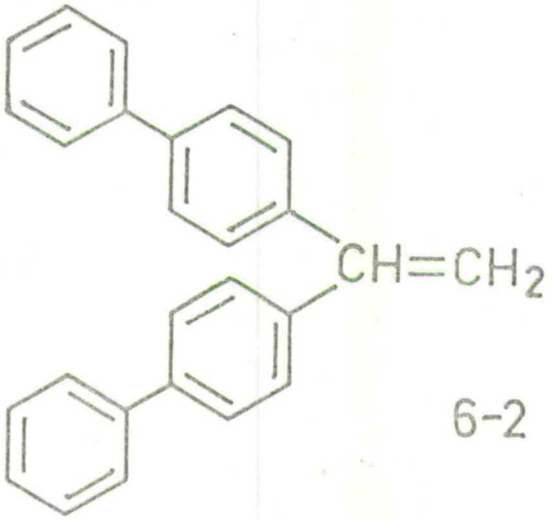
Figure 6-4. N. m. r. Spectrum of $C_{26}H_{20}$

of 179-180° after recrystallisation from ethanol. M. s. indicated a molecular weight of 332 and exact mass measurement showed this to be 332.156405. $C_{26}H_{20}$ requires 332.156493, a difference of less than 1 ppm. N. m. r., (100MHz, $CDCl_3$ and CH_2Cl_2) Fig. 6-4, showed signals only in the aromatic region, 2-3 τ. Closer inspection showed that this consisted of a sharp singlet (2.81 τ) and a multiplet, (2.2 τ - 2.7 τ), the integral ratio being 1 to 9. The i. r. spectrum (CCl_4) showed only hydrocarbon absorptions. This evidence and likely path of the reaction suggested a compound of the type 6-1.



6-1

However, of such compounds, 4,4'-diphenyl-trans-stilbene has a recorded m. p. of 300-302° [83, 84] and the cis-isomer has a recorded m. p. of 222-223° [84]. Other positional isomers have not been reported. There existed the possibility of the compound being 1,1-bis(4-biphenylyl)ethylene, (6-2):



6-2

but this has a recorded m. p. of 211°. [85]

Yields have not been calculated for these products because of the very inefficient methods used to separate them.

6C Attempted Vinylation of Furan

Ethylene was bubbled (40 ml/min) into a mixture of furan (34 g, 500 mmoles, 1000 equiv.), palladium acetate (112.2 mg, 0.5 mmoles, 1 equiv.), acetic acid (50 ml 1 mole, 2000 equiv.) and cupric acetate, (2 g, 10 mmoles, 20 equiv.) boiling under a reflux condenser cooled by solid carbon dioxide. After 12 hours, the mixture was worked up in the manner previously described to give a pungent smelling brown oil (107 mg). G. c. analysis (5% SE30, 50-250°) showed this to contain no volatile products.

6D Attempted Reaction Between Ethylene and Hexamethylbenzene.

Ethylene and oxygen were bubbled (40 ml/min for each) into a mixture of hexamethylbenzene (32.5 g, 200 mmole, 1000 equiv.) palladium acetate (44.9 mg, 0.2 mmole, 1 equiv.), cupric acetate (400 mg, 2 mmole, 10 equiv.) and acetic acid (120 ml 2 moles 20000 equiv.) boiling under reflux with stirring for 14 hours. The greater quantity of acetic acid was used to achieve a more homogeneous solution. After work-up in the manner previously described, a residue consisting mainly of unreacted starting material was obtained. Several methods were used in an attempt to separate this from any reaction products, including distillation, sublimation and d. c. c. However, none were successful and work on this mixture was abandoned. G. c. analysis (5% SE30, 175-250°) of such concentrates as were obtained showed the presence of many products.

6E Attempted Vinylation of Naphthalene

Ethylene and oxygen were bubbled (40 ml/min) into a mixture of naphthalene (14.2 g, 111 mmoles, 111 equiv.), palladium acetate (224 mg, 1 mmole, 1 equiv.), cupric acetate (1.82 g, 10 mmoles, 10 equiv.), acetic acid (15 ml 250 mmoles, 250 equiv.) and n-heptane (50 ml) boiling under reflux, for eight hours. n-Heptane was used as a solvent in an attempt to alleviate the difficulty of removing large quantities of unreacted solid starting material. After work-up in the manner previously described, g.c. analysis (10% APL 198^{o}) showed the presence of two products in low yield. Attempts to separate these from the bulk of the starting material by such methods as sublimation, distillation and chromatography were again unsuccessful so work on this mixture was not pursued.

DISCUSSION

Page

CONTENTS

DISCUSSION

1. OXIDATIVE RECYCLING PROCEDURES

Palladium assisted synthesis was changed from a curiosity to an economic industrial process after the discovery of an oxidative palladium recycling process.[3-5] As the reactions now became catalytic in the precious metal, research, and hence the number of useful syntheses, grew rapidly.[6] Most workers were content, however, to follow the precedent of the Wacker reaction[3-5] and use Cu (II) salts or Fe (III) salts as oxidants, and little work was done to determine the most efficient oxidant for a particular system.[6c] This was despite the fact that many of these new reactions were completely different from the Wacker reaction, in terms of reactants, products and solvent medium. Therefore, as stated previously, part of the aim of the present work has been to determine whether this extension of the methods used in the Wacker reaction is experimentally justifiable and if not, to discover a useful oxidant for the palladium assisted alkenylation reaction.

Superficially it might be expected that the standard redox potential, E^o, would be a useful guide to the oxidising power of a chosen system. It has been stated by Maitlis,[86] that any oxidising agent with a redox potential higher than that of Pd (II) can be used. However, on closer inspection this proves not be the case. For example the E^o value for palladium is given thus:[87]

$$Pd \longrightarrow Pd^{2+} + 2e \quad E^o = -0.987\ v$$

The two commonly used oxidants in the Wacker process have E^o values thus:

$$CuCl \longrightarrow Cu^{2+} + Cl^- + e \quad E^o = -0.538\ v$$

$$Fe^{2+} \longrightarrow Fe^{3+} + e \quad E^o = -0.771\ v$$

Therefore, it would appear that rather than oxidise palladium metal to Pd^{2+}, both of these metals should themselves be oxidised in the presence of Pd^{2+}, leading to a rapid precipitation of palladium! The experimental observation that this does not occur merely serves to indicate that the conditions under which the Wacker reaction is carried out are so far removed from those under which E^o values are measured, that such values cease to have any use or meaning. Maitlis' statement could therefore be misleading, unless the nature of the solvent system used and the other ions present in the system is taken into account. In the present work, ionic strengths and the solvent systems used (usually; non-aqueous) were even further removed from standard E^o measurement conditions than those of the Wacker reaction. Choice of oxidants was therefore governed by their availability and their estimated effect on the organic materials present in the mixture.

At the temperature and concentration of the mixture which was used, sodium dichromate was found to be the most efficient recycling oxidant. The results obtained are shown in Table 1-1.

Table 1-1 Palladium-assisted phenylation of styrene: use of oxidants (see Experimental Section p. 34)

Oxidant	Equiv. used	Yields %	
		a	b
$Fe(OAc)_2OH$	2	1.8	37
Anthraquinone	1	1.9	37
$Cu(OAc)_2 \cdot H_2O + O_2$	1	5.7	114
$K_2S_2O_8$	1	5.9	118
O_2 gas	-	6.4	152
$Cu(OAc)_2 \cdot H_2O$	1	7.6	127
$NaClO_3$	1	8.8	176
AgOAc	2	9.8	196
$NaBO_3 \cdot 4H_2O$	1	10.6	212

Table 1-1 (cont.)

Oxidant	Equiv. used	Yields %	
		a	b
Chloranil	1	15.5	310
$Na_2CrO_4 \cdot 10H_2O$ *	1	18.1	362
Quinone	1	18.3	366
$Na_2Cr_2O_7$	1	21.0	421
$Na_2Cr_2O_7$	1	27.3	546
$Na_2Cr_2O_7 \cdot 2H_2O$	1	28.2	564
None	-	1.46	20

Yields in col. (a) are based on starting styrene

Yields in col. (b) are based on palladium acetate.

* This experiment was carried out by Mr. J. A. M. Bayne.

However, consequent upon the foregoing argument concerning E^o values is the corollary that by changing the temperature, the nature of the solvent etc, an oxidant may change in efficiency by an unknown amount. Thus the order of efficiency of the oxidants as given in Table 1-1 must be regarded as specific for the reaction conditions as used. Nevertheless, the concentration dependence of the efficiency of sodium dichromate was determined (see Experimental Section, Figures 3-1 and 3-2, p.34-35).

The shape of these curves may be accounted for by assuming that two competing processes are occurring. Before the maximum, recycling efficiency increased almost linearly with oxidant concentration. After the maximum, the yield of product fell. The inference must be that destruction of the organic materials in the mixture has become more important than the synthesis of product. Less product was being formed due to loss of starting material and also some of the product formed was being destroyed by dichromate oxidation. In addition, Henry[88, 89] and Heck[32] have also observed the interference of side reactions, including isomerisations and rearrangements in oxidatively recycled palladium assisted alkenylations, although they both used copper salts to effect oxidation.

It was anticipated that if the oxidant concentration could be maintained on the rising portion of the curve product yield might be increased without suffering the penalty of its oxidative destruction. This was found to be the case. When a solution of sodium dichromate was added dropwise into the oxidant-free reaction mixture, the yield rose to 46% (based on styrene). A control reaction, in which the same quantity of oxidant was present in a similar reaction mixture right from the beginning gave a yield of only 27%. With more careful control of the dropping rate, a still further improved yield might be anticipated.

It is likely that a curve similar to Fig. 3-1 and 3-2 (p. 34-35) exists for all oxidants. Also the optimum concentration for each oxidant could be expected to be dependent on temperature, and the nature of the solvent. Thus, the choice of an oxidant is probably very dependent on the reaction in which it is to be used, and subject to the consideration of rather more factors than just the standard redox potential. It would be possible to determine exhaustively the concentration and temperature dependence of the efficiency of an oxidant for any given reaction, but such an approach would be very costly in terms of time and effort. The result would again probably be specific for the particular reaction under study, and not of any general applicability. It might perhaps be a profitable exercise to investigate the usefulness of direct electrochemical oxidation of the palladium. Two patents have appeared describing industrial processes which used such methods, one concerning a continuous process,[58] and the other involving batch recycling.[59] These might well provide a starting point for further work.

Despite these drawbacks, dropwise addition of sodium dichromate has so far provided the best yield obtained in a palladium-assisted alkenylation with oxidative palladium recycling (see for instance Table 6-1, Introduction, p.19.)

2. SYNTHETIC EXPLORATION

The attempts to explore the synthetic usefulness of the reaction were carried out at an early stage of the work, before a satisfactory appreciation of the likely reaction mechanism had been gained. They were also performed using cupric acetate and oxygen to recycle the palladium, as described by Moritani.[13, 15] This probably produced a reaction mixture which was too strongly oxidising for two of the reactants, (furan and phenylacetylene) producing only tars. Also, side reactions induced by Cu^{II} as reported by Heck[32] and Henry[88-89] might have occurred. Use of Moritani's reactant proportions[15] also led to the use of such a great excess of solid reactants that only in the case of biphenyl were any products separable. Due to these experimental difficulties, little useful information could be obtained from this short series of reactions. Further work of this type would be best carried out with no oxidants present, and with less generous quantities of starting materials.

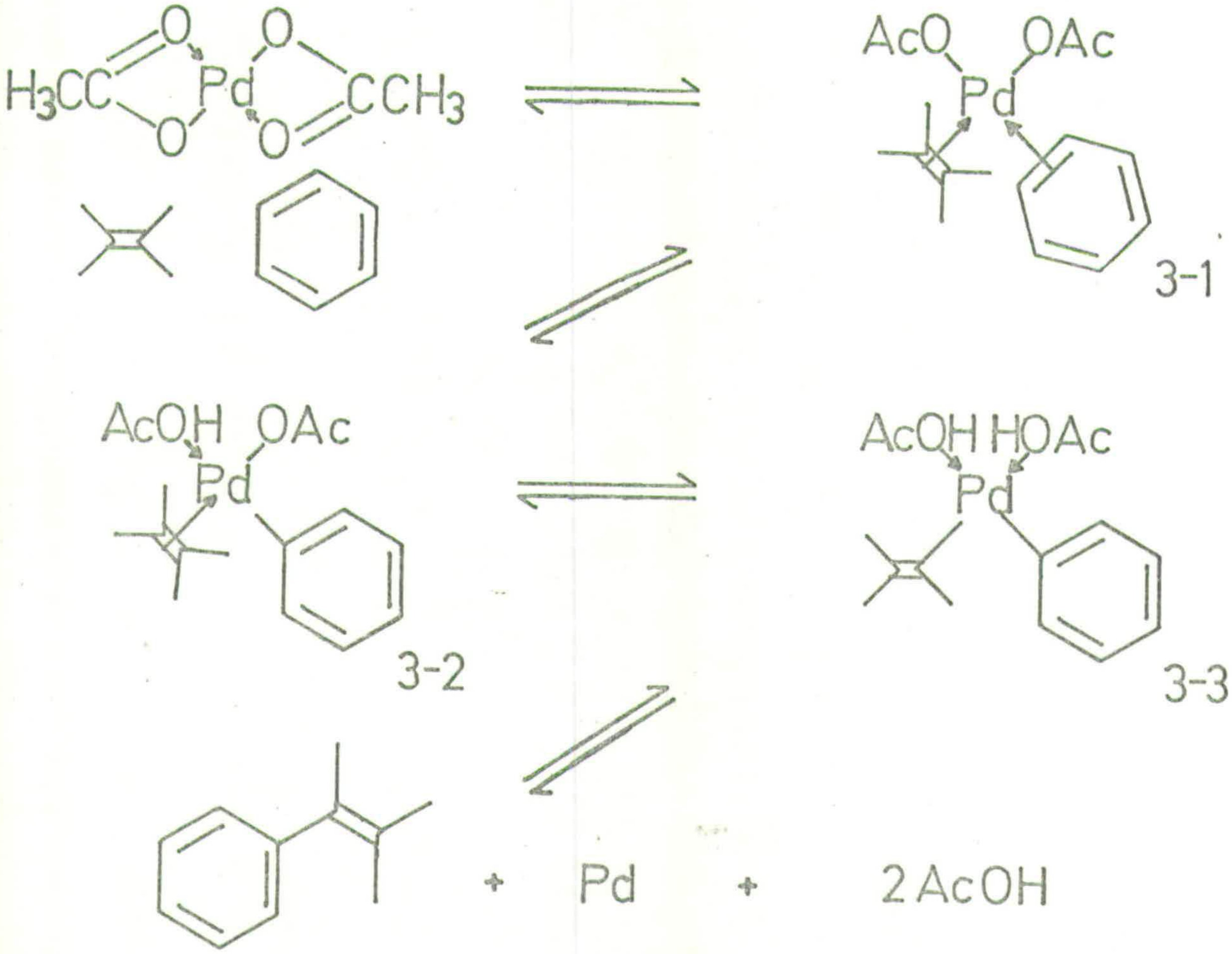
3. THE MECHANISM OF PALLADIUM-ASSISTED ALKENYLATION OF AROMATIC COMPOUNDS

Despite a quantity of work by Moritani[10-27] and a number of other workers, notably Shue[35-37] and Heck,[25-34, 42-44] the mechanism of palladium assisted alkenylation was still uncertain at the start of this investigation. Stoichiometrically the reaction is an oxidative coupling. The alkene and the aromatic compound are joined and one hydrogen atom is lost from each at the coupling sites.

Palladium acetate appears to be virtually specific for the reaction during which it is reduced to palladium metal. The displaced hydrogen atoms finally appear as part of the acetic acid solvent.

$$\mathrm{ArH + RCH{:}CH_2 + Pd(OAc)_2 \rightarrow ArCH{:}CHR + Pd + 2AcOH}$$

Based on his own published and unpublished work, Moritani has suggested a mechanism for the reaction,[18] (Scheme 3-1):



Scheme 3-1

The alkene and the aromatic compound both coordinate with the palladium acetate to form π-complex, 3-1. This transforms, in two steps via 3-2, to give the double σ-complex 3-3, which subsequently decomposes to the products.

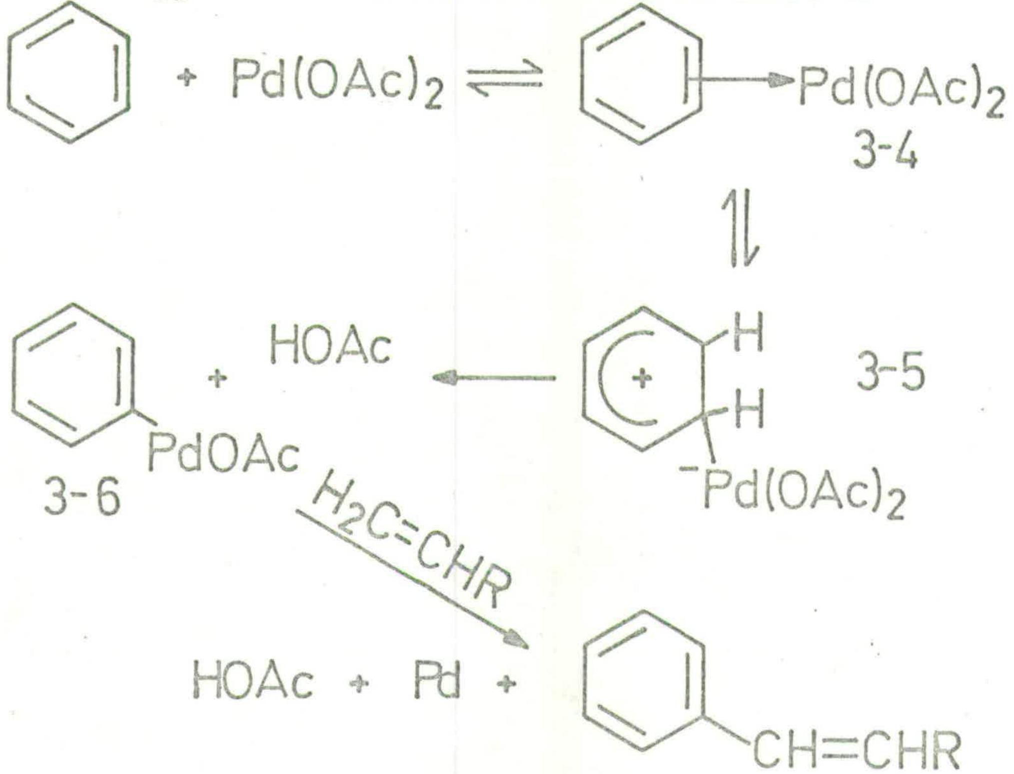
It is doubtful, however, if the work cited to support this mechanism is of a sufficiently systematic nature to justify its use for this purpose.[14, 16-18] Reasons for this statement are discussed in the Introduction (p. 8) and rest largely on the published work of

Shue concerning isotope effects observed with this reaction.[36] It will now be shown that the current work with substituents in the alkene and the aromatic compound, makes support of the Moritani mechanism[18] even more difficult.

3A Another Mechanism for the Palladium Assisted Alkenylation Reaction

Based on the current work and evidence in the literature relating to this and allied reactions it is now possible to suggest a satisfactory partial reaction mechanism. It will be shown that this mechanism can account for the product distribution and partial rate factors observed in competition reactions, the observed kinetics of the reaction and the isotope effect observed by Shue.[36] A review of the ancestry of the vital reactive intermediate, 3-6, will also be given.

The suggested mechanism is shown in Scheme 3-2.



Scheme 3-2

As depicted above, this partial mechanism does nothing to explain the reaction of intermediate 3-6 with the alkene to give products. This is believed to be the fast step of the reaction and is discussed in greater detail later, p.75. The slow step of the reaction is believed to be the formation of 3-6 by an electrophilic substitution closely related to the normal electrophilic substitution reaction of aromatic compounds.[51]

3B Evidence from Competition Reactions

The product isomer distributions found in this investigation after competitive reaction of styrene for mixtures of various monosubstituted benzenes with benzene are given in Table 3-1 (see also Experimental, p.40, Table 4-3).

Table 3-1 Competition Reactions

$$PhX + PhH + Ph\,CH{=}CH_2 \xrightarrow{Pd(OAc)_2} Ph\,CH{=}CH_2 + PhCH{=}CH\,C_6H_4X$$

X	Product isomer distrib. %			Total Yield of subst. stilbene %	Total Yield of stilbene %
	o-	m-	p-		
CH_3	27.9	72.1*		35.3	22.1
OCH_3	35.8	5.8	58.4	51.4	20.1
Br	18.8	17.7	63.5	17.3	34.3
NO_2	14.9	77.7	7.4	3.5	36.7
CF_3	1.4	80.4	18.2	6.9	38.2

* Combined value for m- and p-isomers.

All yields are based on starting styrene.

For further details of these reactions, see Experimental, p.38 et seq.

The observed distribution is that which would be expected from an electrophilic aromatic substitution. With electron withdrawing substituents, e.g. $-CF_3$, $-NO_2$, substitution is predominantly at the meta-position, and the total yield of substituted product is lowest, lower than the unsubstituted product. With electron donating substituents, e.g., $-CH_3$, $-OCH_3$, ortho- and para-substitution are predominant and the yield of substituted product is at its highest, higher than the unsubstituted product. (For the case of methyl substituted stilbene see page 39). Intermediate between these is Br which, with its mixed electronegative and electron donating properties, gives a yield predominantly of the para-isomer intermediate between the other two cases, but still lower than the unsubstituted case. All the substituents, except $-NO_2$, show ortho-deactivation. $-NO_2$ gives the statistically required ortho:para ratio of 2, the others much less.

Further quantitative assessment follows from the calculation of partial rate factors (Table 3-2) (see also Experimental, p.40).

Table 3-2 Partial Rate Factors and Reactivity Ratios for Competition Reactions

$$\mathrm{PhX + PhH + PhCH{:}CH_2 \xrightarrow{Pd(OAc)_2} PhCH{:}CHPh + PhCH{:}CH\,C_6H_4X}$$

X	Partial Rate Factors			Reactivity Ratios
	f_o	f_m	f_p	kX/kH
CH_3	1.3	2.4*		1.6
OCH_3	2·75	0.44	9·0	2.6
Br	0.3	0.3	1.9	0.5
NO_2	0.04	0.2	0.04	0.1
CF_3	0.008	0.4	0.2	0.2

* Combined value, see p. 39.

The partial rate factors and reactivity ratios observed in the competition reactions cover a narrow range. Over the entire range of substituents used the reactivity ratios vary by a factor of 25 and the partial rate factors vary by about 2.5×10^3. However, the isomer distribution is that of an electrophilic substitution reaction, and it is illuminating to compare the results obtained from other electrophilic substitutions on the same substituted benzenes used in the present work. (Tables 3-3 and 3-4)[51]

Table 3-3 Reactivity Ratios for Electrophilic Substitution of Substituted Benzenes.
(Compared to reaction with benzene=1)

$PhX + Y \longrightarrow C_6H_4XY$

X \ Y	NO_2	Br	SO_3	OH	$PhCH_2$
Me	2.5	605	ca.40	12	3.2
OMe				530	
NO_2	$<10^{-5}$				
Br	0.03		0.035		0.2

Table 3-4 Partial Rate Factors for Electrophilic Substitutions of Substituted Benzenes

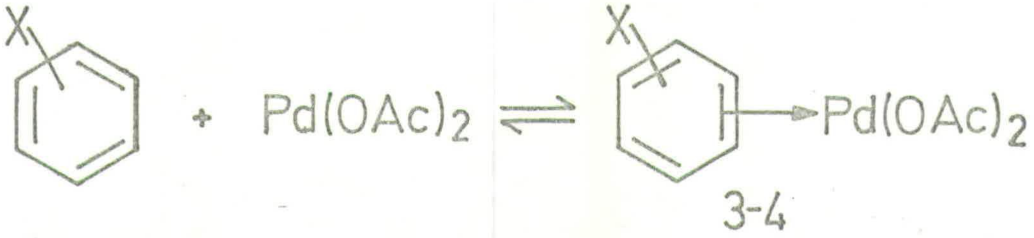
$PhX + Y \longrightarrow C_6H_4XY$

Y	NO_2			OH			Br			Ph CH_2		
X	f_o	f_m	f_p	f_o	f_m	f_p	f_o	f_m	f_p	f_o	f_m	f_p
Me	40	2	60	28	0.8	14	600	5.5	2420	4.9	2.3	9.4
OMe				1170		830		1.1×10^{10}				
NO_2							ca 10^{-4}					
Br	0.03	0.001	0.1							0.18	0.004	0.72

The range of effects observed for the palladium-assisted alkenylation (Table 3-2, p. 58) is narrower than that usually observed for an electrophilic substitution reaction. A narrow range of partial rate factors indicates a lack of selectivity of position of attack by the electrophile and has been interpreted as an indication of a highly reactive attacking species.[90]

As mentioned in the Introduction (p. 10), Shue has observed a positive deuterium kinetic isotope effect in the palladium-assisted reaction between hexadeuterobenzene and styrene, kH/kD = 5.3.[36] He also reported the absence of any such effect in the reaction between benzene and β,β'-dideuterostyrene. This suggests very strongly that the rate determining step of the reaction is cleavage of a hydrogen-aromatic compound bond. In addition, in the reaction using hexadeuterobenzene, no isotopic scrambling was observed in the unreacted benzene. This significant observation indicates that the H-C bond-breaking step in the reaction of the aromatic compound is irreversible.

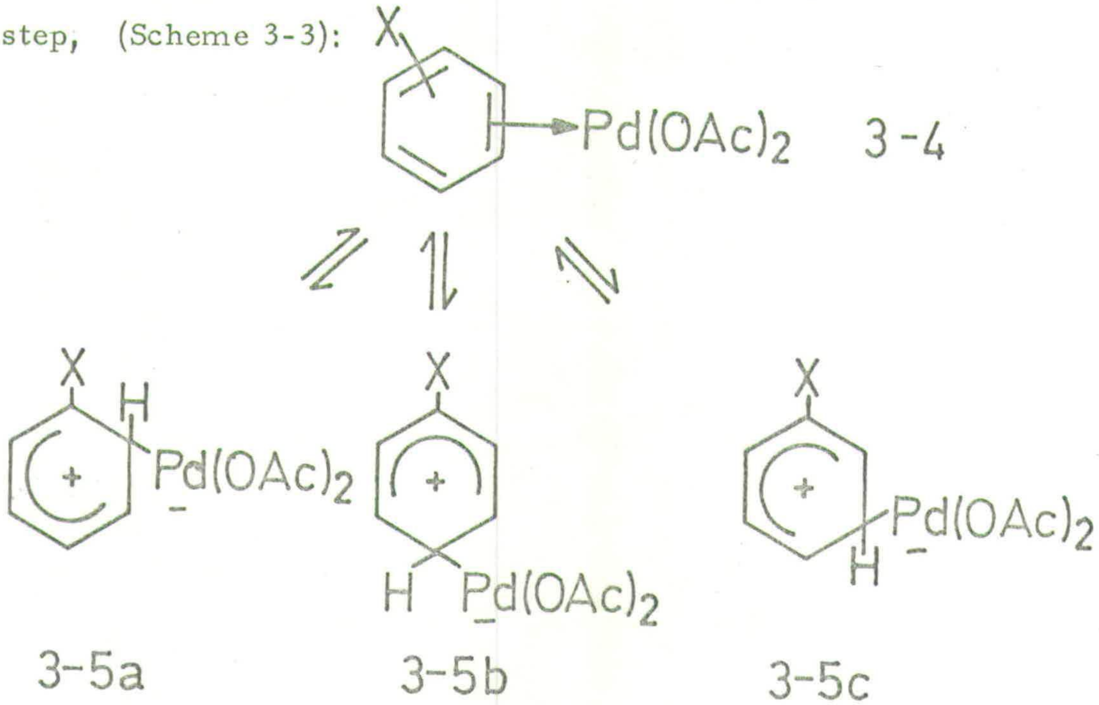
From the evidence set out above it is possible to examine the new reaction sequence in more detail (see p. 56). A likely first step is the reversible formation of a π-complex between palladium acetate and the aromatic compound:



3-4

Complexes of aromatic compounds with palladium (and its immediate neighbours in the periodic table, nickel platinum, etc.) in which the metal is bonded to the ring as a whole, are unusual.[91] Also, 3-4 would require a 5-coordinate palladium atom which is the exception rather than the rule.[92] Ease of formation of metal-aromatic compound complexes has been observed to be favoured by electron donating groups,[91] which agrees with the order of reactivities observed in the present work. It is at this step therefore that discrimination between substituents in the benzene ring occurs. This can be rationalised by the increased availability of ring electrons for the palladium-benzene ring bond in the presence of an electron donating substituent, and vice-versa for an electron withdrawing substituent.

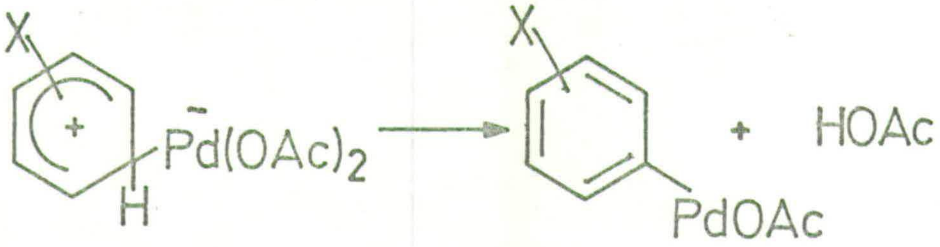
Palladium-carbon σ-bond formation is proposed as the next step, (Scheme 3-3):



Scheme 3-3

As the palladium atom in 3-4 is associated with the ring as a whole, formation of each of the isomeric intermediates 3-5a, b, c is possible. Product orientation is decided at this stage, according to the usual criteria applied in electrophilic substitution reactions; a charge separation has occurred and the most stable isomer of 3-5 will be the one in which these charges can be most easily accommodated with the electron donating or withdrawing properties of the substituent X. This step is reversible. The lack of strong selectivity observed in the competition reactions may also be accounted for at this stage. The palladium atom is well able to dilute the effect of the negative charge which develops on it by distribution of electron density through vacant d-orbitals, and transfer to the electron-withdrawing acetate groups remaining attached. This results in a decrease of the importance of the electronic effect of X. A considerable spatial requirement for the palladium acetate group is indicated by the low ortho/para ratio observed.

There occurs finally, the non-reversible, rate determining loss of a proton from the aromatic ring, and an acetate from the palladium:



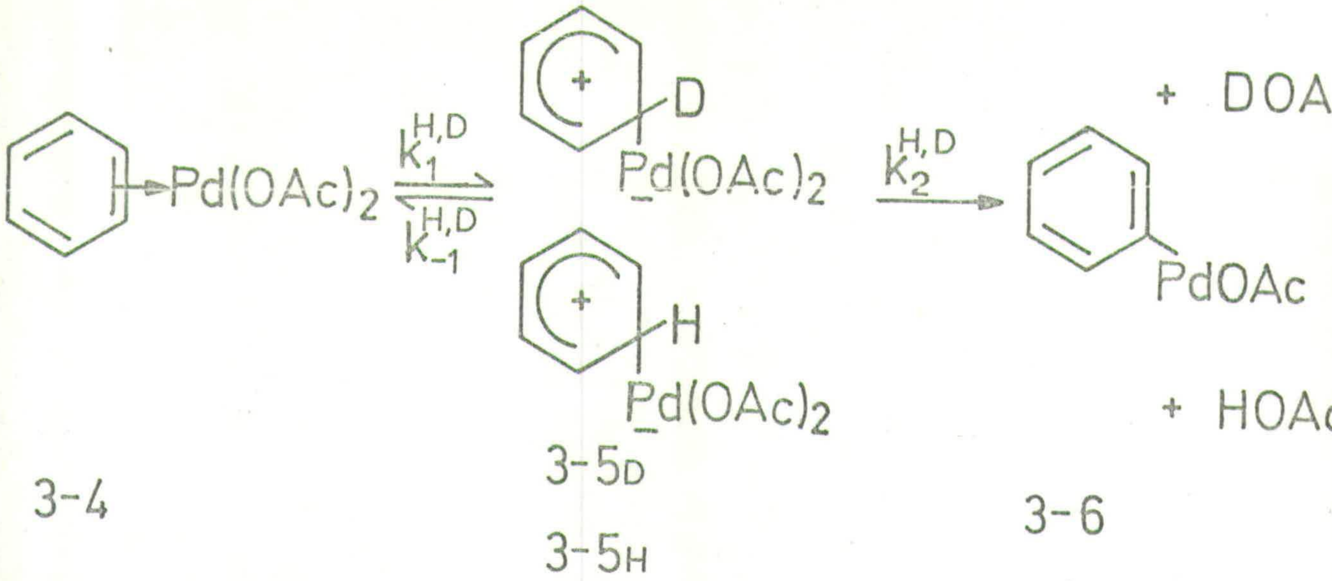
3-5 3-6

It is quite unusual for the restoration of aromaticity to a ring to be rate-determining in a reaction, but the evidence from Shue's work with hexadeuterobenzene certainly implies that it is so in this case.[36] The kinetic isotope effect, kH/kD = 5.3, is too large for a secondary effect, and the absence of isotopic scrambling is strongly in favour of proton loss being non-reversible. Normal electrophilic aromatic substitutions do not show a primary kinetic isotope effect, as re-aromatisation of the ring has such a low energy barrier. However, there are exceptions, the most significant being mercuration.

Electrophilic mercuration occurs when an aromatic compound is allowed to react with a mercury salt, e.g. mercuric acetate:

$$\mathrm{ArH} + \mathrm{Hg(OAc)_2} \longrightarrow \underset{3\text{-}7}{\mathrm{ArHgOAc}} + \mathrm{HOAc}$$

Formation of the mercurated product, 3-7, is accompanied by a kinetic isotope effect which is, in the case of benzene, kH/kD = 6.0.[51] The explanation for the effect invokes the weakness of the carbon-mercury bond compared to the carbon-hydrogen bond. It is likely that an analogous situation occurs during the formation of 3-6 and the process may be depicted in the following manner, (Scheme 3-4).



Scheme 3-4

If the C-Pd bond is weak the rate of back reaction, k_{-1} will be significant. It will also be independent of the presence of hydrogen or deuterium on 3-5. However, k_2^H is faster than k_2^D and a kinetic isotope effect will be observed if k_2^D is comparable with $k_{-1}^{H,D}$. More protiated molecules, of species 3-5H will go through the final irreversible step, while the deuterated molecules are still caught up in the equilibrium step, 3-4 $\rightleftharpoons$ 3-5D. The product 3-6 will therefore be composed of mainly non-deuterated species.

A further similarity of mercuration to the reaction under study is in the nature of the partial rate factors observed in competition reactions of mercuric acetate with benzene and substituted benzenes similar to those used in the present work, (Table 3-5):

Table 3-5 Partial Rate Factors for the Mercuration of Monosubstituted Benzenes[51]

$PhX + Hg(OAc)_2 \longrightarrow C_6H_4XHgOAc + HOAc$

X	f_o	f_m	f_p
Me	5.8	2.3	23.2
OMe	188	-	2310
Br	0.07	0.06	0.28

Though wider than that observed for the palladium reaction this is still a narrow range. Compare, for example, results obtained for partial rate factors in electrophilic nitration, (Table 3-6):

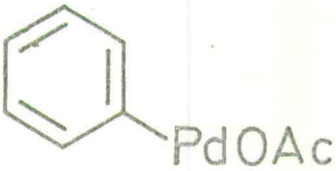
Table 3-6 Partial Rate Factors for the Nitration of Monosubstituted Benzenes.[51]

X	f_o	f_m	f_p
Me	42.4	1.9	62.6
Br	0.033	0.0011	0.112
NO_2	1.8×10^{-7}	2.8×10^{-5}	1.9×10^{-6}

Mercuration has also been observed to have a low ortho/para ratio, indicating a large spatial requirement for the mercury.

3C EVIDENCE FOR THE EXISTENCE OF ARYLPALLADIUM SALTS

The formation of intermediate 3-6, an arylpalladium salt, or σ-bonded arylpalladium-II complex, has been postulated for a number of related reactions and there is evidence that its formation as the vital reactive intermediate is the rate determining step of the reaction.



3-6

Its existence has not been conclusively proved but there is strong circumstantial evidence for its formation in several reactions. Due to the work of van Helden[7] Davidson,[8,9] Unger,[93] Henry[94] and Heck[28-34] it has gained a considerable measure of acceptance.

Species 3-6 contains an aryl-carbon to palladium sigma bond. Complexes of this type were first prepared by Calvin and Coates[95] in 1960 from, for example, bis(triethylphosphine)dibromopalladium

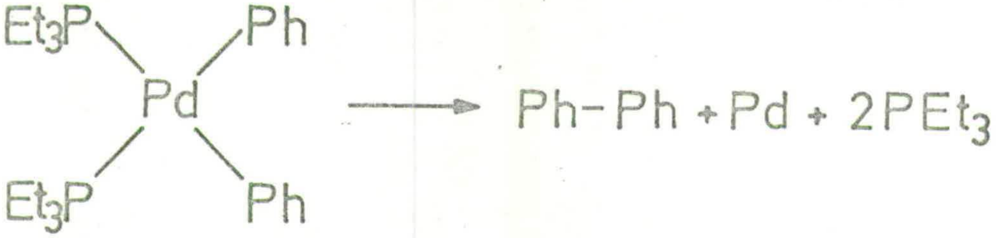
(II) after reaction with phenyllithium, (Scheme 3-4);

$$(\mathrm{PEt_3})_2\,\mathrm{PdBr_2} \xrightarrow{\mathrm{Ph\,Li}} \underset{3\text{-}8}{(\mathrm{PEt_3})_2\,\mathrm{PdBrPh}} + \mathrm{LiBr}$$

$$\xrightarrow{\mathrm{Ph\,Li}} \underset{3\text{-}9}{(\mathrm{PEt_3})_2\,\mathrm{Pd\,Ph_2}} + \mathrm{Li\,Br}$$

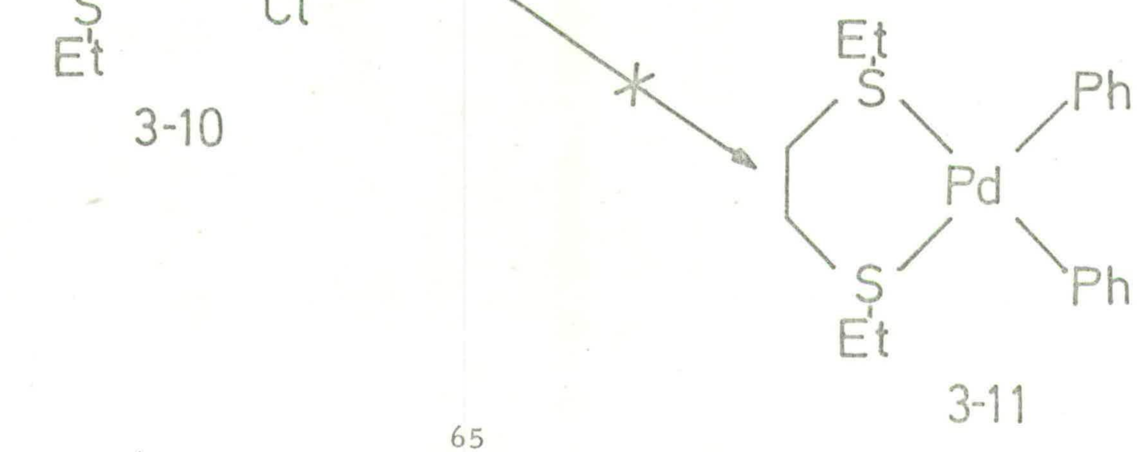
Scheme 3-4

Complexes such as 3-8 which retained a halogen atom were more easily formed and more stable than the diaryl complexes. All complexes similar to 3-9 were found to have <u>trans</u>-stereochemistry, and despite numerous attempts, <u>cis</u>-complexes could not be prepared. It was suggested that this could be because of the existence of a low energy barrier to complex decomposition and biphenyl formation:

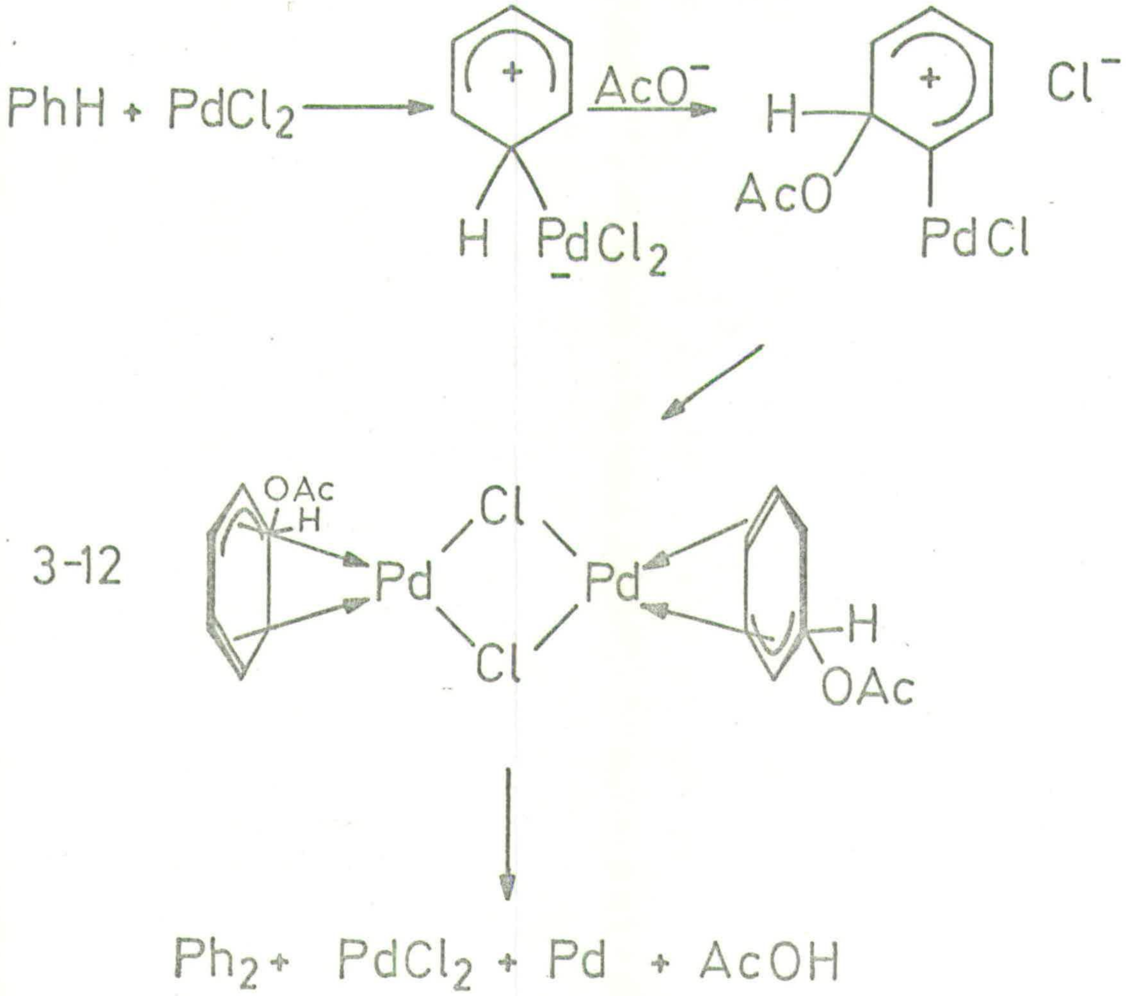


3-9

Biphenyl was in fact found in the mixture after an attempt to prepare 3-11 from phenyllithium and a complex already held in a <u>cis</u>-conformation, 3-10:

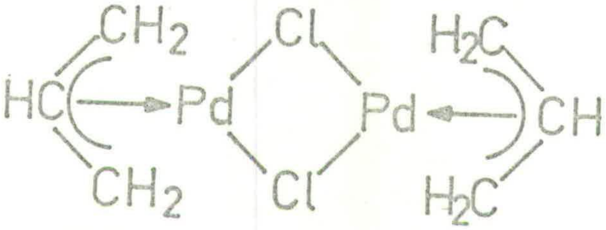


In 1965 van Helden and Verberg[7] obtained biphenyl in 60% yield from a mixture containing benzene, palladium chloride and sodium acetate in acetic acid. To account for this they suggested the intermediacy of a benzene-palladium chloride complex, in a reaction thus, (Scheme 3-5):



Scheme 3-5

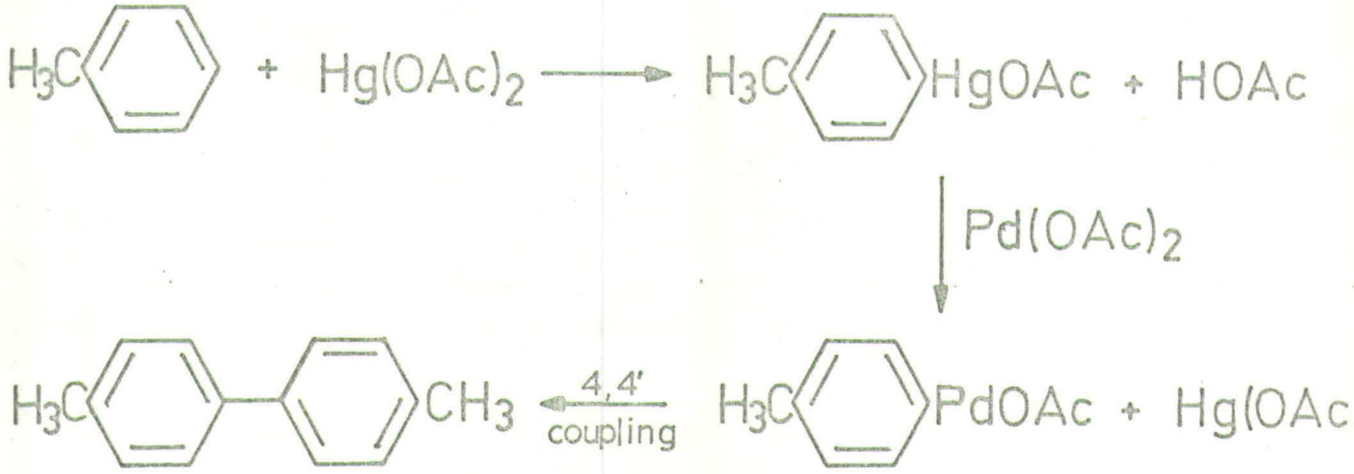
Complex 3-12 was said to have a structure and bonding akin to that found in π-allyl palladium chloride dimer:



However, compounds of this type have not been observed to dimerise,[6a] which cast some doubt on the mechanism.

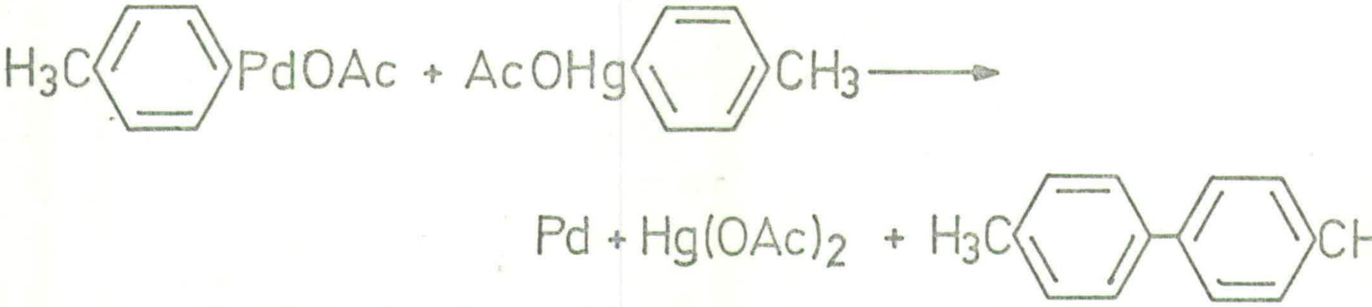
In 1966 and 1968, Davidson and Triggs[8,9] published accounts of their work on this reaction and, for the first time, proposed, by analogy with other metals, the existence of σ-bonded aryl palladium salts as intermediates. They found that if platinum (II), gold (III), mercury (II) and thallium (III) salts were subjected to the reaction conditions under which palladium (II) salts gave biphenyl from benzene, the platinum and gold salts did just this, while the mercury and thallium salts gave phenylmercury and phenylthallium salts, respectively. These were previously known stable compounds. They suggested that all the metal salts took part in an electrophilic substitution reaction, similar to mercuration or thallilation, displacing one of the hydrogens on the aromatic ring and forming the phenylmetal salt. The thallium and mercury compounds were stable, whereas the palladium and platinum ones decomposed immediately to give biphenyl. Both Davidson and van Helden discounted the presence of radicals in the reaction, due to the non-interference of oxygen and the appearance of isomer distributions from the coupling of substituted benzenes which agreed closely with what could be expected from electrophilic substitution of the ring.

Further insight into this system came in 1969 when Unger and Fouty[93] published the results they had obtained from a study of the coupling of toluene, under the influence of palladium salts. The most significant observation made in this study was the dramatic increase in yield which occurred when a mercury salt was included in the reaction mixture. Previously, yields of biaryls approaching 60% had been obtained, but by the addition of a mercury salt a practically quantitative yield was possible (based on palladium). It was previously known that mercuration of toluene takes place preferentially in the 4-position.[96] This fact, when combined with the observation that on adding increased quantities of mercuric acetate to a palladium acetate-toluene mixture, the proportion of 4,4'-bitolyl was increased, led to the inference that a double substitution reaction was taking place, i. e. mercuration followed by palladodemercuration, (Scheme 3-6):



Scheme 3-6

Unger also observed that if palladium acetate were added to a solution of pre-formed 4-tolylmercuric acetate in toluene, palladium was precipitated and 4, 4'-bitolyl produced, and no other isomer. The implication here is that the tolylpalladium acetate survives long enough in the solution to encounter a tolylmercuric acetate molecule before coupling:



Attack on the other positions in toluene to give other bitolyl isomers did occur on the addition of perchloric acid to the mixture. The rate of reaction was also considerably increased. This effect had also been reported by Davidson.[9] It is presumed to be due to the formation of a more electrophilic palladium species by the strong acid. Consequently the step where electrophilic attack occurs is accelerated leading to an overall rate increase.

Garves[45] in 1970, set out deliberately to prepare aryl-palladium salts by another route. As a starting point he also took a reaction by which arylmercury salts had been produced, the desulfination of aromatic sulfinic acids:

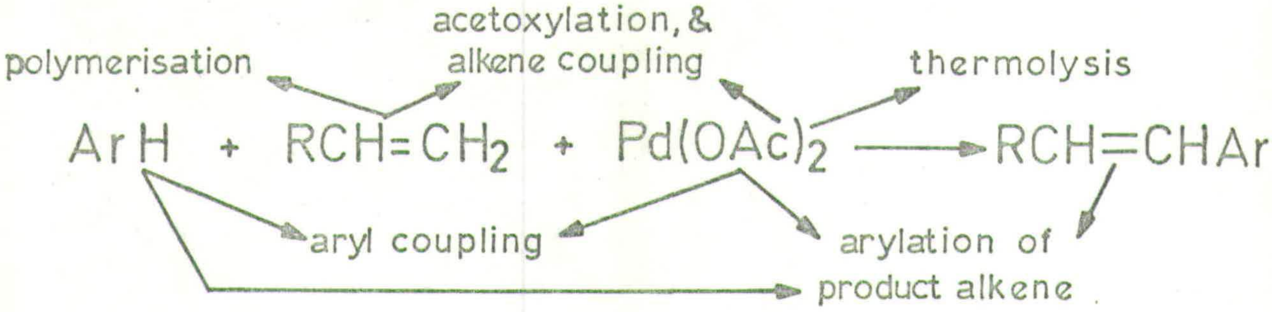
$$ArSO_2H + HgCl_2 \xrightarrow[80^\circ]{EtOH/H_2O} ArHgCl + SO_2 + HCl$$

If a palladium salt was used in a similar reaction in place of mercuric chloride, biaryls were formed. Also, in agreement with the work of Unger and Fouty,[93] the addition of mercuric chloride to the mixture improved the biaryl yield. (This reaction was also reported by Selke and Thiele, in 1971,[39] though they had observed it independently in 1968). The explanations for these observations are, in the first case, palladodesulfination, and in the second case mercurodesulfination followed by palladodemercuration to give the arylpalladium salt which reacts as previously described.

The evidence for the existence of an aryl palladium salt is thus quite strong, (but entirely circumstantial). An example has never been either isolated, or detected spectroscopically. Its formation appears to be an extension of the general electrophilic aromatic substitution reaction, resulting from a palladium for hydrogen (or mercury), substitution. Its lifetime appears to be dependent on the nature of reaction medium, as the experiments using perchloric acid have shown, but can be sufficiently long to allow some degree of specificity of reaction to occur. Presumably in such cases, it is protected by a solvent sheath which, in most cases, is acetic acid.

3D EVIDENCE FROM KINETIC STUDIES

No kinetic investigation of this reaction has been published to date. Both Moritani[17] and Shue[36] report that they have carried out kinetic experiments, but give no further details. One reactant plot has appeared, but no rate constants or half lives. The reasons for this soon become apparent when a closer study of the reacting system is made, and they are stated quite neatly by Shue for his particular case.[37] Briefly, the difficulty lies in the tendency for side reactions to occur, involving the loss of both starting materials catalyst and products, by various competing and consecutive paths, (Scheme 3-7):



Scheme 3-7

Some of these pathways are of quite minor importance, for instance aryl coupling and polymerisation of which no evidence could be detected in the present work, but thermolysis of palladium acetate was strongly suspected and product alkene arylation was detected. Of course, in the presence of a recycling oxidant further side reactions are possible and have been reported[32, 88, 89] (see page 53).

However the major reaction was found to be monoarylation of starting alkene so, as described in the Experimental Section, 4B, page 41, kinetic runs were carried out. The loss of alkene starting material was followed by g.c. and reactant plots, shown in Figure 3-1, were obtained. These data were then plotted as logarithmic and reciprocal values and found to be a better fit to a straight line as the former. This, of course, indicates a closer similarity to a first order reaction than a second order reaction. The log. plots are shown in Figure 3-2.

This is a little surprising for, if the styrene disappears in a bimolecular reaction with phenylpalladium acetate, it should show a disappearance which fits a second order (reciprocal) plot closer than a first order (logarithmic) plot. A first order disappearance might be approximated if the concentration of the phenylpalladium acetate intermediate remained fairly constant in the mixture during the reaction, and this can be explained as follows. The reaction

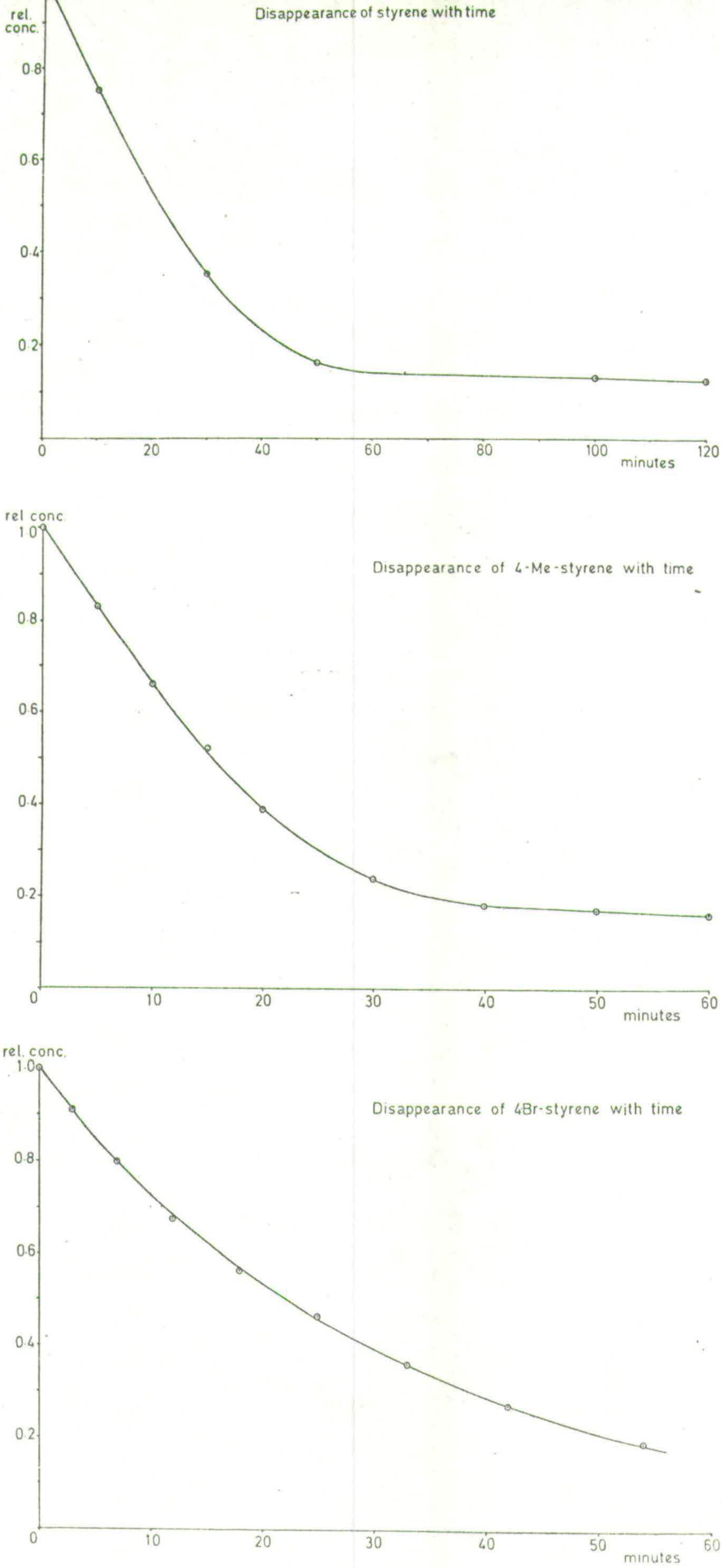


Figure 3-1. Reactant Plots

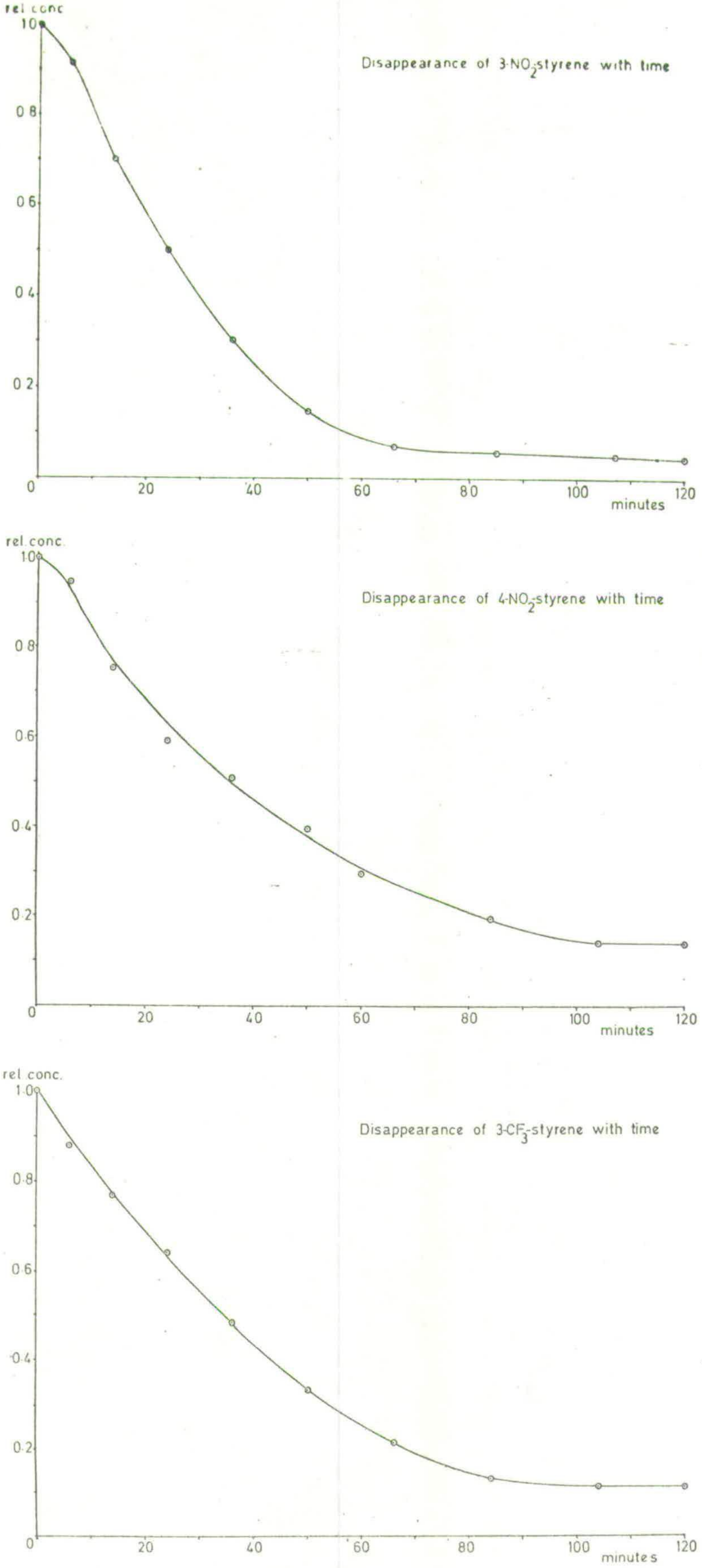


Figure 3-1 (continued). Reactant Plots

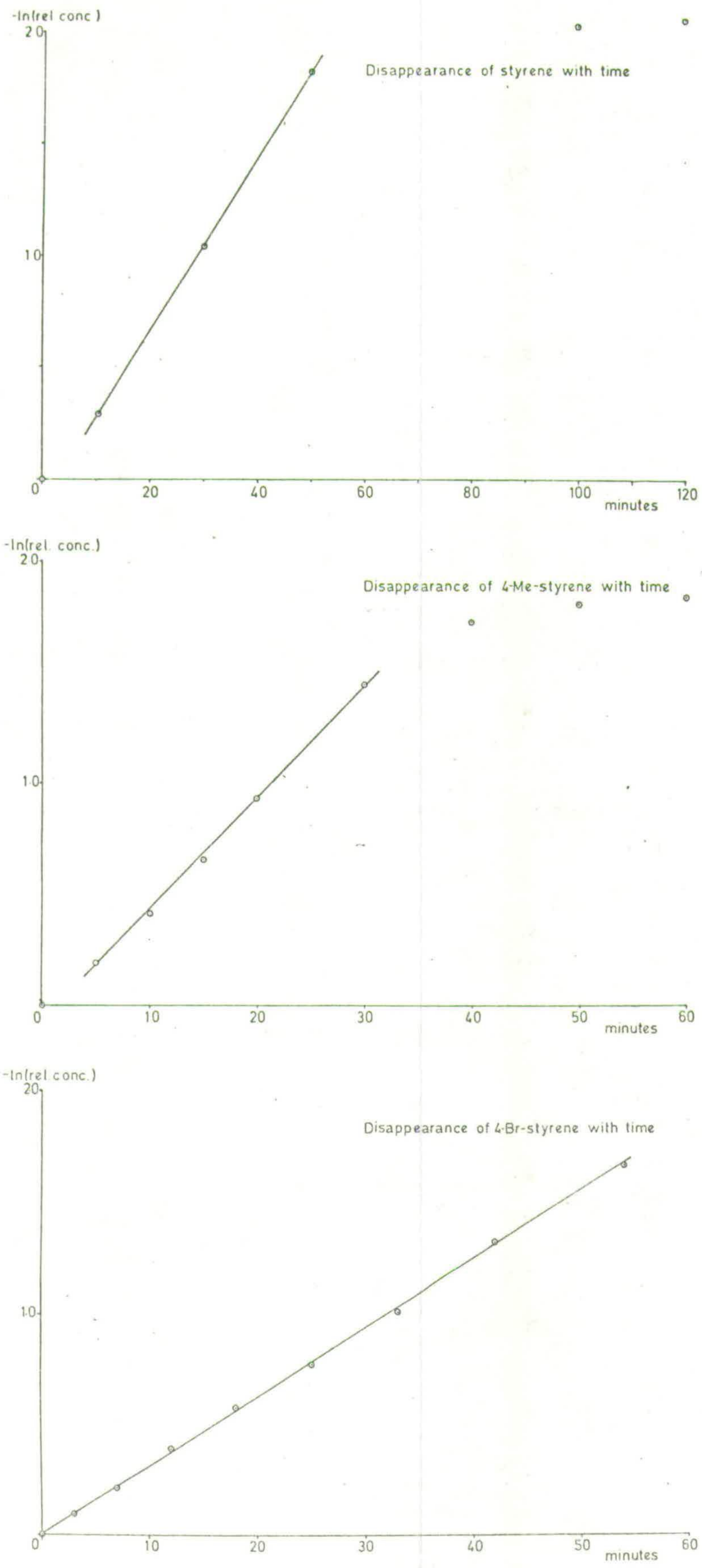


Figure 3-2. Log. Plots

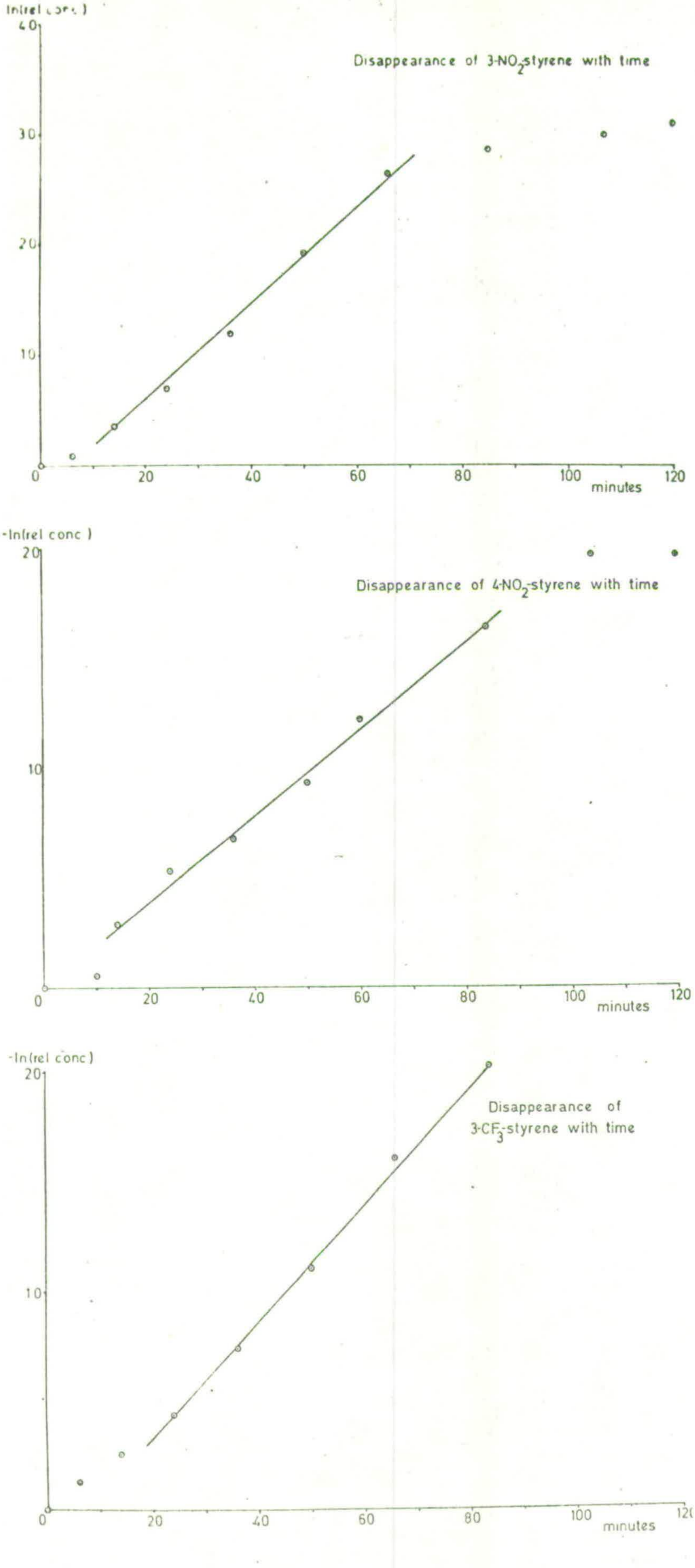


Figure 3-2 (continued). Log. Plots.

studied can be written as a series of steps, thus, (Scheme 3-8):

$$PhH + Pd(OAc)_2 \xrightarrow{k_1} PhPdOAc + HOAc$$

$$PhPdOAc + PhCH{=}CH_2 \xrightarrow{k_2} PhCH{=}CHPh + HOAc + Pd$$

k_1 and k_2 are rate constants. Scheme 3-8

The kinetics of these reaction steps can be described by the following equations:

$$\frac{-d\,[Pd(OAc)_2]}{dt} = k_1[PhH][Pd(OAc)_2]$$

$$\frac{-d\,[PhCH{=}CH_2]}{dt} = k_2[PhPdOAc][PhCH{=}CH_2]$$

In the reaction mixture benzene is in considerable excess and its concentration is virtually static. So the first of these equations can be rewritten thus:

$$\frac{-d\,[Pd(OAc)_2]}{dt} = k'_1\ [Pd(OAc)_2]$$

k'_1 is now a pseudo-first order rate constant which includes the static concentration of benzene. Similarly, if the phenylpalladium acetate stays at a steady concentration it can be combined with the second order rate constant of the second step to give another pseudo-first order rate constant, k'_2, and the kinetic equation can be written thus:

$$\frac{-d\,[PhCH{=}CH_2]}{dt} = k'_2\ [PhCH{=}CH_2]$$

Thus, the disappearance of styrene will now appear to be first order.

It was suspected that if the second step was much faster than the first, then the phenylpalladium acetate would be consumed just as fast as it was made and would remain at a steady, low concentration. The observed kinetics would then be accounted for.

To test this theory it was desirable to have an account of the behaviour of the suggested kinetic system using various ratios of k'_1 to k_2. A mathematical analysis of the system has been done,[97] but the solutions are complex and approximate. To use it, lengthy calculations using a digital computer would be required, with all that that implies in terms of numerical analysis and (error-free) programming. To obtain reactant and product plots a much faster and simpler method was found to be simulation of the proposed system using an analogue computer.[79] This instrument will imitate and display the form of any desired variable (reactants and products in this case) in a system of differential equations, as it changes with respect to any other variable, (time in this case). The kinetic system was reduced to its simplest form (Scheme 3-9) and a programme, or circuit, was developed as described in the Experimental Section, 5, p. 43.

$$A \xrightarrow{k'_1} B$$

$$B + C \xrightarrow{k_2} D$$

A set initially at 1, = $Pd(OAc)_2$
B set initially at 0, = PhPdOAc
C set initially at 1, = $PhCH{=}CH_2$
D set initially at 0, = $PhCH{=}CHPh$

k'_1 and k_2 have the same meaning as before.

Scheme 3-9

Various runs were carried out using different ratios of k'_1 and k_2, and for each run the variation of A, B, C and D was plotted against time, maintaining as far as possible the same half life for the disappearance of A in each case. (Benzene and acetic acid do not appear in the simulation since they were in excess in the real system and their effect would have been invariant with time). It is doubtful if a similar series of plots could have been obtained from a digital computer in the same time (one day).

It was found that when k_2 was greater than k'_1 by a factor of approximately 10 or more, disappearance of C did follow very closely the disappearance of A, and did therefore exhibit first order kinetics. More significantly, the shape of the C-plots, and the log. plots derived from these, were found to be very similar to those observed in the real system over a range of k_2/k'_1 from approximately 2 upwards. In particular, a short induction period observed in the real system was reproduced in the simulation, as was a fall-off in the reaction rate after about 2.5 half-lives. The computer plots and the log. plots derived from the C-variation in them are illustrated in Figures 3-3 and 3-4 and the observed styrene reactant and log. plots are shown in Figures 3-1 and 3-2.

It will be observed that in computer plots that agree closely with the observed disappearance of C (i.e. styrene), the concentration of B (i.e. phenylpalladium acetate) rises to quite a high level. Whether this is as a consequence of using a simplified kinetic scheme, or is a real effect is impossible to tell. Such a high level of the phenylpalladium salt is not consistent with its probable stability as determined by previous workers unless it exists as a heavily solvated species. Also, no biphenyl was detected in any of the reactions, which would not be expected from the salt's known propensity to dimerise.[7]

Rate constants obtained from the log. plots of the observed reactions would be of dubious validity. This is because of the mixed order of the reaction and the probable interference of side reactions. However, the slope of the longest straight line portion of the log. plot of each reaction is given in Table 3-7, as is the half life of the styrene. This provides some indication of the effect of the substituent on the rate of disappearance of the styrene.

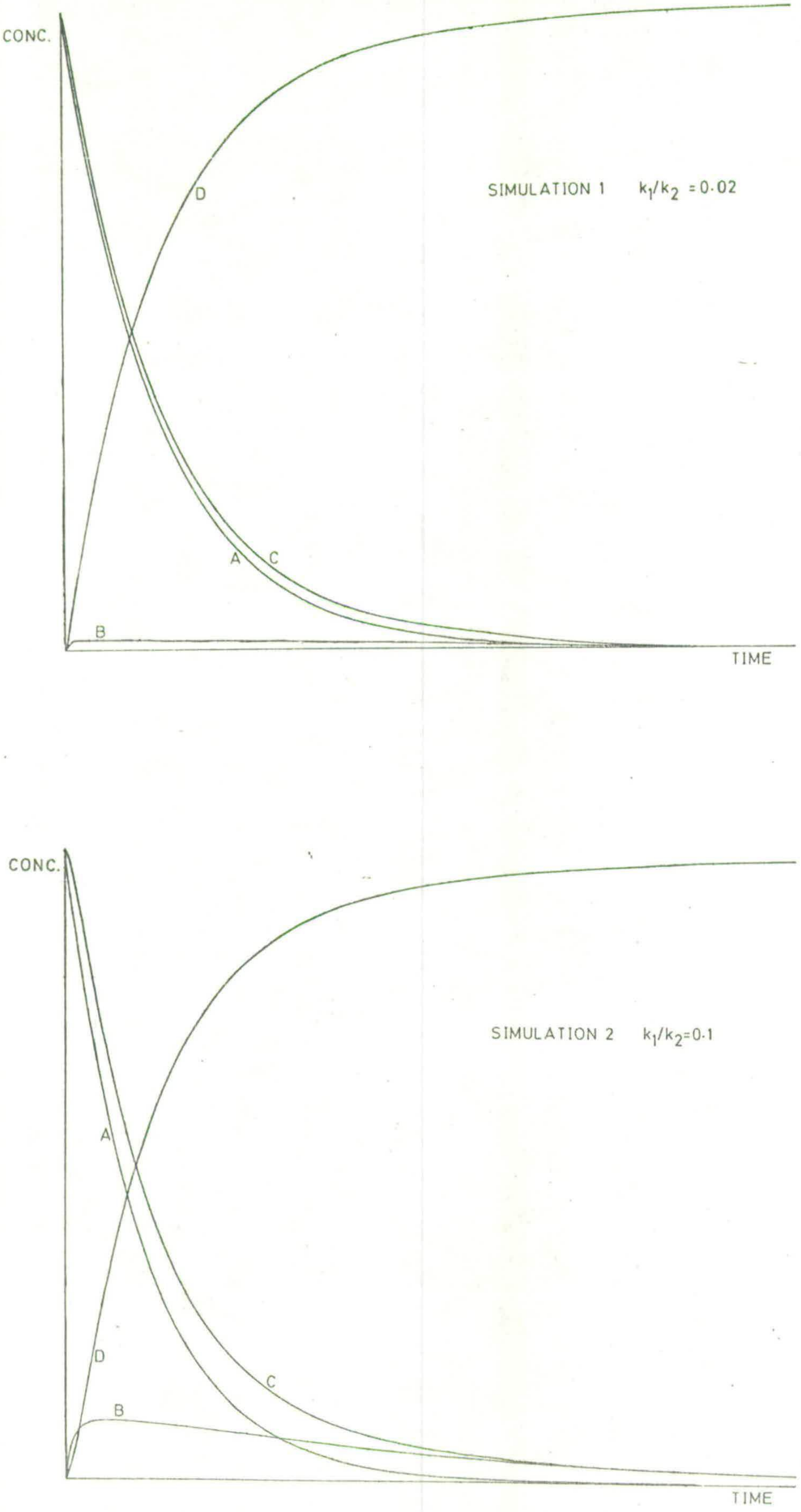
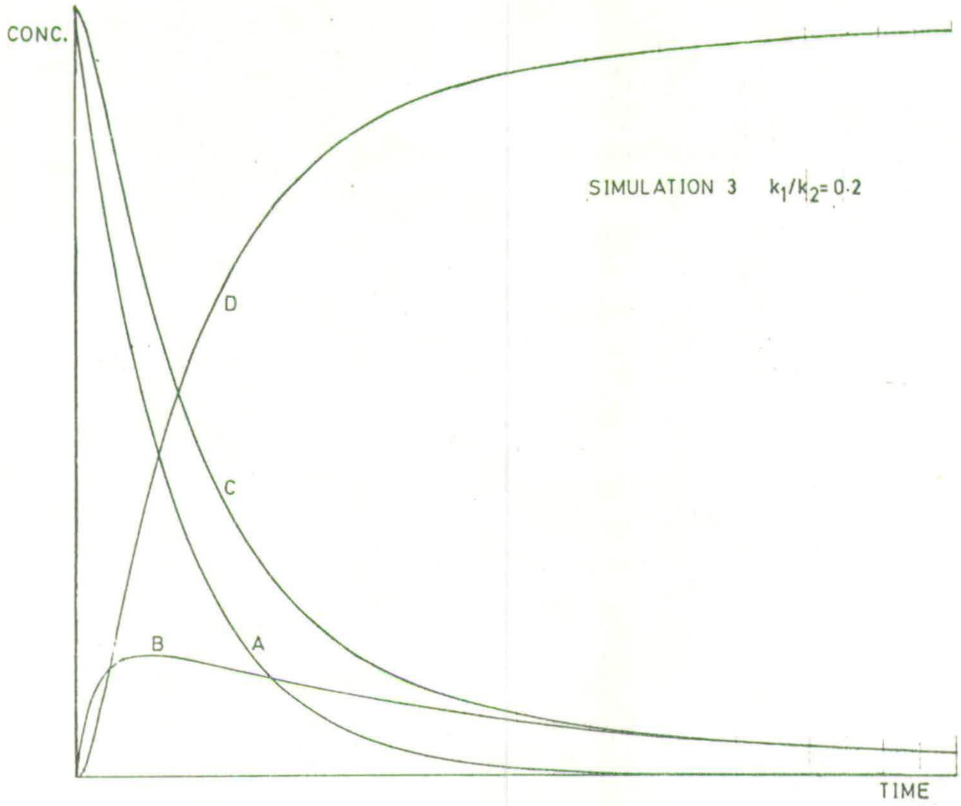


Figure 3-3. Analogue Computer Simulations



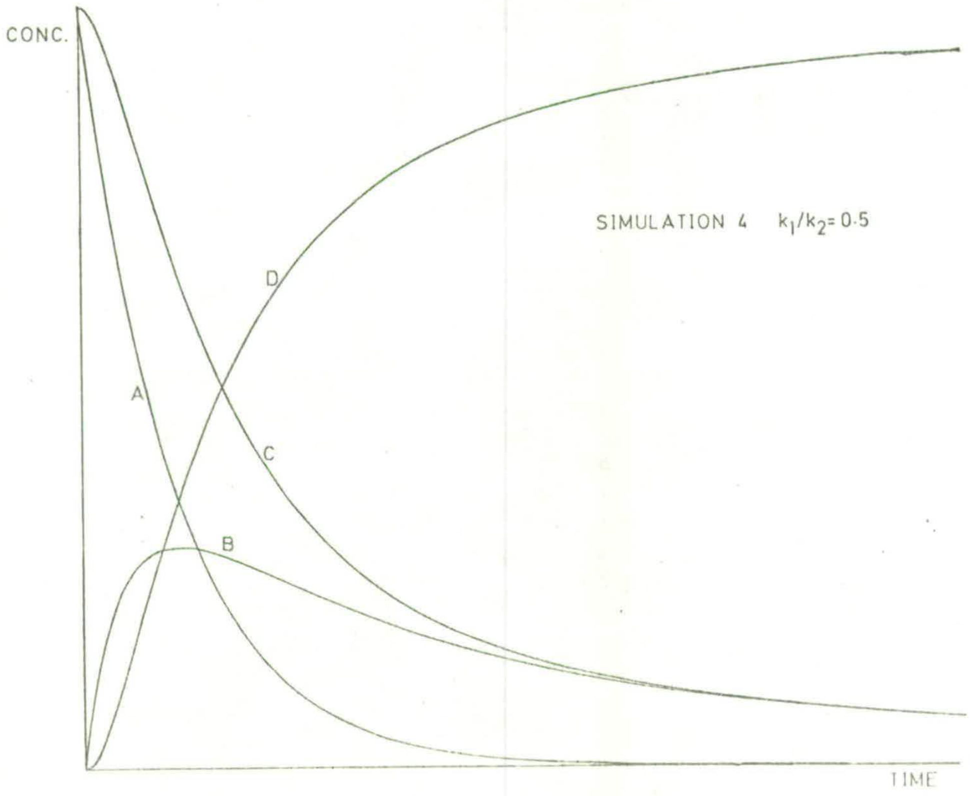
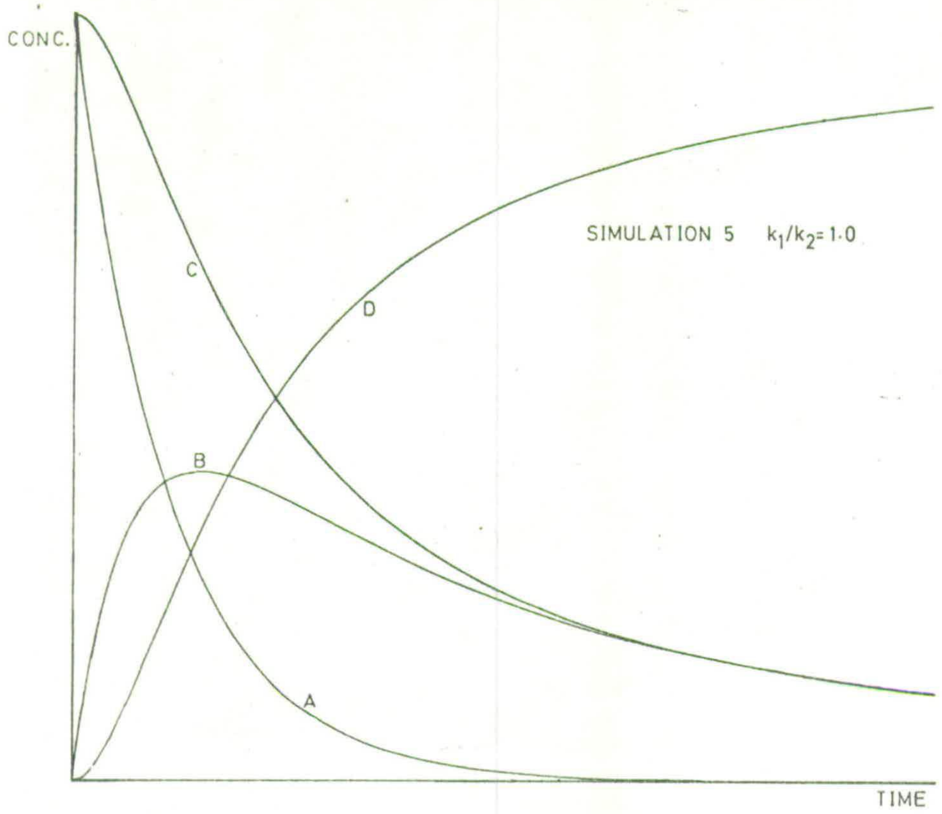


Figure 3-3 (continued). Analogue Computer Simulations



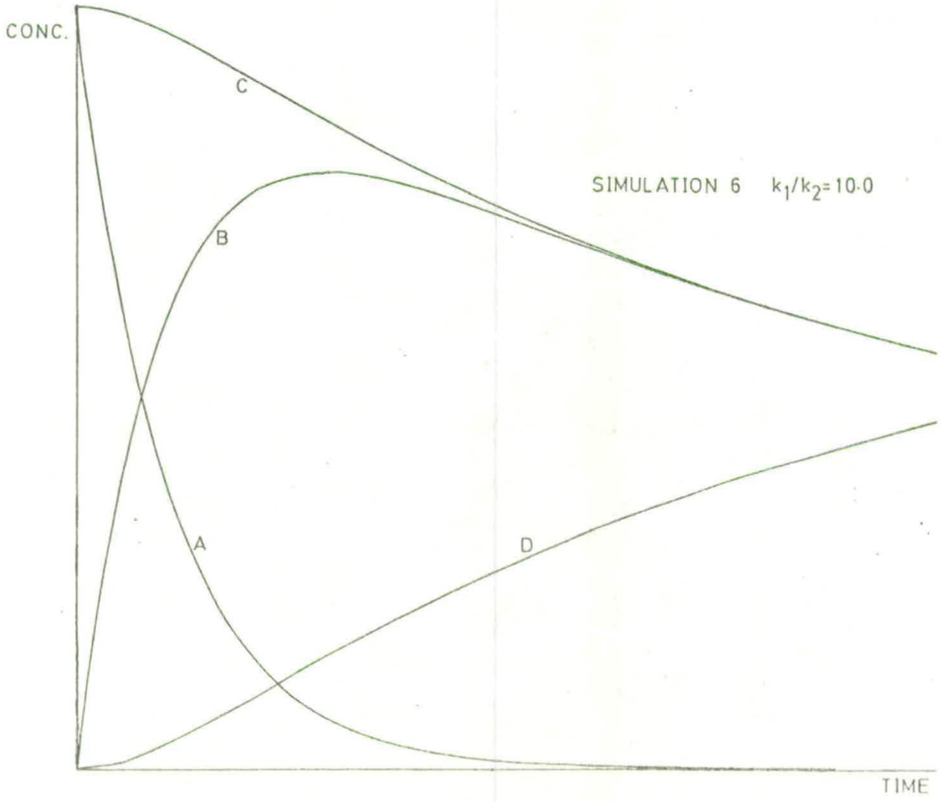


Figure 3-3 (continued). Analogue Computer Simulations

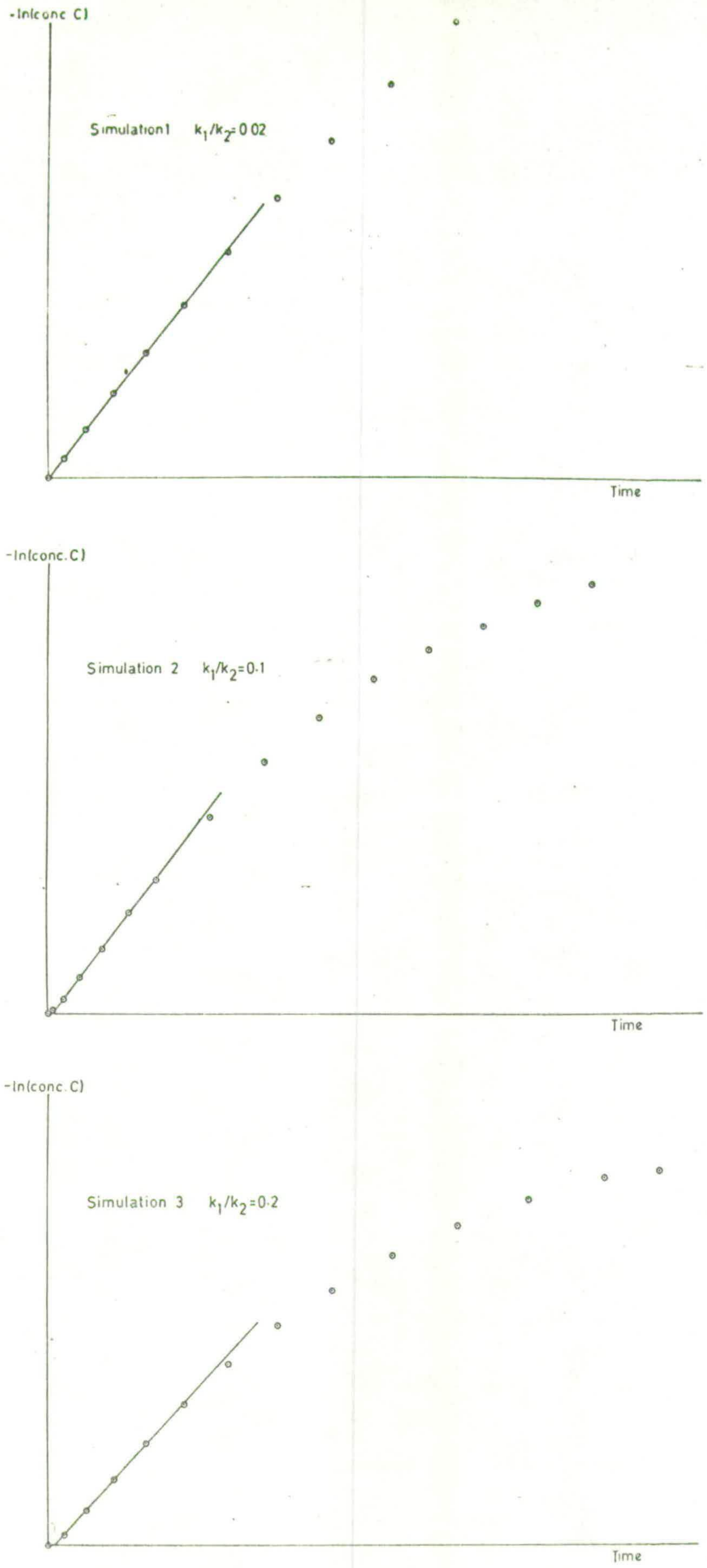


Figure 3-4. Log. Plots Derived from Computer Simulations

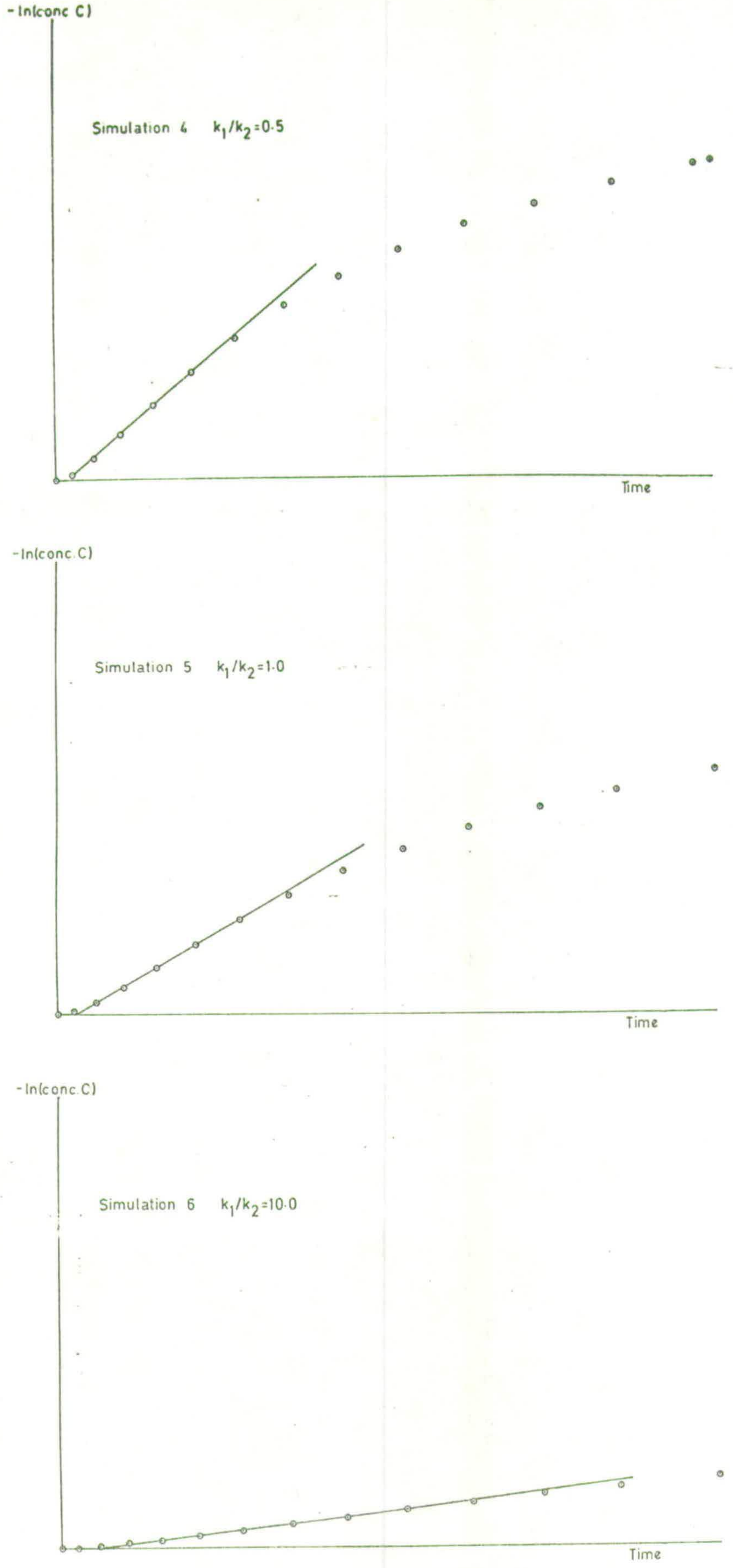


Figure 3-4 (continued). Log. Plots Derived from Computer Simulations

Table 3-7 Results Obtained from Kinetic Experiments

$$PhH + XC_6H_4CH{:}CH_2 + Pd(OAc)_2 \longrightarrow PhCH{:}CHC_6H_4X$$

X	$t_{\frac{1}{2}}$ mins.	log. plot slope
H	21.6	3.82×10^{-2}
$4CH_3$	15.8	5.05×10^{-2}
$3CF_3$	34.1	2.64×10^{-2}
4Br	22.1	3.10×10^{-2}
$3NO_2$	22.0	4.30×10^{-2}
$4NO_2$	35.8	1.98×10^{-2}

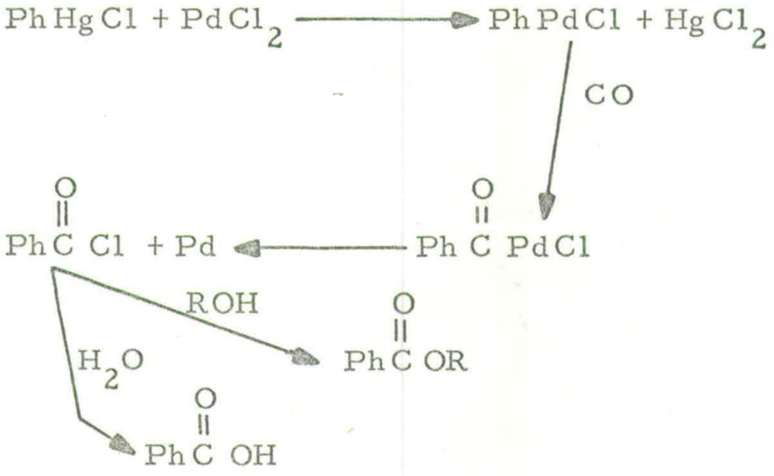
The reaction temperature was 84°. (Experiments were also carried out using 3-OMe and 4-OMe styrene, but due to analytical difficulties, no meaningful results were obtained).

No large-scale effect is visible in these results. There is a slight increase in half life for electron withdrawing groups, but it is not maintained in the case of 3-nitrostyrene. It is likely that if the reaction of the alkene is a fast step in the mechanism, substitution effects observed on it will be of a secondary nature and consequently small. The evidence from the competition reactions and the computer simulations seem to point to this being the case. For the simulations to match the observed plots the second rate constant, k_2, must be faster than the first, k_1', by a factor of at least two. Similarly, for the substituent on the aromatic compound to have such a clear effect on the reaction products, this species must be concerned in a kinetically more significant part of the sequence of steps. Taken in conjunction with the deuterium isotope effects observed by Shue[36] and observations in the literature reviewed in Section 3C, the above evidence makes the Moritani mechanism[18] quite unlikely.

3E THE REACTION OF ARYLPALLADIUM SALTS WITH MULTIPLE BONDS

The work described below will, it is hoped, shed some light on the nature of the final step in the palladium-assisted alkenylation of aromatic compounds. This reaction is quite difficult to study as it occurs as a fast step in the systems in which it is presumed to occur. Most of the work has concerned analysis of the products from the reactions, rather than kinetic studies.

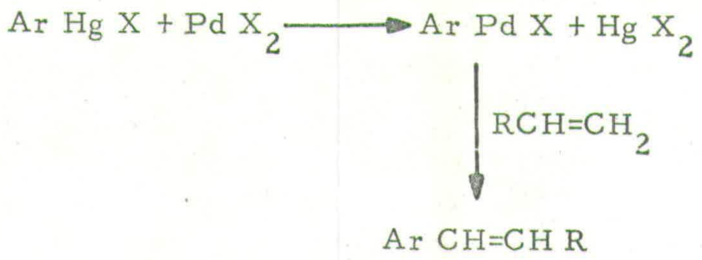
Davidson[98] had found that carboxylic acids were formed by the reaction of carbon monoxide with arylmercury salts under forcing conditions. In 1968 Henry[94] found that the addition of palladium chloride to a similar reaction mixture made the reaction go easily at room temperature and atmospheric pressure. The products were acid chlorides and palladium metal and the reaction scheme suggested is shown, (Scheme 3-10):



Scheme 3-10

The final products were derived from reaction with either the solvent, or water during aqueous work-up. A little biphenyl was also found in the mixture. It was also found that mercury alkyls give this reaction.

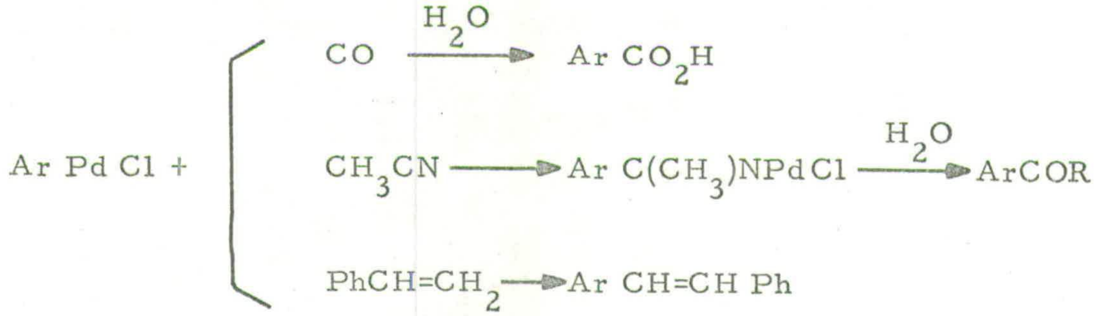
Almost at the same time Heck published his reports of alkene arylation using arylpalladium salts formed via aryl mercury salts.[28-34] This reaction is described in the Introduction (p. 5) but briefly Heck's proposed mechanism is thus, (Scheme 3-11):



$$\begin{tikzcd} \mathrm{Ar\,Hg\,X} + \mathrm{Pd\,X_2} \arrow[r] & \mathrm{Ar\,Pd\,X} + \mathrm{Hg\,X_2} \arrow[d, "\mathrm{RCH{=}CH_2}"] \\ & \mathrm{Ar\,CH{=}CH\,R} \end{tikzcd}$$

Scheme 3-11

The reaction of arylpalladium salts with multiple bonds was used by both Garves,[45] and Selke[39] as evidence of their formation from the desulfination reaction (see p. 68). The results of reactions with various systems were as shown, (Scheme 3-12):



$$\mathrm{Ar\,Pd\,Cl} + \left\{ \begin{array}{l} \mathrm{CO} \xrightarrow{H_2O} \mathrm{Ar\,CO_2H} \\ \mathrm{CH_3CN} \longrightarrow \mathrm{Ar\,C(CH_3)NPdCl} \xrightarrow{H_2O} \mathrm{ArCOR} \\ \mathrm{PhCH{=}CH_2} \longrightarrow \mathrm{Ar\,CH{=}CH\,Ph} \end{array} \right.$$

Scheme 3-12

The precise nature of the interactions observed in these reactions was not understood, but at the time it was suggested that an insertion into the aryl-palladium bond took place. Further insight into these reactions has been gained by the work of Heck, who has published a detailed study of the factors affecting the reaction, along with mechanistic suggestions.[42-44] As Heck's reaction probably has the reaction between the arylpalladium salt and the alkene in common with the present work, it is likely that his results are applicable to it, at least in general. Heck's findings are reviewed below.

One of the earlier observations made by Heck was that the rate of reaction of alkenes apparently depended to a large extent on steric factors, and little on the ability of the alkene to delocalise any charge or free electron produced during the reaction. Thus the relative reactivities of some simple alkenes was found, from competitive reaction, to be thus:[28]

$$C_2H_4 > AcOCH{=}CH_2 > CH_3CH{=}CH_2 > PhCH{=}CH_2 > PhC(CH_3){=}CH_2$$

14000 970 220 42 1

This series suggested to Heck that the reaction was neither radical nor ionic, and that the intermediates involved were probably of a covalent "organometallic" nature. To support this argument, Heck carried out three series of reactions to investigate the effect of electronic and other effects on the way in which the alkene reacted with the arylpalladium salt.

A series of simple alkenes with electron-donating and withdrawing groups attached was studied. The results are shown in Table 3-8.

Table 3-8 Reaction of Phenylpalladium Acetate with various substituted Alkenes (after Heck[43])

$$PhPdOAc + CH_2{=}CHX \longrightarrow PhCH{=}CHX + CH_2{=}C(Ph)X$$

X	Substitution position, %		
	Terminal	Non-terminal	
$-CO_2CH_3$	100	0	Reactions carried out in acetonitrile solution at room temperature
$-CHO$	100	0	
$-AcO$	99.6	0.4	Phenylpalladium acetate produced from phenylmercuric acetate and palladium acetate.
$-Ph$	ca. 100	0	
$-CH_3$	74	26	
$-C_4H_9$	75	25	
$-CH_2OAc$	95	5	

The variation in direction of addition is quite small when compared with the effect that the same substituents would have on an ionic or radical reaction. For example, hydrogen halide addition to the same series of alkenes would probably vary from predominantly terminal (or anti-Markovnikov) for the electron-withdrawing methoxycarbonyl group, to non-terminal (or Markovnikov) for the electron-donating n-butyl group.

A similarly narrow range of effects was observed in the reaction between propylene and various substituted arylpalladium salts. These, as determined by Heck, are shown in Table 3-9.

Table 3-9 Reaction of Propylene with various substituted Arylpalladium Salts (after Heck[43])

$$XC_6H_4PdOAc + CH_2{=}CHCH_3 \longrightarrow ArCH{=}CHCH_3 + CH_2{=}C(Ar)CH_3$$

X	Substitution Position %	
	Terminal	Non-terminal
p-OCH_3	57	43
-H	74	26
p-CO_2CH_3	76	24

Reactions done in acetonitrile at 30° under 30 psig. propylene for 1 hr.
Arylpalladium acetates were produced from the corresponding arylmercury acetates and palladium acetate.

Again, despite a complete change in the substituent from electron-donating to electron-withdrawing, the direction of substitution of the aryl group onto the alkene remains virtually unchanged.

Finally, changing the solvent was also found to have only a small effect on the reaction, both on the direction of substitution of the aryl group onto the alkene and the yield of product. Heck's results are shown in Table 3-10.

Table 3-10 Effect of various solvents on the Phenylation of Propylene with Phenylpalladium Acetate (after Heck[42,43])

$$\mathrm{PhPdOAc} + \mathrm{CH_2{=}CHCH_3} \longrightarrow \mathrm{PhCH{=}CHCH_3} + \mathrm{CH_2{=}C(Ph)CH_3}$$

		Product Substitution Position	
Solvent	Yield %	% Terminal	% Non-terminal
CH_3CN	100	74	26
CH_3OH	66	84	16
AcOH	87	84	16
THF	100	84	16
PhH	95	84	16
CH_2Cl_2	100	84	16
Monoglyme	96	83	17
Diglyme	71	83	17

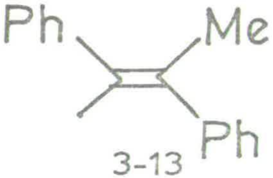
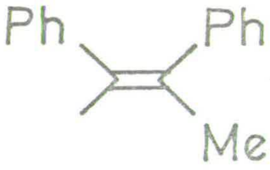
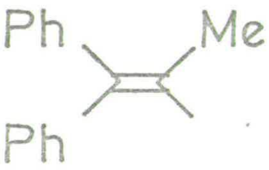
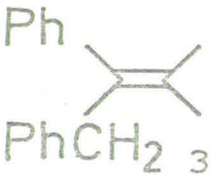
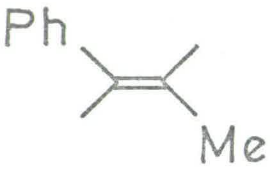
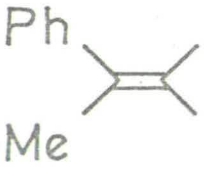
Reactions done at 30° under 30 psig. of propylene for 1 hr.

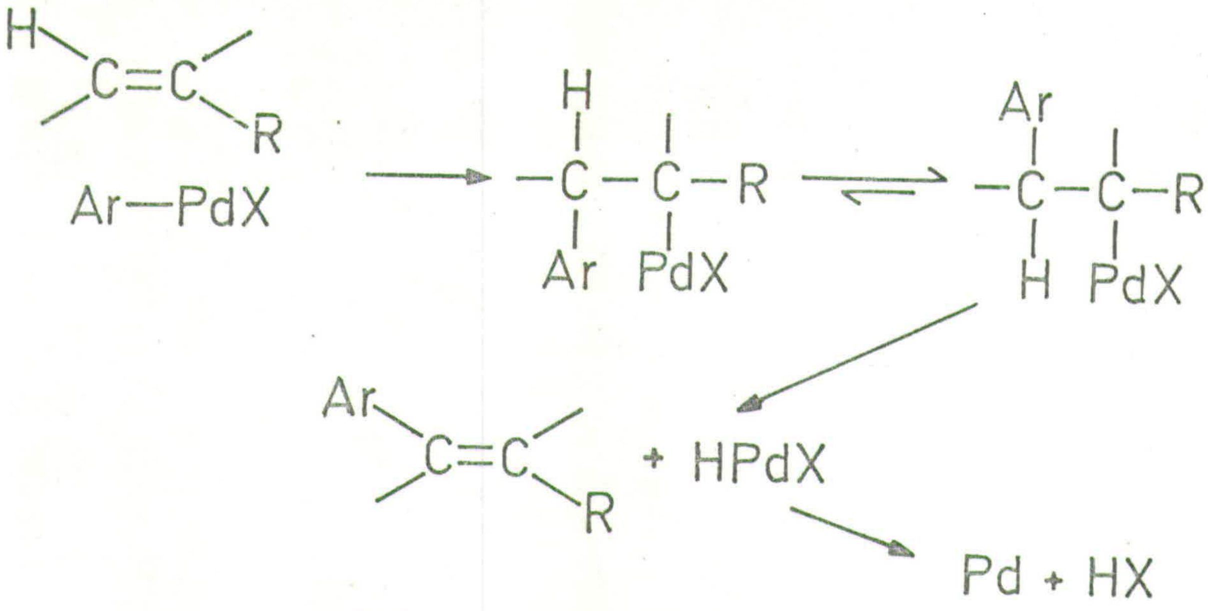
Phenylpalladium acetate prepared from phenylmercuric acetate and palladium acetate.

The small variation in yield here is fairly unexpected, since the reactive arylpalladium salt is almost certainly stabilised in solution by a co-ordinated solvent sheath. Acetonitrile shows the only real variation in direction of addition, but this could be due to the ready co-ordinating ability of the nitrogen lone pair of electrons.

Heck proposed that the reaction proceeded through a 4-centre, covalent cis-addition of the arylpalladium salt to the alkene, followed by cis-elimination of a hydridopalladium salt species which rapidly decomposed to give palladium and the acid,[42] (Scheme 3-13):

Table 3-11. Reaction of Phenylpalladium Acetate with α- and β-Methylstyrenes, in Methanol at 30° (after Heck[42]).

Starting Material	Product Distribution %			
	 3-13			 3-15
	98.5	0	1.0	0.5
 3-14	22.0	65.0	3.0	10.0
	57.0	0	0	43.0



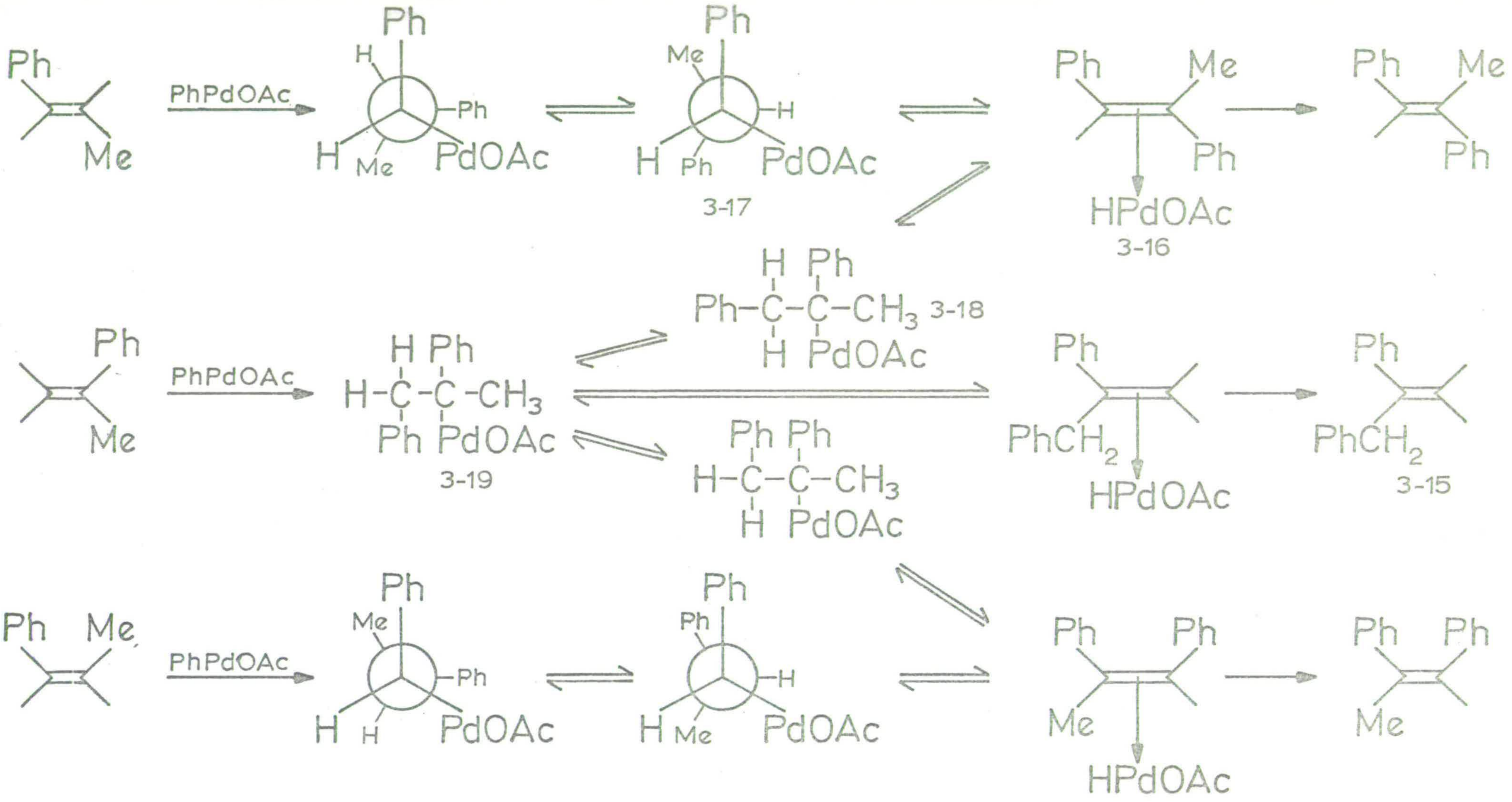
Scheme 3-13

The direction of addition of the arylpalladium salt to the alkene is governed primarily by steric factors. As noted, electronic and solvent effects play little part in determining this. Palladium is, apparently,[43] effectively the smallest part of the arylpalladium salt. This is due to the long carbon-palladium bond-length and the square planar geometry of palladium complexes. Consequently, the larger aryl group becomes positioned closer to the less substituted carbon atom at the double bond. However, in terminal alkenes, non-terminal substitution products are found, and a series of reactions of phenylpalladium acetate with α- and β-methyl styrenes carried out by Heck[42] provided some evidence for the reason why.

The products obtained from these reactions and their distributions are shown in Table 3-11, opposite.

The cis-addition, cis-elimination sequence outlined above does not wholly explain the products formed in these reactions. In particular, the production of α-methyl-trans-stilbene (3-13) from cis-β-methylstyrene (3-14), and the formation of 2, 3-diphenylpropene (3-15), from any of the starting materials cannot be accounted for.

To account for these observations Heck suggested[42] that loss of the hydridopalladium acetate species was a reversible step,



Scheme 3-14 (after Heck[42] and Maitlis[6a]) proceeding through the formation of a palladium-alkene π-complex, (3-16). The sequence of steps he suggested is shown in Scheme 3-14, opposite.

Immediately after the addition of phenylpalladium acetate across the alkene double bond, rotation takes place and the hydridopalladium acetate may be formed, e.g. 3-17. However, Heck suggests that instead of immediately leaving the reformed double bond, the palladium species remains attached by π-bonding through the metal, as in 3-16. Re-addition to the double bond is now possible either as before, retracing the reaction path, or in the opposite sense leading to 3-18. The acetatopalladium group is now adjacent to a methyl group and hydridopalladium acetate elimination may again take place (reversibly) to give, via 3-19, the otherwise unaccounted for 2, 3-diphenylpropene, (3-15).

Various other ramifications of this ingenious system may be envisaged and can account for all observed products. They are shown in Scheme 3-14.

4 CONCLUSION

The possible usefulness of palladium-assisted arylation, for cutting short otherwise lengthy synthetic routes to substituted alkenes (or aryl compounds), was the original reason for carrying out the work described here. However, it became clear that knowledge of the reaction mechanism was so sketchy as to make it almost impossible to obtain predictable results from synthetic attempts. Previous work on the reaction had been carried out mainly by chemists with inorganic or industrial leanings and consequently the emphasis in the published work was somewhat different from that of the synthetic organic chemist.

In particular, little kinetic work had been published and none of the mechanistic analysis had been based on kinetic studies. The kinetic experiments described here, and the analysis and simulations presented are an attempt to fill this gap. More remains to be done, however, especially in the area of improving the accountance of starting material at the end of the reaction and in the study of the fast step of the reaction. Also, the kinetics of the reaction in the presence of oxidising agents, used for palladium recycling, have not been studied. However, from the work described here the reaction is seen to be quite similar to electrophilic aromatic substitution and closely related to other metal-organic reactions, especially mercuration.

Much of the potential usefulness of this type of reaction lies in the possibility of recycling the precipitated palladium with an oxidant. The prime example is, of course, the Wacker reaction. The reacting entities and reaction medium are though, quite different from those in the arylation reaction as studied here and this is a fact that has previously been somewhat overlooked. The range of oxidants examined here is more comprehensive than that studied by other workers and illustrates quite clearly the pitfalls of choosing a suitable reagent. The success of dropwise addition of oxidant points the way towards further study of continuous oxidative recycling procedures.

An aspect of the reaction only briefly mentioned here is its sensitivity to the state of the palladium acetate. This is manifested as a batch effect and was observed,but avoided rather than investigated. Subsequent work[99] has shown that the presence of small amounts of impurities in the palladium acetate can have a disproportionate effect on the outcome of the reaction.

It still remains to be seen how all these factors will combine to affect the synthetic usefulness of the reaction. Commercially it is not usable due to the difficulty of effectively recycling the precipitated palladium. Synthetically the prospects are more hopeful but there is still some work to be done before the reaction can be shown to be useful for a wide range of structural types and reactivities.

References Part One

1 F.C.Phillips, Amer.Chem.J., 16, 255(1894); Z.Anorg.Chem., 6, 213 (1894).

2 S.C.Ogburn, W.C.Brastow, J.Amer.Chem.Soc., 55, 1307 (1933).

3 J.Smidt, W.Hafner, R.Jira, J.Sedlmeier, R.Sieber, R.Rutlinger, H.Kojer, Angew.Chem., 71, 176 (1959).

4 J.Smidt, W.Hafner, R.Jira, J.Sedlmeier, R.Sieber, A.Sabel, Angew.Chem., 74, 93 (1962); Angew.Chem. Int.Ed., 1, 80 (1962).

5 J.Smidt, W.Hafner, R.Jira, J.Sedlmeier, R.Sieber, A.Sabel, Chem.Ind.(Lond.), 54 (1962).

6 See for instance: a) P.M.Maitlis, "The Organic Chemistry of Palladium," Academic Press, 1971.

b) J.Tsuji, Adv.Org.Chem., 6, 109 (1969); Acc.Chem.Res., 2, 144 (1969).

c) C.W.Bird, "Transition Metal Intermediates in Organic Synthesis," Academic Press, 1967.

d) A.Aguilo, Adv.Organometal.Chem., 5, 327 (1967).

e) E.W.Stern, Annals.N.Y.Acad.Sci., 516 (1971).

f) I.Moritani, Y.Fujiwara, Synthesis, 524 (1973).

7 R.van Helden, G.Verberg, Rec.Trav.Chim., 84, 1263 (1965).

8 J.M.Davidson, C.Triggs, Chem.Ind.(Lond.) 457 (1966).

9 J.M.Davidson, C.Triggs, J.Chem.Soc.(A), 1324, 1331 (1968).

10 I.Moritani, Y.Fujiwara, Tet.Lett., 1119 (1967).

11 Y.Fujiwara, I.Moritani, M.Matsuda, S.Teranishi, Tet.Lett., 633 (1968).

12 Y.Fujiwara, I.Moritani, M.Matsuda, Tetrahedron, 24, 4819 (1968).

13 Y.Fujiwara, I.Moritani, M.Matsuda, S.Teranishi, Tet.Lett., 3863 (1968).

14 Y.Fujiwara, I.Moritani, R.Asano, S.Teranishi, ibid, 6015.

15 Y.Fujiwara, I.Moritani, S.Danno, R.Asano, S.Teranishi, J.Amer.Chem.Soc., 91, 7166 (1969).

16 S. Danno, I. Moritani, Y. Fujiwara, Tetrahedron, 25, 4809 (1969).

17 Y. Fujiwara, I. Moritani, R. Asano, H. Tanaka, S. Teranishi, ibid, 4815.

18 S. Danno, I. Moritani, Y. Fujiwara, ibid, 4819.

19 Y. Fujiwara, I. Moritani, K. Ikegami, R. Tanaka, S. Teranishi, Bull. Chem. Soc. Japan, 43, 863 (1970).

20 R. Asano, I. Moritani, Y. Fujiwara, S. Teranishi, Chem. Comm., 610 (1970).

21 R. Asano, I. Moritani, Y. Fujiwara, S. Teranishi, ibid, 1293.

22 S. Danno, I. Moritani, Y. Fujiwara, S. Teranishi, J. Chem. Soc. (B), 196 (1971).

23 S. Danno, Bull. Chem. Soc. Japan, 43, 3966 (1970).

24 I. Moritani, S. Danno, Y. Fujiwara, S. Teranishi, Bull. Chem. Soc. Japan, 44, 578 (1971).

25 I. Moritani, Y. Fujiwara, S. Danno, J. Organometal. Chem., 27, 279 (1971).

26 R. Asano, I. Moritani, A. Sonoda, Y. Fujiwara, S. Teranishi, J. Chem. Soc. (C), 3691 (1971).

27 M. Yamamura, I. Moritani, A. Sonoda, S. Teranishi, Y. Fujiwara, J. Chem. Soc. Perkin I, 203 (1973).

28 R. F. Heck, J. Amer. Chem. Soc., 90, 5518 (1968).

29 R. F. Heck, ibid, 5526.

30 R. F. Heck, ibid, 5531.

31 R. F. Heck, ibid, 5535.

32 R. F. Heck, ibid, 5538.

33 R. F. Heck, ibid, 5542.

34 R. F. Heck, ibid, 5546.

35 R. S. Shue, Chem. Comm., 1510 (1971).

36 R. S. Shue, J. Amer. Chem. Soc., 93, 7116 (1971).

37 R. S. Shue, J. Catal., 26, 112 (1972).

38 A. J. Bingham, L. K. Dyall, R. O. C. Norman, C. B. Thomas, J. Chem. Soc. (B), 1879 (1970), and refs. therein.

39 R. Selke, W. Thiele, J. Prakt. Chem., 313, 875 (1971).

40 M. S. Kharasch, R. C. Seiler, F. R. Mayo, J. Amer. Chem. Soc., 60, 882 (1938).

41 I. I. Moiseev, A. P. Belov, V. A. Igoshin, Ya. K. Syrkin, Dokl. Akad. Nauk. S. S. S. R., 173, 863 (1967), (Eng. Trans. p. 256).

42 R. F. Heck, J. Amer. Chem. Soc., 91, 6707 (1969).

43 R. F. Heck, J. Amer. Chem. Soc., 93, 6896 (1971).

44 R. F. Heck, J. Organometal. Chem., 37, 389 (1972).

45 K. Garves, J. Org. Chem., 35, 3273 (1970).

46 K. Kikukawa, T. Yamane, M. Takagi, T. Matsuda, Chem. Comm., 695, (1972).

47 T. Yamane, K. Kikukawa, M. Takagi, T. Matsuda, Tetrahedron, 29, 955 (1973).

48 R. F. Heck, J. P. Nolley, J. Org. Chem., 37, 2320 (1972).

49 T. Mizoroki, K. Mori, A. Ozaki, Bull. Chem. Soc. Japan, 44, 581 (1971).

50 P. M. Henry, Annals N. Y. Acad. Sci., 483 (1971).

51 R. O. C. Norman, R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, 1965.

52 L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, N. Y., 1960.

53 G. N. Schrauzer, J. Amer. Chem. Soc., 81, 5310 (1959).

54 K. Yamamura, S. Watarai, T. Kinugasa, Tet. Lett., 2829 (1972).

55 I. I. Moiseev, M. N. Vargaftik, Ya K. Syrkin, Dokl. Akad. Nauk. S. S. S. R., 153, 140 (1963).

56 P. M. Henry, J. Amer. Chem. Soc., 88, 1595 (1966).

57 Johnson-Matthey Ltd., Hatton Garden, London.

58 D. L. Klass, (Pure Oil Co.), U. S. Patent 3147203 (1964); Chem. Abs., 61, 13195 (1964).

59 Farbwerke Hoechst, A. G., Belgian Patent 648304 (1964); Chem. Abs. 63, 13082 (1966).

60 H. Itatami, H. Yoshimoto, Chem. Ind. (Lond.), 674 (1971).

61 A. J. P. Martin, A. T. James, Biochem. J., 63, 138 (1956).

62 J. I. G. Cadogan, I. H. Sadler, J. Chem. Soc. (B), 1191, (1966), and refs. therein.

63 D. W. Grant, A. Clarke, Anal. Chem., 43, 1951 (1971).

64 B. Loev, M. Goodman, Chem. Ind. (Lond.), 2026 (1967);
B. Loev, M. Goodman, Prog. Separ. Purif., 3, 73 (1970).

65 H. Brockmann, H. Schodder, Chem. Ber., 74, 73 (1941).

66 A. I. Vogel, "A Textbook of Practical Organic Chemistry," (3rd Edition), Longmans, 1959, p. 173.

67 T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, G. Wilkinson, J. Chem. Soc., 3632 (1965).

68 R. Wiley, N. Smith, Org. Synth., 33, 62 (1953).

69 S. Dolad, S. Rajagopal, Org. Synth., 46, 13 (1966).

70 J. Brown, C. Suckling, W. Whalley, J. Chem. Soc., S95 (1949).

71 A. M. Shur, N. A. Barba, Zhur. Obshch. Khim., 33, 1504 (1963); (Eng. Transl. p. 1468).

72 G. Smets, A. Reckers, Rec. Trav. Chim., 68, 9831 (1949).

73 A. Klages, Chem. Ber., 36, 3584 (1903).

74 C. S. Marvel, C. Overberger, R. Allen, J. Saunders, J. Amer. Chem. Soc., 68, 736 (1946).

75 A. Maercker, Org. React., 14, 270 (1965).

76 O. Wheeler, H. Batlle de Pabon, J. Org. Chem., 30, 1473 (1965).

77 F. Bergman, D. Schapiro, J. Org. Chem., 12, 57 (1947).

78 C. Wood, F. Mallory, J. Org. Chem., 29, 3373 (1964).

79 For Chemical applications of analogue computing, see e. g.
T. Crossley, M. Slifkin, Prog. React. Kin., 5, 409 (1970).
F. Tabutt, J. Chem. Ed., 44, 64 (1967).

80 e. g. J. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, 1965, p. 52.

81 I. V. Rodnikova, O. K. Surnina, Zh. Fiz. Khim., 36, 1287 (1962); (Eng. Transl. p. 680).

82 B. Drake, Arkiv. för Kemi, 8, 1, (1955).

83 G. Drefahl, K. Ponsold, Chem. Ber., 93, 472 (1960).

84 E. E. Baroni, K. A. Kovyrzina, T. A. Tsvetkova, Zh. Org. Khim., 1, 513 (1965).

85 P. Pfeiffer, P. Scheider, J. Prakt. Chem., 129, 129 (1931).

86 Ref. 6A, Vol. 2, p. 77.

87 W. M. Latimer, "Oxidation Potentials," 2nd Edition, Prentice-Hall, N. Y. 1952.

88 P. M. Henry, J. Org. Chem., 32, 2575 (1967).

89 P. M. Henry, J. Org. Chem., 36, 1886 (1971).

90 Ref. 51, p. 57.

91 Ref. 6A, Vol. 2, p. 259.

92 F. A. Cotton, G. Wilkinson, "Advanced Inorganic Chemistry," 2nd Edition, Interscience, N. Y. 1966.

93 M. O. Unger, R. A. Fouty, J. Org. Chem., 34, 18 (1969).

94 P. M. Henry, Tet. Lett., 2285 (1968).

95 G. Calvin, G. E. Coates, J. Chem. Soc., 2008 (1960).

96 H. C. Brown, C. W. McGary, J. Amer. Chem. Soc., 77, 2300 (1955).

97 Jen-Yuan Chen, J. Amer. Chem. Soc., 70, 2256 (1948).

98 J. M. Davidson, L. R. Barlow, Chem. Ind. (Lond.), 1656 (1965).

99 J. A. M. Bayne, unpublished results.

100 H. A. Dieck, R. F. Heck, J. Amer. Chem. Soc., 96, 1133, (1974).

101 M. Julia, M. Duteil, Bull. Soc. Chim. France, 2790, 2791 (1973).

PART TWO

Free-Radical Addition of Caprolactam to Alkenes

INTRODUCTION

CONTENTS

INTRODUCTION

1 Organic Free Radicals in Solution

Gomberg's observation in 1900 that hexaphenylethane was not formed from the reaction of triphenylmethylchloride with silver powder[1] was the first postulation of a three-valent carbon atom to be supported by a subsequent molecular weight determination.[2] However, although it was rarely asserted that carbon had a fixed valency, the concept of the highly reactive, electrically neutral and electron deficient free-radical, which subsequently emerged from Gomberg's work could not be fitted into the classical picture of valency. It required the postulation of the electron-pair bond[3] to provide a theoretical model which was compatible with the experimental observations. Even so, several years elapsed before free radicals were really accepted as legitimate chemical species.

Careful work by Kharasch and Mayo,[4] Hey and Waters,[5] and others established the existence of organic free radicals in solution during the 1930's and 1940's and their intermediacy in many reactions has been demonstrated and exploited over several decades since. Several textbooks and reviews have been written which give comprehensive accounts of free-radical chemistry and its history and applications.[6]

One of the more important and stimulating areas of study has been the investigation of the reaction between free radicals and carbon-carbon double bonds.[4b, 5] This may lead to the addition of the radical species to the unsaturated species thus providing a synthetic short cut. The present work has been concerned with such a reaction.

2 Free Radical Alkylation

The pathway of this type of reaction can be represented in a general form thus, (Scheme 2-1):

$$\dot{R}' + XY \longrightarrow R'Y + \dot{X} \qquad 2\text{-}1$$

$$\dot{X} + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2X \qquad 2\text{-}2$$

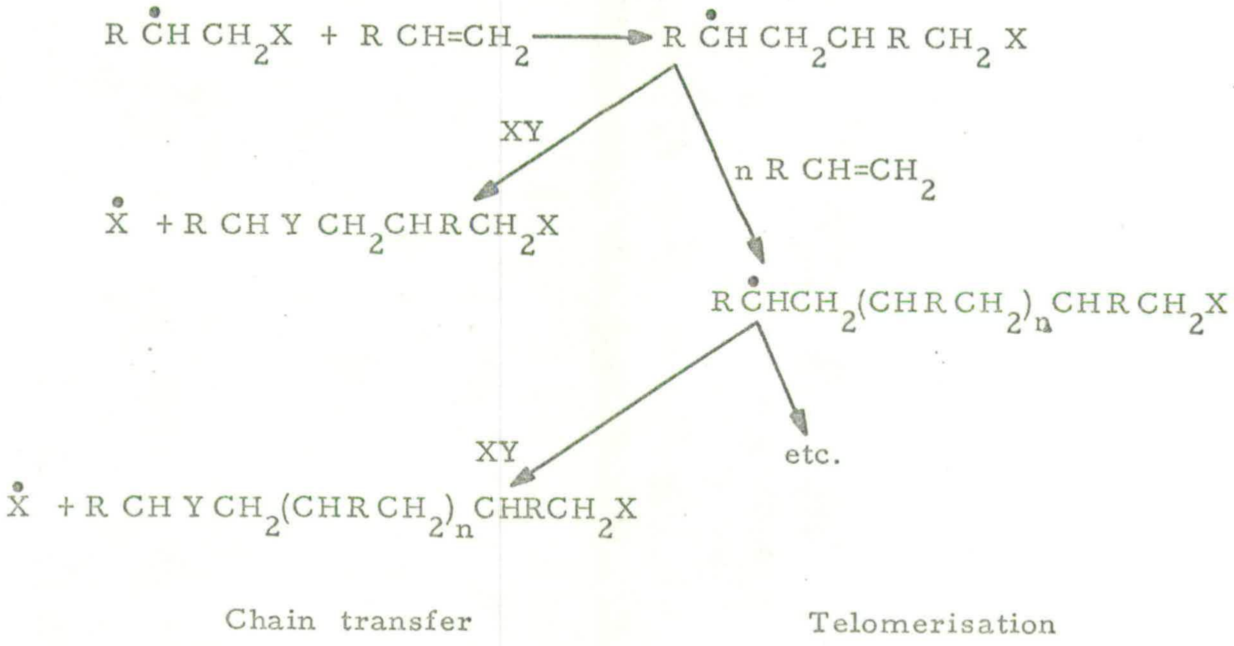
$$R\dot{C}HCH_2X + XY \longrightarrow RCHYCH_2X + \dot{X} \qquad 2\text{-}3$$

Scheme 2-1

The species $\dot{R}'$ may be derived from a free radical initiator, which is a compound containing a weak bond susceptible to thermal homolysis under mild conditions. This is frequently (and exclusively in the present work) a dialkyl or diaryl peroxide. Alternatively the initiator or one of the reactants may be homolysed photolytically or by another form of radiation, e.g. gamma-rays.

The species $\dot{X}$, the chain carrying radical is produced in both steps 2-1 and 2-3. This is important, since under favourable circumstances a chain reaction may ensue leading to a high yield of product, also formed in step 2-3 from a low initial production of $\dot{X}$.

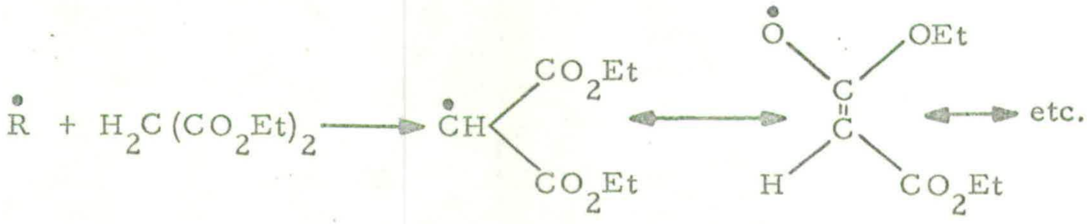
The extent of the reaction chain may readily be curtailed if any of the intermediate radicals undergo a side reaction. Such chain termination processes may be radical dimerisation, or radical disproportionation but more common and illustrated in Scheme 2-2, are telomerisation and chain transfer.



Scheme 2-2

Such side reactions may be quite favoured, energetically, and reaction conditions are adjusted to avoid them. In particular the technique of dropwise addition[7] of the initiator and the alkene to the heated mixture to maintain a high dilution of these species in the reaction has been very important. This reduces the probability of the intermediate radical, formed in step 2-2, Scheme 2-1, meeting anything except a molecule of the type XY, and thus similarly reduces the probability of the side reactions shown in Scheme 2-2 happening.

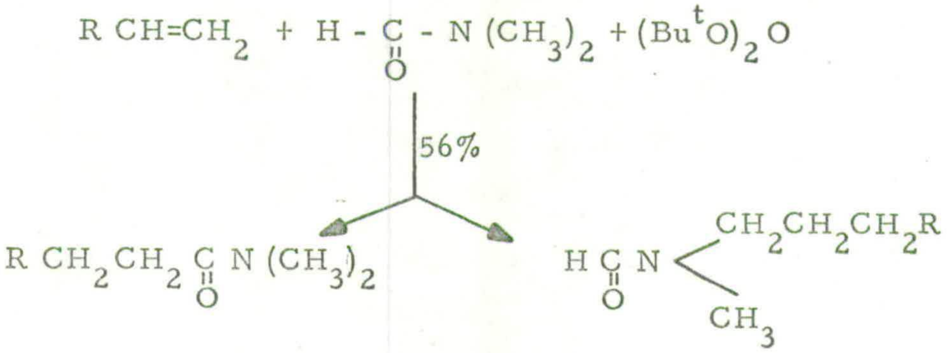
If, in the above schemes, Y is taken to be hydrogen it can be seen that the overall result of Scheme 2-1 is the alkylation of X by an alkyl chain derived from the alkene. The synthetic possibilities of the reaction are now clear; with a suitable choice of reagents and conditions, a one-step alkylation may be performed. For a predictable and useful result to be obtained, hydrogen abstraction must always occur at effectively the same site. Thus the stability of $\dot{X}$ must be sufficient for it to be the favoured product of any abstraction process, and for it to survive without disproportionation long enough to encounter an alkene molecule. A site often successfully provided for this purpose has been the activated methylene ($>CH_2$) or methine ($\geqslant$CH) group. The adjacent electron-withdrawing group, usually a carbonyl or a related group, acts as a sink for the odd electron created in the radical-forming process and the radical is thus stabilised by delocalisation. Alternatively the situation can be visualised as a resonance hybrid, for example the radical formed from diethyl malonate can be represented:



Carbonyl compounds of this type have been well investigated in their reactions with free radicals,[8] and the present work was directed towards extending this study into the reaction of є-caprolactam, an important industrial monomer.

3 Free Radical Addition of Amides to Alkenes

The literature of free-radical alkylation of amides is not large and much of it concerns photochemical- and radiation-initiated reactions.[9-14] The first report of amide alkylation was by L. Friedman[15] in 1961. He described dropwise addition of 1-octene (20 equiv) and tert-butyl peroxide (1 equiv) to heated dimethylformamide (600 equiv). After addition over 16 hours there followed an equal period of further heating resulting in the formation of two 1:1 adducts in 56% yield, plus an assortment of higher telomers. The reaction can be represented thus; (Scheme 3-1):

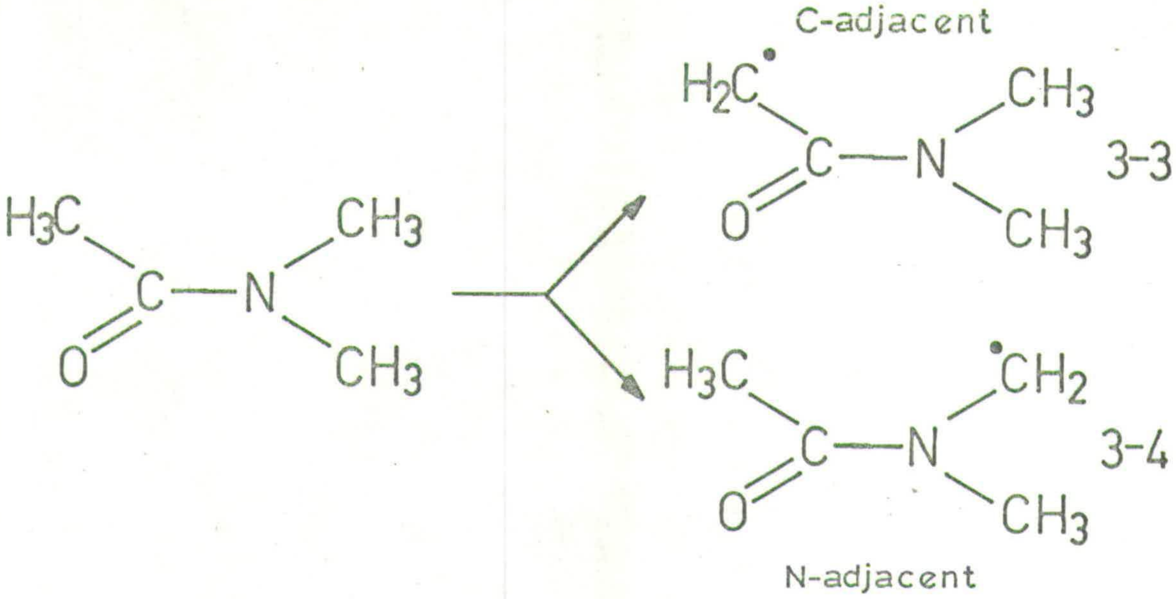


3-1 3-2

R = e.g., C_6H_{13} (3-1):(3-2) = 3:2

Scheme 3-1

Compounds 3-1 and 3-2 represent one of the significant features of the reaction of free radicals with amides. This is the production of two isomeric 1:1 adducts when the amide has an N-alkyl substituent.[9-12, 15, 16] This arises from hydrogen abstraction from both the carbon atom next to the carbonyl group and the carbon atom next to the nitrogen atom. (Here designated C-adjacent and N-adjacent abstraction, respectively). Thus, for N, N'-dimethylacetamide the two radicals 3-3 and 3-4 may be formed, (Scheme 3-2):



Scheme 3-2

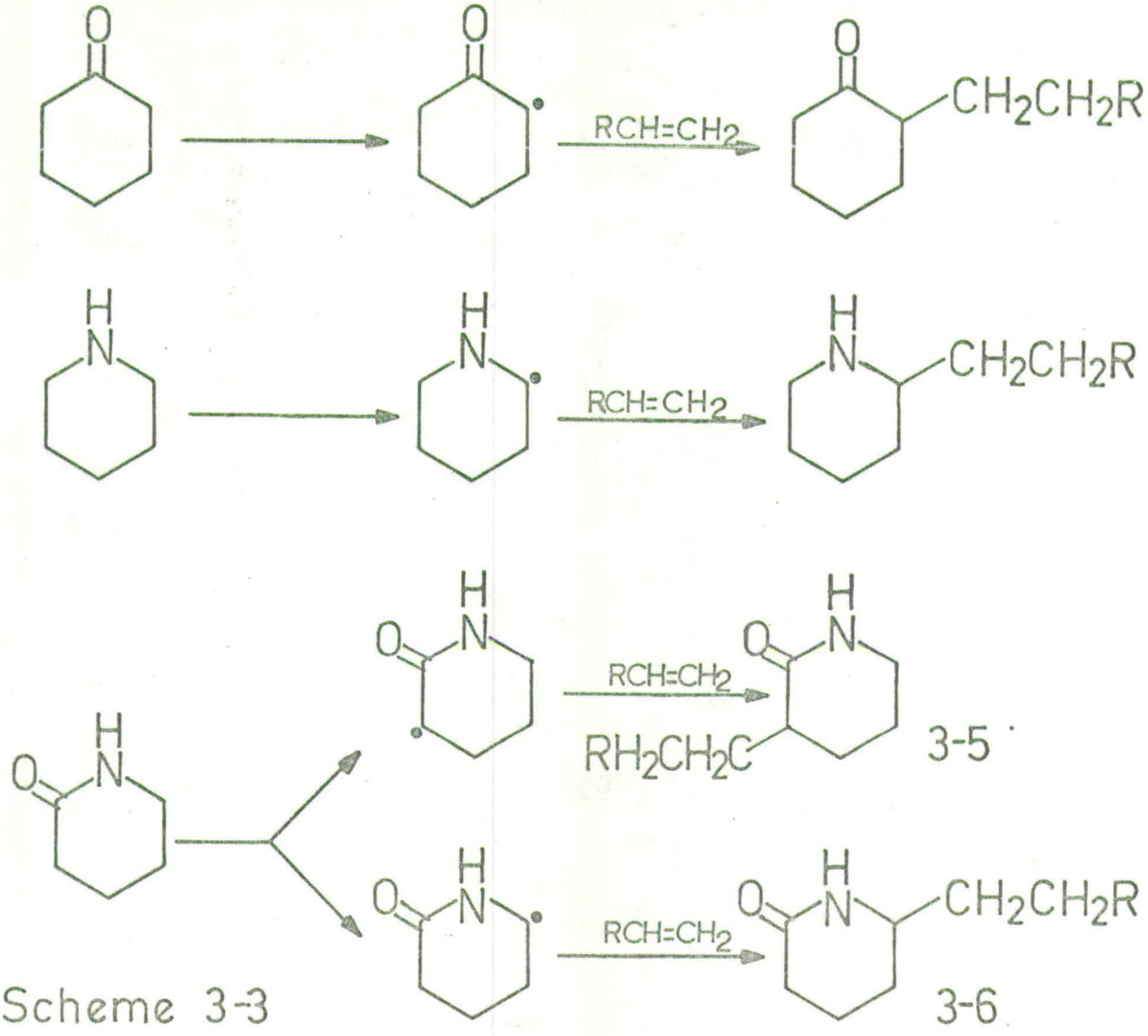
Many amides of this type behave this way leading to product mixtures which can pose some awkward separation problems. In addition to such difficulties, some workers also reported poor yields,[9, 14, 16, 17] and difficulty in obtaining homogeneous reaction mixtures.[9, 12, 14, 17]

The first report of work on cyclic amides, i. e. lactams, was by G. I. Nikishin[19] in 1964. He had previously reported successful radical alkylation reactions carried out on cyclopentanone and cyclohexanone.[20] Alkylation was known to be successful with piperidine.[21] He therefore reasoned that a molecule containing the structural features of both these types should also undergo free radical induced alkylation. This was realised with the alkylation of piperidone, (Scheme 3-3), overleaf.

Various alkenes were used, 1-heptene, 1-octene and 1-decene, and in addition to 2-piperidone, 2-pyrrolidone and caprolactam*

---

* This report of radical addition to caprolactam is not recorded in the entry in Chemical Abstracts, 62, 2753h (1965), and only came to light after most of the present work was completed.



Scheme 3-3

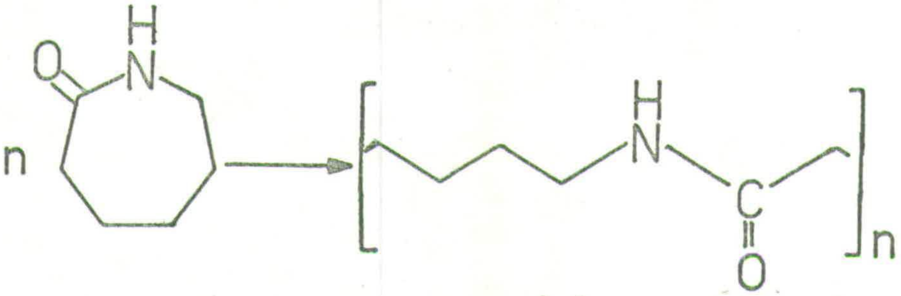
were also alkylated.

With all the lactams used, two isomeric products were obtained, similar to 3-5 (N-adjacent) and 3-6 (C-adjacent). Nikishin's reactions were carried out at 150-160° using DTBP as an initiator, but UV and sunlight have also been used. In 1965 Elad and Sinnreich[22] reported that a similar reaction, using photochemical initiation, could be performed at room temperature. Again, C-adjacent and N-adjacent products were found from the reaction of 2-pyrrolidone with various alkenes. The reaction was also carried out using acetone as a photo-initiator which resulted in greater yields of a similar product mixture, but otherwise had no effect on the outcome of the reaction.

4 Programme of Work

It has been shown that free-radical alkylation can provide a short one-stage synthetic procedure, often superior to a conventional multi-stage synthesis. With this in mind the work described here was directed to synthesizing an alkyl substituted caprolactam with a view to its eventual polymerisation.

Caprolactam itself is the monomer for nylon 6, (4-1) :



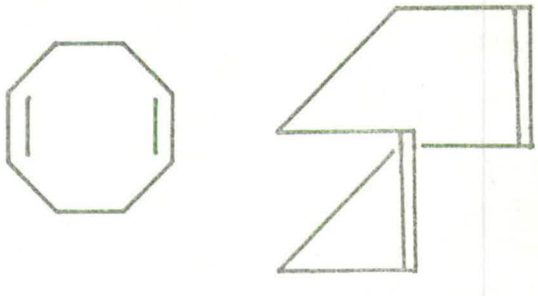
4-1

The anticipated result of the polymerisation of substituted caprolactam was the formation of a polymer chain with long side chains, (4-2), opposite.

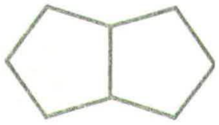
Such a polymer could be expected to have interesting physical properties since in the solid state adjacent chains would be tangled with one another through the presence of the long alkyl groups. This would be expected to lead to an abnormal resistance to shear and deformation resulting in possible uses as an engineering plastic.

Towards this end caprolactam was treated with several different alkenes under conditions of free-radical alkylation, and an attempt was made to polymerise one of the products isolated.

One of the alkenes used was cis, cis-1, 5-cyclooctadiene (cyclooctadiene), (4-3). This is known to undergo transannular ring closure under free-radical conditions, to give derivatives of bicyclo-[3, 3, 0]-octane[23] (4-4).



4-3



4-4

It was, however, found that after reaction with caprolactam and cyclohexanone some unsaturated products remained which could only be accounted for by a non-transannular reaction to give derivatives of cyclooctadiene. This has not previously been noted.

The results of these experiments are further elaborated in the Discussion Section, page 107.

EXPERIMENTAL AND RESULTS SECTION

CONTENTS

EXPERIMENTAL AND RESULTS SECTION

1 Instrumentation and Techniques

The instruments and techniques used for this work were the same as those described in Part One of this thesis with the additions described below.

1A High-Efficiency Fractional Distillation

A Nester-Faust annular teflon spinning-band distillation apparatus was used when normal distillation techniques were unable to provide an adequate separation. In general, the manufacturers' instructions were followed, although a lower reflux ratio than recommended was found adequate for almost all separations, (ca. 5 to 1). The composition of collected fractions was monitored using g. c. analysis.

1B Elemental Analyses

Elemental analyses for carbon,hydrogen and nitrogen were carried out on a Perkin-Elmer 240 automatic analyser.

2 Preparation of Compounds

One alkene was synthesised for use as a starting material and two substituted caprolactams were made for comparison with materials obtained from free-radical induced alkylations.

2A 1, 5-Hexadiene

This was prepared by the method of Cortese,[24] from allyl chloride (38. 25 g, 0. 5 mole) and magnesium turnings (10 g, 0. 4 mole). After separation from the reaction mixture using the spinning-band distillation apparatus, 6. 3 g of the diene were available for reaction, equivalent to a yield of 15% of theoretical. This low yield was attributed to loss by evaporation for, despite the compound's moderate b. p., it is extremely volatile. B. p. 59-61° (Lit. b. p. 60° [24]). N. m. r. (60 MHz, CCl_4): 3. 8-4. 6τ, m, 2H (H-2 and H-4); 4. 8-5. 3τ,

Table 2-1 Analytical Data for Substituted Cyclohexanones

Alkene	Product	B. p., °/mm	Lit. b. p., °/mm	Yield%	Infra-red spectra, cm^{-1}
1-Octene	2-1	146-8/7.5	96-7/1.5[20]	49	2930, s, C-H stretch; 2855, s, C-H stretch; 1705, s, C=O stretch; 1459, m, CH_2 bend; 715, w, $(CH_2)_n$ bend.
COD*	2-2	160/20, 80/0.05	-	34	2920, s, C-H stretch; 2840, s, C-H stretch; 1704, s, C=O stretch; 1450, s, CH_2 bend.

* COD = cis, cis-1, 5-cyclooctadiene

2-bicyclo-[3, 3, 0]-octylcyclohexanone (2-2), was a new compound and the following additional data was obtained.

N.m.r. (100 MHz, CCl_4) 7.4-9.2τ, envelope with prominent peaks at 7.8τ, 8.2τ and 8.5τ

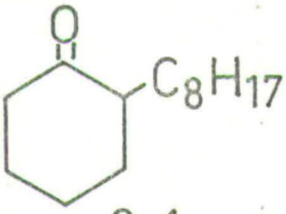
Elemental Analysis C, 82.19%; H, 11.01%. ($C_{14}H_{22}O$ requires C, 81.50%; H, 10.70%)

Mass Spectrum (m/e, relative intensity %); 206, 12.7 (parent); 109, 23.8; 108, 98.4; 99, 57.1; 98, 100; 97, 27; 83, 25.4; 81, 31.7; 80, 44.4; 70, 42.9; 67, 71.4.

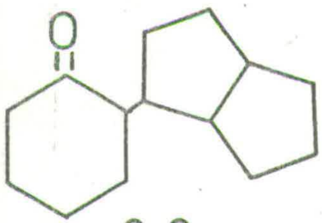
m, 4H (terminal = CH_2); 7.9-8.0τ, 4H (central -CH_2=).

2B Alkyl-Substituted Cyclohexanones

These were prepared by the method of Nikishin,[20] as follows. The alkene (0.1 mole), di-t-butyl peroxide (0.02 mole) and cyclohexanone (0.1 mole), were added dropwise to cyclohexanone (0.9 mole), boiling vigorously under reflux. Addition was carried out for from one to three hours and boiling was continued after that for a similar period. The products were then separated from the mixture by fractional distillation. Two compounds were prepared in this way, 2-octylcyclohexanone, (2-1), and 2-bicyclo-[3, 3, 0]-octylcyclohexanone (2-2).



2-1



2-2

Their analytical data is given in Table 2-1, opposite.

2C 2-Bicyclo-[3, 3, 0]-octylcyclohexanone Oxime

The ketone (4.0 g, 19.0 mmoles), hydroxylamine hydrochloride (1.5 g, 22 mmoles) and anhydrous sodium acetate (3.0 g, 37 mmoles) were dissolved in aqueous ethanol (ca. 100 ml) and stirred overnight at room temperature. The mixture changed colour from yellow to orange-brown and g.c. analysis of the chloroform extract indicated that reaction had taken place. A brown oil (2.7 g, ca. 67%) was obtained after d.c.c. separation and was subjected to i.r. and n.m.r. analysis. I.r. (cm^{-1}), 3200, s, b, OH stretch; 1650, m, C=N stretch. N.m.r. 0.15τ, s, broad, 1H, (N-H) 6.4-9.4τ, envelope, 22H. The oxime was used without further purification.

2D Alkyl-substituted Caprolactams

Two methods were used to prepare the two substituted caprolactams that were required. The oxime prepared in 2C was subjected

Table 2-3 N. m. r. and i. r. Spectra of Mixtures AB and CD

AB	N. m. r. (100 MHz, CH_2Cl_2) 2.6τ, b, s, 1H, (N-H); 6.85τ, b, s, 2H, $[C(7)\text{-}H_2]$; 7.4-9.3τ, envelope, 20H, with prominent peaks at 7.7τ, 8.2τ, 8.6τ, 8.8τ, and 9.1τ. I. r. (cm^{-1}) 3200, m. (N-H stretch); 3070, w; 2930, s; 2860, m, sharp, (C-H stretch); 1665, s, sharp (C=O stretch).
CD	N. m. r. (100 MHz, CH_2Cl_2) 2.55τ, b, s, 1H, (N-H); 6.9τ, b, s, 1H, $[C(7)\text{-}H]$; 7.4-9.3τ, envelope, 21H, with prominent peaks at 7.75τ, 8.2τ, 8.6τ and 9.15τ. I. r. (cm^{-1}) 3200, m, (N-H stretch); 3060, w; 2930, s; 2855, m, sharp, (C-H stretch); 1660, s, (C=O stretch); 1440, m, sharp, (C-H bend).

to a Beckman rearrangement,[25] but the 2-octylcyclohexanone was converted directly to the required amide in a single step reaction.[26]

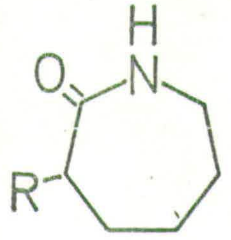
The oxime, prepared in 2C, (2.7 g, 13 mmoles) was stirred with polyphosphoric acid (90 g) at 190° for twenty minutes. After cooling and the addition of ice and water (ca. 500 ml) the solution was extracted continuously overnight with light petroleum. G.c. analysis (2% NPGS, 225°) of the residue remaining after solvent removal showed the presence of four peaks in two poorly resolved pairs, AB and CD. These were separated by preparative g.c. (7 ft, 10% NPGS, 190°), giving AB (72 mg) and CD (230 mg) were available for characterisation and comparison. At room temperature AB was an oil but CD had a melting range of 67-77°.

Bearing in mind the probable reaction path it was suspected that the four compounds present were isomers, and further analysis tended to confirm this. Mass spectra were recorded for each mixture and proved to be very similar. Only one molecular ion was apparent and exact mass measurement gave the results in Table 2-2.

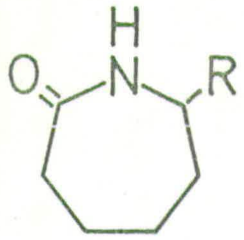
Table 2-2 Exact mass measurement of molecular ion of mixtures AB and CD.

Mixture	Mass of Molecular Ion	Mass of $C_{14}H_{23}NO$
AB	221.177841	221.177955
CD	221.178104	

N.m.r. and i.r. spectra were recorded also and are shown in Table 2-3. Although not identical the i.r. spectra were quite similar to one another and of little use of determining the composition of either mixture. The n.m.r. spectra were rather more useful and, on the evidence of the multiplicity of the signal from the proton attached to C(7), allowed an assignment of each mixture thus, (overleaf):

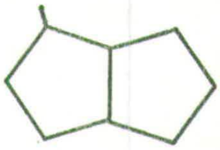


AB

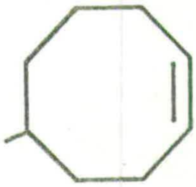


CD

R is, in each case either [3, 3, 0]-bicyclooctyl:



or cyclooctenyl:



The presence of the cyclooctenyl species was confirmed by the appearance of n. m. r. signals in the region of 4. 5τ under conditions of greater sensitivity. (This is coincident with the signals from cyclooctadiene itself.) The species was present in very small quantity but not well enough resolved for an accurate determination. It was probably less than 10% of the total mixture and slowly disappeared with time. Yields have not been determined for these compounds as only partial separations were achieved.

2-Octylcyclohexanone, obtained as described in Section 2B, was converted into octylcaprolactam by a one stage oximation and Beckman rearrangement[26] carried out as follows. The ketone (20. 6 g, 98 mmoles) and hydroxylamine sulfate (8. 2 g, 50 mmoles) were added slowly over 30 minutes to stirred sulfuric acid (50 ml, excess) held at 104° in a stirred oil bath. When addition was complete the mixture was stirred for a further ten minutes and then poured into a 500 ml beaker half-full of crushed ice. The acid was then neutralised with calcium carbonate and after filtration, drying

Table 2-4 Analytical Data for Octyl Substituted Caprolactams

7-Octylcaprolactam	N. m. r. (60MHz, CCl_4): 2.0τ, b, d, 1H, (N-H); 6.9τ, b, s, 1H [C(7)-H]; 7.7τ, b, s, 2H, [C(3)-H_2]; 8.0-9.4τ, envelope, 23H, prominent peaks at 8.7τ and 9.1τ. I. r. (cm^{-1}): 3200, m, (N-H); 3060, w, (C-H); 1670, s, sharp, (C=O); 805, m, [$(CH_2)_n$]. M. p. 58.5 - 59° (recrystallised from light petroleum). Elemental analysis: C 74.82%, H 12.11%, N 6.1% ($C_{14}H_{27}$ NO requires C 74.67%, H 12.00%, N 6.22%). Mass spectrum (m/e, relative intensity %); 225, 12.0 (parent); 113, 66.7; 112, 100.
3-Octylcaprolactam	N. m. r. (60 MHz, CCl_4): 2.5τ, b, t, 1H, (N-H); 6.8τ, b, s, 2H, [C(7)-H_2]; 7.8τ, b, s, 1H [C(3)-H); 7.9τ - 9.4τ, envelope, 23H, with prominent peaks at 8.4τ, 8.8τ and 9.1τ. I. r. (cm^{-1}) 3200, m, (N-H); 3060, w, (C-H); 1650, s, sharp, (C=O), 805, m, [$(CH_2)_n$]. No meaningful m. p. or mass spectrum could be obtained due to contamination with g. c. stationary phase.

and evaporation of solvent, a tarry residue was obtained. G.c. examination of the mixture (2% NPGS, 225°) showed two major products, E and F in the ratio of 1:1.4.

Chromatography of the mixture on alumina gave, on elution with a 40% ether/benzene mixture, F in a pure state (3.65 g). Its analytical data are given in Table 2-4. From them it is possible to identify the compound as 7-octylcaprolactam. Further elution of the column gave E mixed with more F, (7-octylcaprolactam). By subjecting this mixture to preparative g.c., (15 ft 20% PEGA, 192°), a sample of pure E was obtained (250 mg). It differed significantly from 7-octylcaprolactam only in its n.m.r. spectrum and was assigned using this as 3-octylcaprolactam. Analytical data obtained are also given in Table 2-4, opposite.

Unexpectedly, in each isomer the proton attached to the nitrogen atom reveals by the multiplicity of its splitting the position of substitution of the octyl group. Splitting of imino protons by adjacent protons is not usually observed due to the quadrupolar broadening effect of the attached ^{14}N nucleus.

3 Free Radical Induced Alkylation of Caprolactam: General Procedure

Radical-induced alkylation was carried out with five alkenes using the same procedure for each one. The alkene (0.1 mole) and di-tertiarybutyl peroxide (DTBP) (0.02 mole), which acted as a radical source after thermolysis, were added dropwise to caprolactam (1 mole). The caprolactam was stirred and maintained at 160°. The addition was carried out under a reflux condenser, and under dry, oxygen-free nitrogen. Prior to reaction the apparatus was flushed with nitrogen for half an hour. Dropwise addition of the alkene was continued for six to seven hours, and the reaction mixture heated for a further six to seven hours after addition was complete.

Excess caprolactam, other unreacted materials, and low boiling products were removed by distillation at reduced pressure. Caprolactam, (m.p. 69°; b.p. 124°/5 mm) was distilled over a short path length and condensed by a cold-finger type condenser projecting into the collecting flask. This condenser had hot (ca. 95°) water passing through it to minimise blockage by solid caprolactam. Any blockage that did occur was cleared using a hot-air blower.

The red-brown tarry residues remaining after distillation were treated by several methods in attempts to extract the reaction products. The most generally useful method was found to be extraction with hot light petroleum which left all the tars and polymeric material undissolved, followed by preparative g.c. separation of the resulting pale brown or yellow-green semicrystalline mixture. Prior analysis of the tar-free mixture by various means was usually carried out to see if it was worthwhile spending the time required for a preparative g.c. separation. Other separation methods, when used, are detailed for each individual alkene.

3A <u>1,5-Hexadiene and 1,7-octadiene</u>

Reactions using both of these alkenes produced complex mixtures from which no products could be isolated. After tar removal by the usual method, each mixture was subjected to g.c. analysis (2% NPGS, 100-225°). They showed a succession of six to eight large, highly asymmetrical and overlapping peaks and many more small ones. No major product was apparent.

Separation by column chromatography was attempted for both mixtures with little success. The components from the mixture from 1,7-octadiene which had been detected by g.c., eluted as a single band, using ether, and could not be separated. No further work was carried out on this mixture. The mixture from 1,5-hexadiene was reduced to three inseparable major components after elution with 99.5% ether/methanol. This mixture was an oil at room temperature and when examined by n.m.r. (60 MHz, CCl_4) showed at 3.8 -4.8τ and 4.9-5.3τ multiplets similar to those observed in the spectrum of 1,5-hexadiene and attributed to the olefinic protons. This indicated that the hoped for 1:2 (alkene:caprolactam) adduct had probably not been formed, but that a simple 1:1 adduct had. If the 1:2 adduct had been present no olefinic signals would have been observed, and the g. c. retention time would probably have been somewhat longer than that observed for any of the major products in the mixture eventually obtained.

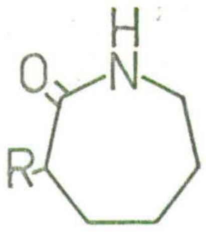
3B *α*-Methylstyrene

G. c. analysis (2% NPGS, 225°) of the tar free mixture obtained after reaction of caprolactam with this alkene showed the presence of three major products, G, H, and J. They were all present in low yield and approximately equal proportions. A small sample of each was obtained after preparative g. c. separation (15 ft CAR 20M, 220°) and n. m. r. and i. r. spectra were recorded.

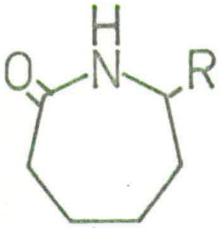
The n. m. r. spectra of H and J suggested that they might have been 3- and 7-(*α*-methylstyryl)caprolactam, but the n. m. r. spectrum of G was not so readily interpreted. As the samples were quite badly contaminated with stationary phase from the preparative g. c. separation and appeared to be unstable on exposure to air, more material was required for a proper identification to be made. However, five further attempts to prepare the compounds were unsuccessful, yielding no products of any kind. The only difference between the first and the subsequent reactions was the batch of *α*-methylstyrene used. In the first reaction the last of an old batch was used. This had been checked for purity by both g. c. and refractive index and found satisfactory. The later, new batch was freshly distilled before the reactions. It must be assumed that an undetected impurity in the older batch was responsible for what must be considered to be the anomalous products obtained from the first reaction. Consequently, no further work was carried out using this alkene.

3C cis, cis-1, 5-Cyclooctadiene

G. c. analysis (2% NPGS, 225°) of this reaction mixture showed the presence of four major products appearing as two pairs of poorly resolved peaks, KL and MN. They were separated as such using preparative g.c. (7 ft, 10% APL, 210^{o}) and sufficient material obtained for mass, i.r., and n.m.r. spectra to be obtained. These spectra were compared with the spectra obtained from the authentic samples of bicyclo-[2, 2, 0]-octylcaprolactams, prepared as described previously (page 97, Section 2D) and found to compare thus: KL had an i.r. spectrum that matched peak for peak with that of AB, and its mass and n.m.r. spectra agreed in all significant details. MN had an i.r. spectrum that matched peak for peak with that of CD and, similarly, its mass and n.m.r. spectra agreed in all significant details. Assignment was therefore made thus:



KL



MN

The group R was assigned, by analogy and by similarity of n.m.r. spectra with the authentic compounds (AB and CD), to bicyclo-[2, 2, 0]-octyl for the major component of each pair, and cyclooctenyl for the minor component of each pair. The n.m.r. spectra showed resonances from the alkenic protons of the latter substituent under conditions of high sensitivity.

3D 1-Octene

G.c. analysis of the tar-free mixture resulting from reaction with this alkene showed the presence of two major products, P and Q. The g.c. characteristics of these were found to be identical with those of authentic octylcaprolactams, E and F, (see page 9) on two different columns, 2% NPGS at 225^{o}, and 2% APL at 220^{o}. These columns are, respectively polar and non-polar. It was thought likely that P and Q were 3- and 7-octyl caprolactam, respectively, so a sample of a mixture of the two was obtained, free from other compounds or starting material, by column chromatography, using 50% ether/benzene to elute. The i. r. spectrum of this mixture was recorded and found to comprise only peaks found in the i. r. spectra of the two authentic octylcaprolactams previously prepared.

A mass spectrum of the mixture, similarly, comprised fragments found in the mass spectra of the two authentic compounds.

The yield of this reaction and the molar ratio of the two isomers were found using the D6 chromatograph[22] and the results are shown in Table 3-1.

Table 3-10 Quantitative data for the radical induced addition of 1-octene and caprolactam.

Total yield (%) of 1:1 adduct	13.9
Yield (%) of 7-octyl isomer	9.6
Yield (%) of 3-octyl isomer	4.3

Ratio, 7-octylcaprolactam : 3-octylcaprolactam = 2.23:1

4 Attempted Polymerisation of 7-Octylcaprolactam

7-Octylcaprolactam (1.0 g), prepared via cyclohexanone (see p. 99) was sealed under nitrogen into a thick-walled glass tube, together with a small amount of water[28] (ca. 0.2 g). The tube was then placed in a steel pressure vessel which was flushed with nitrogen and sealed. The apparatus was heated for a week at 250°.

At the end of this time the contents of the tube were examined and found to be unchanged. The material recovered was recrystallised and left no tarry, amorphous or insoluble residue. Its m. p., i. r. and n. m. r. spectra were found to be identical with starting material and to indicate the presence of no impurities or polymeric material.

DISCUSSION

CONTENTS

DISCUSSION

1 Separation of Isomers

The major difficulty experienced during this work was the separation from the reaction mixture and from one another of the two or more isomeric 1:1 adducts formed in the free-radical alkylation reactions. Even the use of preparative g. c. was only a partial solution since, in one case, materials isolated as apparently pure on the preparative instrument could, under analogous conditions, each be separated into more components on the analytical instrument.

Because of the evidently time-consuming nature of this kind of separation and analysis problem, yields were not optimised for any of the reactions carried out.

The most interesting feature of the production of isomeric 1:1 adducts by radical alkylation of caprolactam is that similar results have been reported from almost all work on free radical alkylation of N-alkylamides. In thermally-induced reactions[15-18] (e. g. using a thermally decomposed initiator such as a peroxide) the N-adjacent adduct is favoured, usually by a factor of about 2:1 over the C-adjacent adduct. On the other hand, in photo-induced reactions the opposite result occurs,[9-14] and the C-adjacent adduct predominates. Apart from its observation little has been written about this effect, and no thorough systematic study has been made of it. Nikishin has suggested, in this connection,[29] that donation of the nitrogen lone pair towards the radical centre can occur, resulting in a nucleophilic radical, but it is by no means certain that this would favour the formation of the N-adjacent product. Until further work is carried out, the cause of this effect remains unknown.

2 Octene and Polymerisation - Comparison with Results from other Sources

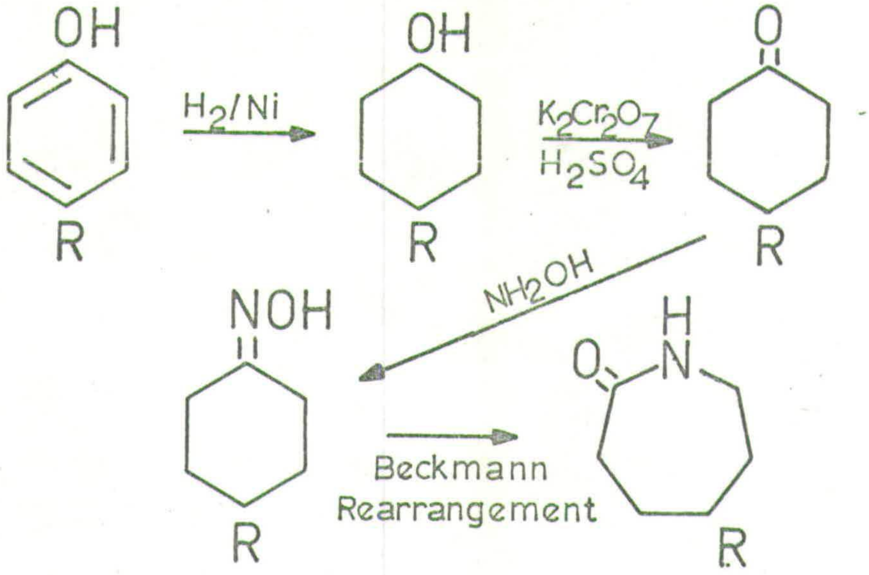
Consequent on the difficulty of separating isomeric products from one another it became clear that any prospect of industrial development of this reaction would founder on this problem alone. However, one reaction was studied in some detail. This was the most successful one and also one that allowed comparison of results with those of other workers.

Free-radical induced alkylation of caprolactam with 1-octene using di-tert-butyl peroxide as initiator resulted in a 14% yield of 1:1 adducts. This consisted of a mixture of N-adjacent and C-adjacent alkylation products in a ration of 2. 2:1 respectively. The products were identified by n. m. r. spectrum and by comparison of infrared spectra and mass spectra with those of authentic materials. This is more fully described in the Experimental Section.

These results are in agreement with those found by Nikishin[19] who did a similar reaction. He obtained a higher yield of 1:1 adducts, 38%, but also used a higher dilution of initiator and octene in caprolactam (0. 15:1:20 respectively) than was used in the present work (0. 2:1:10 respectively). The relative quantities of each 1:1 adduct are not reported, but in an analogous reaction using 2-pyrrolidone mentioned in the same report the ratio is 2. 5:1, (N-adjacent: C-adjacent).

One of the alkylation products obtained in the present work was available in sufficient quantity for an attempt to be made to polymerise it. 7-Octyl caprolactam, the N-adjacent adduct, was the subject of this experiment, but under conditions which would have resulted in the polymerisation of caprolactam,[28] (1 week, 250°, 1% water) no polymerisation was apparent, nor even any decomposition. This is in agreement with results obtained by Ziegenbein.[30] He synthesised various alkylsubstituted caprolactams and attempted their polymerisation with various catalysts.

The alkyl caprolactams were prepared by a four stage route from alkyl phenols. The method is outlined in Scheme 2-1, overleaf. By this method 3-ethyl, 3-i-propyl, 3-t-butyl, 3-hexahydrobenzyl, 3-hexyl, 3-octyl, 3, 5-dimethyl and 7-i-propyl-caprolactam were made.



Scheme 2-1

From the results of various polymerisation experiments in which the alkylcaprolactam was heated with water or other catalysts, Ziegenbein drew the following conclusions:

1) Substitution of an alkyl group into the caprolactam ring makes polymerisation more difficult.

2) 3- and 7-substituted caprolactams are less difficult to polymerise than 4-, 5-, and 6-substituted caprolactams.

3) Polymerisation becomes more difficult as the length of the alkyl chain increases, until it no longer occurs.

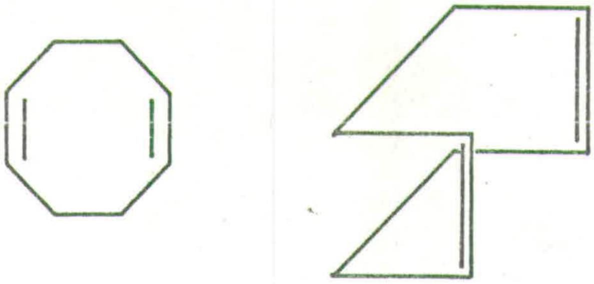
4) Substitution of more than one alkyl group into the caprolactam ring further increases the difficulty of polymerisation.

Later work by Cubbon[31] and Čefelín[32] confirmed these results.

Ziegenbein reported that 3-hexyl and 3-octyl caprolactam could not be induced to polymerise, which would tend to confirm the present observation that successful polymerisation of 7-octyl capralactam did not occur.

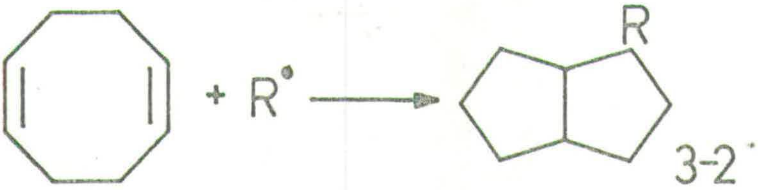
3. Free Radical Alkylation with cis, cis-1, 5-Cyclooctadiene

An attempt was made to alkylate caprolactam with cis, cis-1, 5-cyclooctadiene,(3-1), (cyclooctadiene).



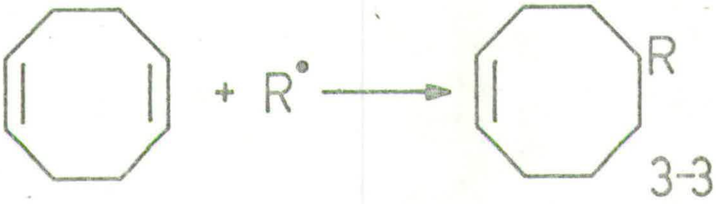
3-1

This is known to undergo transannular ring-closure under free-radical conditions to give bicyclo-[3, 3, 0]octane derivatives,[23, 34, 35] e.g. 3-2 :



This result was indeed observed and the products formed had envelope n.m.r. spectra in the region 7.5-9.0τ which were quite similar to published spectra.[33]

However it was observed that some of the non-rearranged product was also formed, a cyclooctene derivative, e.g. 3-3 :



This product could not be isolated but was detected in the n.m.r. spectrum of a component of the reaction mixture separated by preparative g.c. The conditions of the separation were such that neither cyclooctadiene nor cyclooctene were present in the material trapped out. This was important since the n.m.r. signal attributed to the non-rearranged product was a complex multiplet of similar form and chemical shift to the alkenic signal from each of these compounds. The non-rearranged product could also be detected as a partly resolved peak seen in analytical g.c. traces of components separated by preparative g.c. and in the unseparated reaction mixture. Resolution was not sufficient to allow an accurate estimation of the proportion of non rearranged product, but it was probably less than 15%, when fresh and it decreased with time presumably through rearrangement to the bicyclooctane derivative. Previous reports of work with this alkene have stated that either a cyclooctene derivative[36, 37] or a bicyclooctane derivative[23, 34, 35] is formed to the exclusion of the other. This is the first observation of both being produced from a free-radical reaction. However, it is unlikely that this represents a new chemical phenomenon, more an increase in the sensitivity of instrumental analysis.

4 Conclusion

Contrary to expectations, free radical induced alkylation of caprolactam is unlikely to be a synthetically useful reaction. The disappointingly low yields and complex product mixtures formed all reduce the advantages gained from the single synthetic step.

It was however found that a more efficient method of synthesizing 3- and 7-substituted caprolactams was by the method eventually used to synthesise these compounds for comparison purposes. The yield over two reaction steps, i.e. alkylation of cyclohexanone by Nikishin's method[20] followed by conversion to alkylated caprolactam by Novotný's method,[26] was about twice that of the direct alkylation.

The product is, however, still a mixture of isomeric alkylated caprolactams and the problem of an efficient separation method remains.

References Part Two

1 M. Gomberg, Ber., 33, 3150 (1900); J. Amer. Chem. Soc., 22, 757 (1900).

2 L. H. Cone, M. Gomberg, Ber., 37, 2047 (1904); Ber., 39, 2447 (1906).

3 G. Lewis, J. Amer. Chem. Soc., 38, 762 (1916).

4 a) M. Kharasch, F. Mayo, J. Amer. Chem. Soc., 55, 2468 (1933);

b) M. Kharasch, H. Engelmann, F. Mayo, J. Org. Chem., 2, 288 (1937);

c) F. Mayo, C. Walling, Chem. Rev., 27, 351 (1940).

5 D. H. Hey, W. A. Waters, Chem. Rev., 21, 169 (1937).

6 a) W. A. Waters, 'The Chemistry of Free Radicals,' Oxford University Press, 1946;

b) J. I. G. Cadogan, D. H. Hey, Quart. Rev., 8, 308 (1954).

c) C. Walling, 'Free Radicals in Solution,' John Wiley and Sons, 1957;

d) C. J. M. Stirling, 'Free Radicals in Chemistry,' Oldbourne, 1965;

e) W. A. Pryor, 'Free Radicals,' McGraw-Hill, 1966;

f) I. U. P. A. C. Symposium on Free Radicals in Solution, Ann Arbor, Michigan, 1966, Butterworths, 1967;

g) J. I. G. Cadogan, 'Principles of Free Radical Chemistry,' Chemical Society Monographs for Teachers (1973).

7 See, e.g. J. C. Allen, J. I. G. Cadogan, B. W. Harris, D. H. Hey, J. Chem. Soc., 4468 (1962).

8 H.-H. Vogel, Synthesis, 99 (1970) and refs. therein.

9 D. Elad, J. Rokach, J. Org. Chem., 29, 1855 (1964).

10 D. Elad, J. Rokach, J. Chem. Soc., 800 (1965).

11 D. Elad, J. Rokach, J. Org. Chem., 30, 3361 (1965).

12 J. Rokach, C. Krauch, D. Elad, Tet. Lett., 3253 (1966).

13 J. Rokach, C. Krauch, D. Elad, Tet. Lett., 5099 (1967).

14 D. Gush, N. Marans, F. Wessells, W. Addy, S. Olfky, J. Org. Chem., 31, 3829 (1966).

15 L. Friedman, H. Schechter, Tet. Lett., 238 (1961).

16 J. C. Allen, J. I. G. Cadogan, D. H. Hey, J. Chem. Soc., 1918 (1965).

17 A. Rieche, E. Schmitz, E. Grundemann, Angew. Chem., 73, 621 (1961).

18 R. Gritter, R. Woosely, J. Chem. Soc., 5544 (1963).

19 G. Nikishin, I. Mustafaev, Izvest. Akad. Nauk. S. S. S. R., Ser. Khim., 1843 (1964) (Engl. Trans. p. 1745).

20 G. Nikishin, G. Somov, A. Petrov, Izvest. Akad. Nauk. S. S. S. R., Otd. Khim. Nauk, 2065 (1961); Chem. Abs., 56, 7155 (1962).

21 W. H. Urry, O. O. Juveland, J. Amer. Chem. Soc., 80, 3322 (1958).

22 J. Sinnreich, D. Elad, Chem. Ind. (London), 768 (1965); Tet., 24, 4509 (1968).

23 R. Dowbenko, Tet., 20, 1843 (1964); J. Amer. Chem. Soc., 86, 946 (1964).

24 F. Cortese, J. Amer. Chem. Soc., 51, 2266 (1929).

25 E. Horning, V. Stromberg, J. Amer. Chem. Soc., 74, 2680 (1952).

26 A. Novotný, U. S. Patent, 2 579 851, Dec. 25 1951; Chem. Abs., 46, 6668g, (1952).

27 J.I. G. Cadogan, I. H. Sadler, J. Chem. Soc. (B), 1191 (1966) and refs. therein.

28 a) P. Hermans, J. Appl. Chem., 5, 493 (1955).
b) P. Hermans, D. Heikens, P. van Velden, J. Poly. Sci., 30, 81 (1958).

29 G. Nikishin, R. Mustafaev, Dokl. Akad. Nauk S. S. S. R., 158, 1127 (1964). (Eng. Trans. p. 1069).

30 W. Ziegenbein, A. Schaffler, R. Kaufhold, Ber., 88, 1906 (1955).

31 R. Cubbon, Makromol. Chem., 80, 44 (1964).

32 P. Čefelín, J. Labský, J. Šebenda, Coll. Czech. Chem. Comm., 33, 1111 (1968).

33 N. Moniz, J. Amer. Chem. Soc., 83, 1761 (1961).

34 G. Pregaglia, G. Gregorio, Chim. Ind. (Milan), 45, 1065 (1963); Chem. Abs., 59, 12658h, (1963).

35 L. Friedman, J. Amer. Chem. Soc., 86, 1885 (1964).

36 J. Lock, E. Duck, Chem. Comm., 151 (1965).

37 L. Gale, J. Org. Chem., 33, 3643 (1968).