NEW DEVELOPMENTS IN

PALLADIUM CATALYSED CROSS-COUPLING

a thesis presented by

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ABSTRACT

In Chapter One, the palladium catalysed cross-coupling reaction is reviewed. A summary of the synthetic utility of the reaction is presented, with emphasis placed on the nature and variety of the organic groups involved. Special attention is given to the more recent advances in the subject.

In Chapter Two, the results of the present study are described and discussed. The palladium catalysed cross-coupling reaction is often accompanied by undesired products due to the elimination of β-hydrogens from the organopalladium intermediate. The use of 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride in the suppression of β-elimination was investigated.

Firstly, the reaction of 4-iodoanisole and the Grignard reagent derived from 2-bromopropane, utilising the aforementioned catalyst, was studied. Secondly, the 2-bromopropane was replaced by a variety of primary and secondary alkyl halides.

The synthetic utility of the cross-coupling reaction was extended by the replacement of the aryl iodide with various alkyl iodides and their coupling to both alkyl and aryl Grignard reagents. A series of reactions was investigated which led to the successful cross-coupling of primary-primary, secondary-primary, primary-secondary and secondary-secondary alkyl groups.

In order to further extend the process and to improve yields in reactions involving more sterically demanding substrates, the

catalyst 1,1'-bis(methylphenylphosphino)ferrocene palladium dichloride was prepared. This catalyst was then used in a series of alkyl-alkyl cross-couplings.

Chapter Three contains experimental details along with both the physical and spectroscopic properties of the compounds that were synthesised.

ABBREVIATIONS

cy	-	Cyclohexyl
DIBALH	-	Diisobutylaluminiumhydride
DMA	-	Dimethylacetamide
DME	-	1,2-Dimethoxyethane
DMF	-	N,N-Dimethylformamide
DMSO	-	Dimethylsulphoxide
Et_2O	-	Diethyl ether
GLC	-	Gas Liquid Chromatography
HMPA	-	Hexamethylphosphoramide
LDA	-	Lithium diisopropylamide
MCPBA	-	m-Chloroperbenzoic acid
o-tolyl	-	1,2-Dimethylbenzene
PdL_4	-	Tetrakis(triphenylphosphine)palladium(0)
R.T.	-	Room Temperature
TBDMS	-	t-Butyldimethylsilyl
TBDPS	-	t-Butyldiphenylsilyl
Tf	-	Triflate
THF	-	Tetrahydrofuran
THP	-	Tetrahydropyran
TMEDA	-	N,N,N',N'-Tetramethylethylenediamine

CHAPTER 1: REVIEW

1.1 INTRODUCTION

1.1.1 Scope of the review

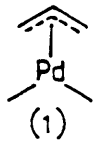
Among the transition metals, palladium is one of the most extensively used for the synthesis of both industrial and fine chemicals. The reasons are partly historical (the Wacker process for the palladium catalysed oxidation of ethylene to acetaldehyde was developed nearly 30 years ago), and partly due to the versatility, availability and utility of organopalladium complex chemistry.

The synthetic usage of palladium compounds has developed into a major branch of organic chemistry[1]. Reactions involving palladium mediated transformations are many and varied, and have been the subject of extensive reviews[2-6].

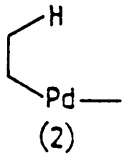
This review will only be concerned with the palladium catalysed cross-coupling reaction. The major aspects of the reaction will be outlined, with special emphasis being placed on the most recent developments.

1.1.2 Formation of coupling products

The organic chemistry of palladium compounds involves two major types of intermediate, π-allyl (1) and σ-organopalladium (2) species.



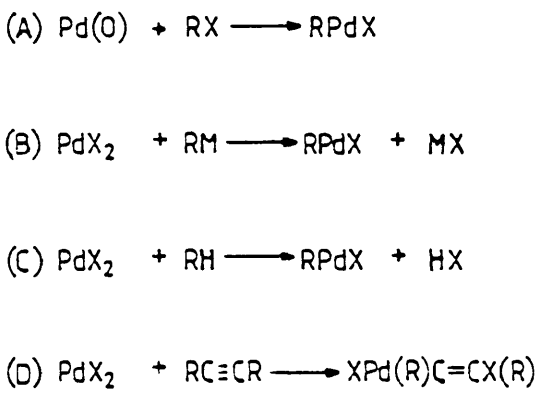
(1)



(2)

Compounds of type (2) which bear cis-β-hydrogens have a tendency to eliminate palladium hydride. This has restricted reactions involving alkylpalladium intermediates and most reactions involving σ-palladium species are those of aryl and vinyl derivatives where such cis-β-eliminations do not occur.

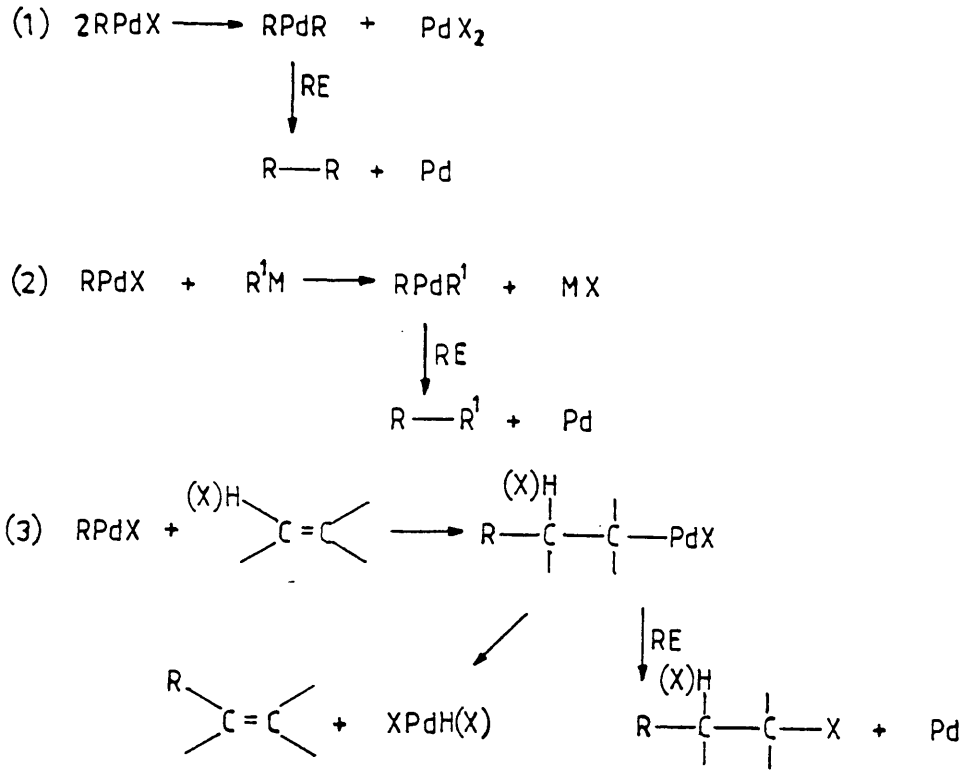
The initial step of a cross-coupling reaction is the formation of an organopalladium salt. This can occur by several methods (Scheme 1).



Scheme 1

Method (A) involves the oxidative addition of an organic halide, acetate, etc to a zero-valent palladium species. In method (B), an organic group from an organometallic reagent, eg Grignard reagent, borane, mercurial, etc is exchanged with an anion (often a halide) on a palladium(II)species. In addition, palladium(II)salts can directly metallate a hydrocarbon (usually aromatic), as shown by method (C). Finally, method (D) shows the addition of a palladium(II)salt to an alkene, diene or acetylene.

These organopalladium species can form coupled products by three pathways (Scheme 2).



RE =Reductive Elimination

Scheme 2

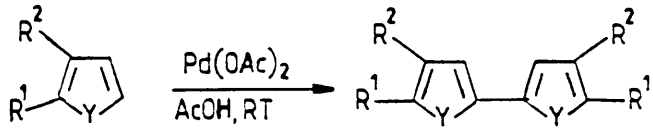
Path (1) involves disproportionation, followed by reductive elimination. In path (2), a diorganopalladium compound is formed by another organometallic reagent (R'M, where R' = alkyl, aryl), which also undergoes a reductive elimination. Addition of the organopalladium species to an alkene, diene or acetylene, path (3), leads to an intermediate which can either eliminate palladium hydride (or halide), or reductively eliminate coupled products.

All the reactions in the following discussion involve variations on a combination of one of the methods A-D, followed by one of the pathways 1-3. For a more detailed mechanistic discussion see section 2.2.

1.2 ARYL COUPLING

1.2.1 Aryl-H

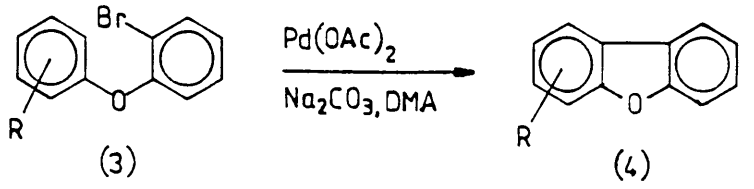
Aromatic compounds often dimerise to biaryls when they are heated with palladium(II)salts and sodium acetate. Isomeric mixtures of biaryls are frequently produced from mono- and disubstituted aromatics[7-9]. Oxidative coupling of thiophenes and furans bearing electron-withdrawing substituents in the presence of $Pd(OAc)_2$ led to 2,2'-bithienyls and 2,2'-bifuryls[10].



Y =S R'=$COCH_3$ R^2=H (70%)
Y =O R'=$COCH_3$ R^2=H (50%)
Y =S R'=CHO R^2=CH_3 (71%)

An intramolecular version of the aryl coupling reaction occurred with diaryl ethers, amines, ketones and benzanilides[4]. Coordination of the palladium acetate with the heteroatom was apparently responsible for the ortho-palladation of both aryl groups with the same palladium atom, and then reductive elimination formed the biaryl derivative[11]. Previous preparations of substituted dibenzofurans by the palladium promoted intramolecular cyclisation of substituted diphenyl ethers, have required heating with stoicheiometric amounts of

$Pd(OAc)_2$ (more than 1 equivalent if an electron-withdrawing group is present) in acidic solvents. The reaction also suffers from a lack of selectivity, due to a competing intermolecular dehydrogenative coupling. However, Ames et al. have reported[12] a general process, using a catalytic amount of $Pd(OAc)_2$, for the cyclisation of substituted 2-bromophenyl phenyl ethers (3) to substituted dibenzofurans (4).

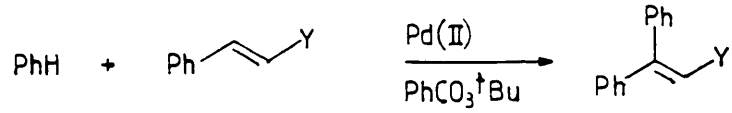


(3) (4)

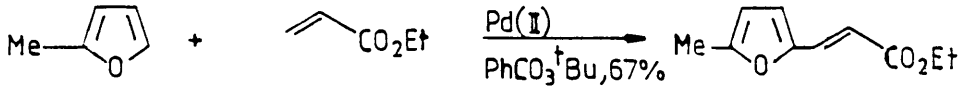
R =2-CN (80%)
4-NO_2 (78%)
H (74%)
2-CO_2H (66%)
1-Me, 3-Me (73%)

The dibenzofurans were prepared in good yields, and the reaction tolerated strongly electron-withdrawing groups as well as electron-releasing groups.

Benzene and furans underwent oxidative coupling with olefins, in the presence of t-butyl perbenzoate and a catalytic amount of a palladium(II)-salt. The perbenzoate acts as a hydrogen acceptor.

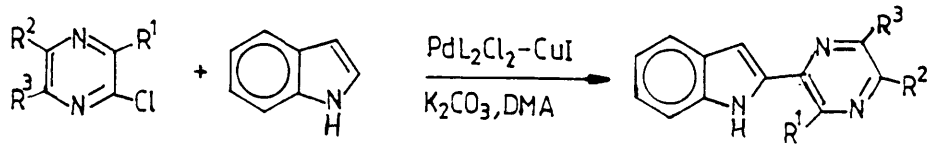


Y =COMe (65%)
CHO (64%)
CO_2Me (56%)



The palladium catalysed coupling reactions of indoles have been extensively investigated in recent years[13]; these involve carbonylation[14], arylation[15], allylation[16] and vinylation[17,18]. In addition, simple procedures were recently reported for the introduction of the cyano[19], alkenyl and alkynyl[20], and methyl[21] groups into the pyrazine ring, with the aid of palladium catalysts.

The palladium catalysed cross-coupling reaction of 2-chloropyrazines with indole proceeded in moderate to good yields, giving 2- (pyrazin-2-yl)indoles, i.e. the coupling occurred at the C-2 position of indole[22]. Reactions with 3-methylindole under the same conditions were equally successful. However, 2-methylindole did not undergo coupling at all.



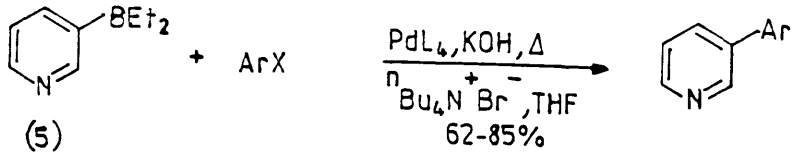
$R^1=R^3=Ph$ $R^2=H$ (70%)
$R^1=R^2=Ph$ $R^3=H$ (79%)
$R^2=R^3=Ph$ $R^1=H$ (68%)

This reaction is attractive because it allows the introduction of the functionalised carbon side-chain necessary for the synthesis of various indole alkaloids.

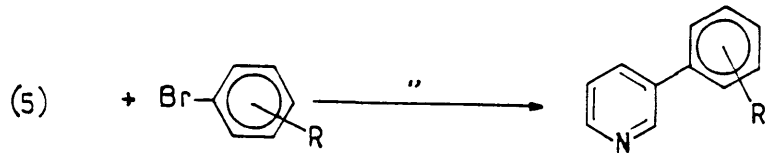
1.2.2 Aryl-Metal

As a result of pharmaceutical interest and their occurrence as tobacco alkaloids, numerous routes have been reported for the synthesis of heteroaryl derivatives of pyridines. However, for the direct introduction of heteroaryl groups in the β-position of pyridines, a number of difficulties have been encountered when using classical methods. The main problems are the lack of regio- selectivity and low yields (Gomberg-Bachmann reaction), the restricted applicability to active halides and the concomitant formation of homocoupled products (Ullmann reaction), or the tedious procedure and limited scope of the reactants (Grignard reaction).

Recently, Terashima et al. have reported[23,24] the synthesis of 3-aryl- and 3-heteroarylpyridines by palladium catalysed cross-coupling of diethyl-(3-pyridyl)-borane (5) with aryl- and heteroaryl halides.

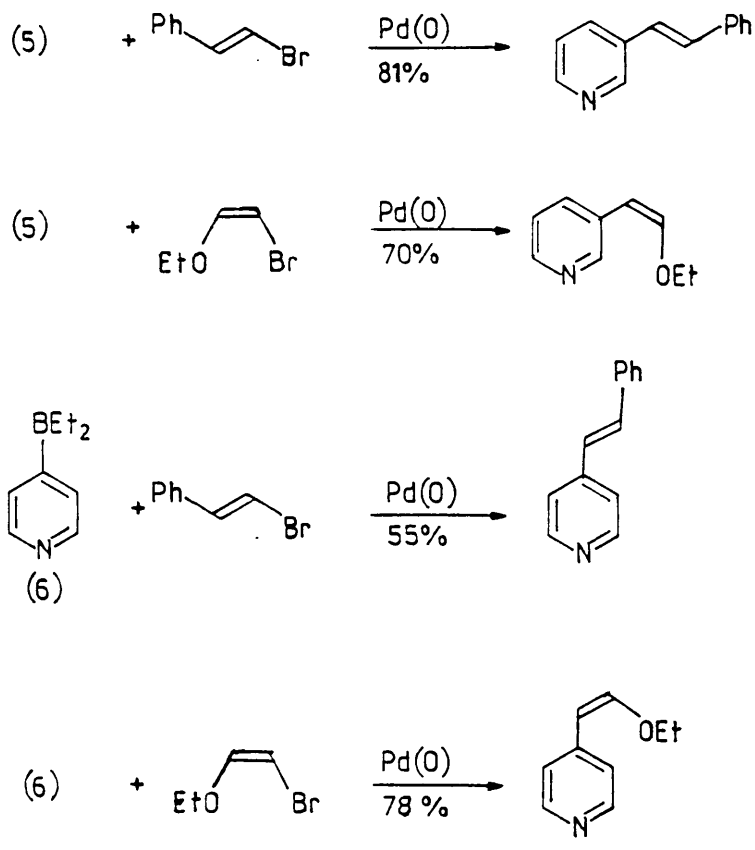


ArX =3-Bromothiophene, 2-Bromofuran, etc

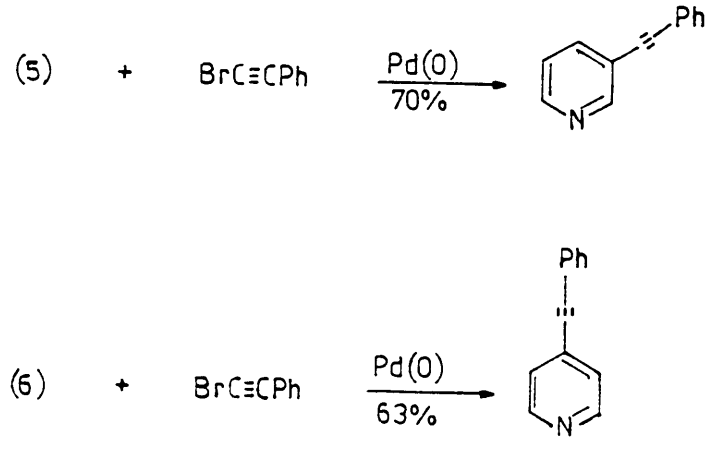


R =H (85%)
4-Me (84%)
4-Cl (86%)
4-OMe (75%)
4-$COCH_3$ (73%)
2-NHCOPh (50%)
2-NO_2 (75%)
2-CO_2Me (59%)

Both 3- and 4-alkenylpyridines have been prepared by palladium catalysed reaction of (5) and diethyl-(4-pyridyl)-borane (6) with vinyl bromides[25].



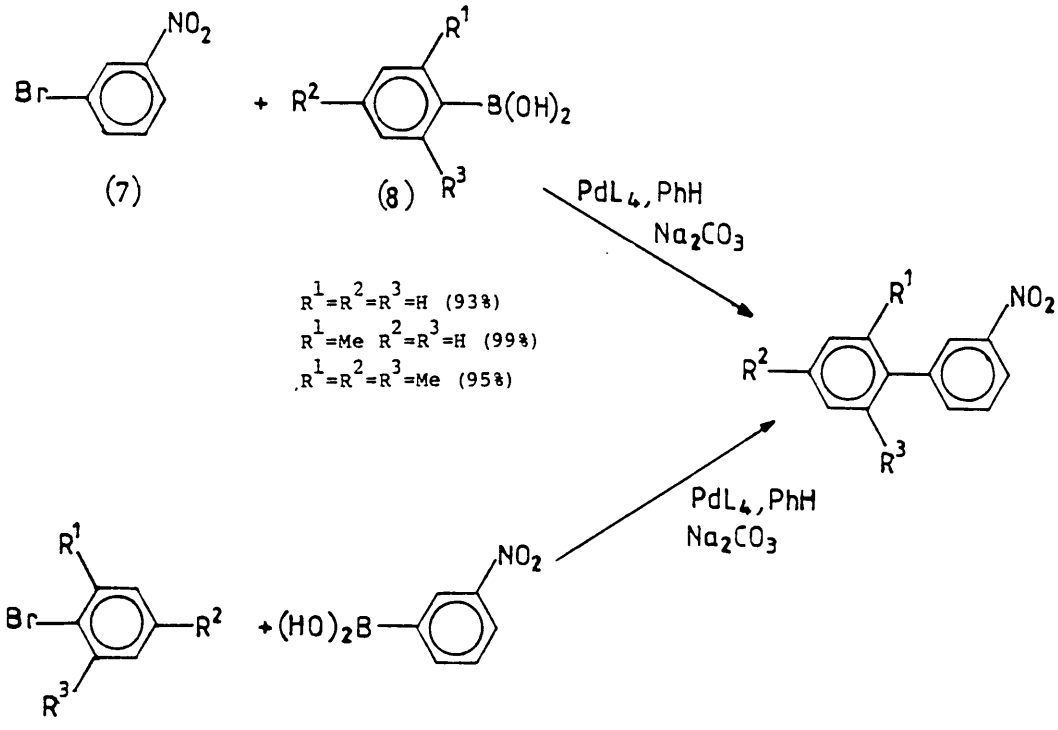
The reaction proceeded regioselectively and stereospecifically to give the corresponding coupled products in good yields. Likewise, reaction with phenylbromoethyne under similar conditions gave phenylethynyl-pyridines.



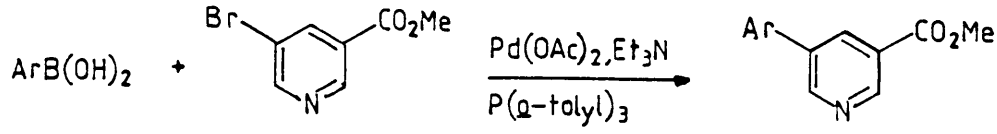
This reaction offers an efficient method for the regioselective synthesis of a wide range of bipyridines, and affords a ready introduction of vinylic groups with various substituents to the 3- or 4-position of pyridine.

Arylmetallic compounds have also been used to synthesise a variety of unsymmetrical biaryls[26,27]. The yields of biphenyl are excellent, especially when the metal is mercury[28] or tin[29].

The cross-coupling of arylboronic acids with aryl bromides produced mononitrobiphenyls in very high yields[30]. The reaction was not sensitive to steric requirements and had the added versatility of allowing the nitro substituent to be on either the aryl bromide (7) or arylboronic acid (8) component.

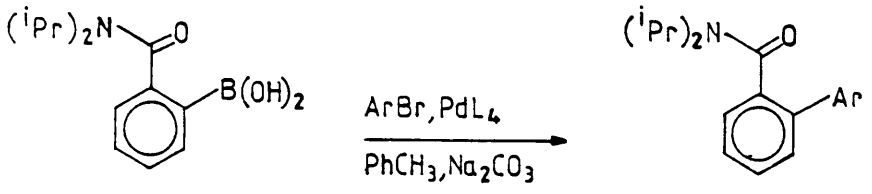


A variety of arylboronic acids have been found to couple efficiently with 5-bromonicotinates to yield 5-arylnicotinates[31].



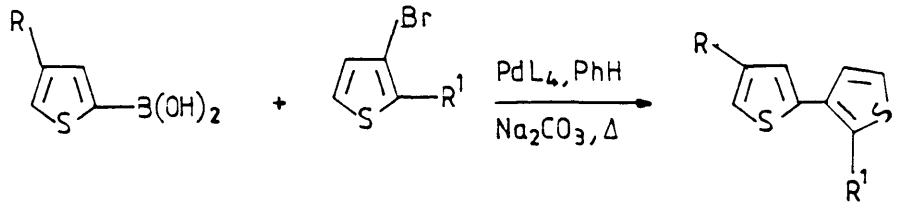
Ar =Ph (98%)
2-furyl (86%)
2-MeC_6H_4 (81%)

Arylboronic acids derived by directed ortho-metallation of benzamides and carbamates, underwent an efficient coupling reaction with a variety of aryl halides to yield unsymmetrical biaryls and hetero-biaryls, with no homocoupled products observed[32].

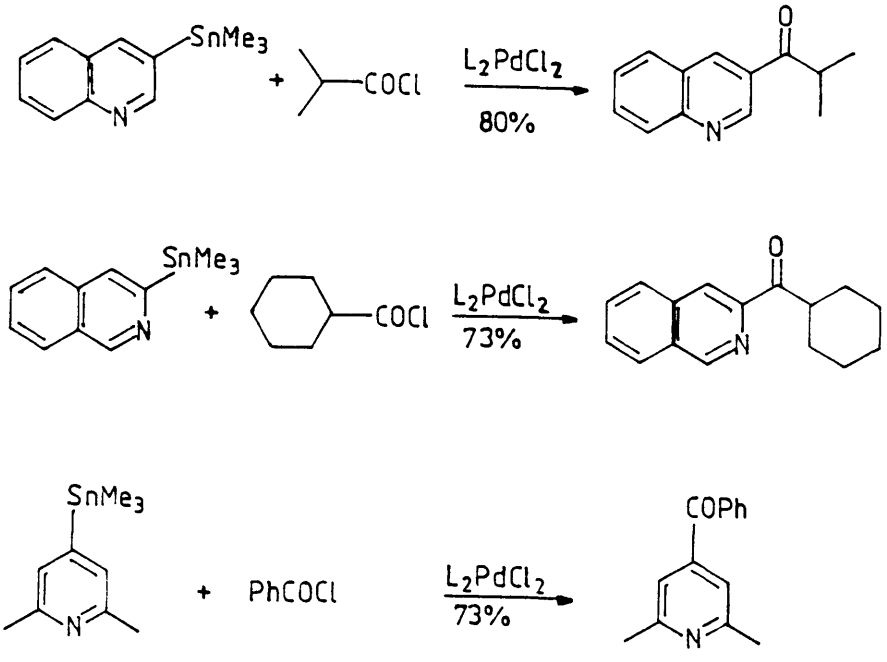


Ar =Ph (82%)
2-MeC_6H_4 (85%)
3-pyridyl (90%)
5-thiazolyl (87%)
6-methoxy-2-naphthyl (95%)
2-thiophenyl (92%)

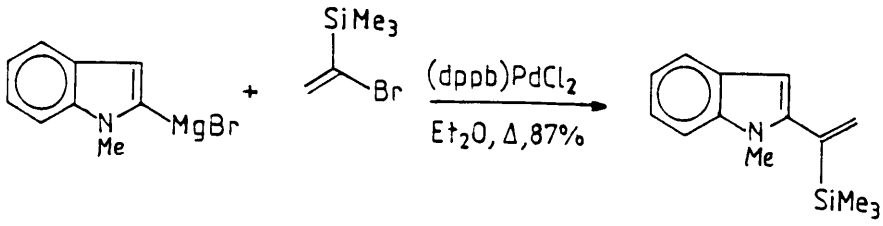
Palladium catalysed coupling of 2-thiopheneboronic acids with halothiophenes provided a convenient method for the synthesis of unsymmetrical substituted bithienyls[35,36].



A number of 2-, 3- and 4-trimethylstannyl aromatic nitrogen heterocycles (e.g. pyridines, quinolines and isoquinolines) reacted smoothly with acid chlorides under catalysis by bis(triphenylphosphine)palladium(II)dichloride (L_2PdCl_2) leading to high yields of aromatic heterocyclic ketones[33,34].



Heteroaryl Grignard reagents reacted with halovinylsilanes, in the presence of dichlorobis-(diphenylphosphinobutane)palladium(II) ((dppb)$PdCl_2$) to form heteroarene-substituted vinylsilanes[37].



1.2.3 Aryl-X

In recent years, many papers have appeared which contain reactions between aryl bromides and tributyltin derivatives. The reaction of N,N-diethylamino-tributyltin with aryl bromides in the presence of a catalytic amount of $(o\text{-tolyl}_3P)_2PdCl_2$ gave N,N-diethyl-amino-benzene derivatives[38].

$$^{n}Bu_3SnNEt_2 + ArBr \xrightarrow[PhCH_3]{PdCl_2(o\text{-tolyl}_3P)_2} ArNEt_2 + {}^{n}Bu_3SnBr$$

The palladium catalysed reaction of aryl bromides with methoxymethyl-tributyltin was found to give arylmethyl methyl ethers[39].

$$Bu_3SnCH_2OCH_3 + PhBr \xrightarrow[HMPA, 73\%]{L_2PdCl_2, 80^{\circ}C} PhCH_2OCH_3 + Bu_3SnBr$$

This novel aromatic methoxymethylation gave moderate yields (60-75%) and could be applied to a wide variety of aryl bromides bearing functional substituents, e.g. cyano, carbonyl and nitro groups. Interestingly, although reactions utilising diethoxymethyltributyltin and thiomethoxymethyltributyltin were unsuccessful, hydroxymethylation

of bromobenzene by using the corresponding organotin reagent produced benzyl alcohol (9).

$$Bu_3SnCH_2OH + PhBr \xrightarrow[THF,\,60\%]{L_2PdCl_2,\,80^\circ C} PhCH_2OH + Bu_3SnBr$$

(9)

The α-arylation of enolates is rather difficult in general. However, tributyltin enolates, prepared <u>in situ</u> from tributyltin methoxide and enol acetates[40], reacted with bromobenzene to give α-phenyl ketones in good yields[41].

$$Bu_3SnOMe + CH_3CO_2\overset{\overset{Me}{|}}{C}=CH_2 \longrightarrow [Bu_3SnO\overset{\overset{CH_2}{||}}{C}CH_3] + CH_3CO_2CH_3$$

$$[Bu_3SnO\overset{\overset{CH_2}{||}}{C}CH_3] \xrightarrow[ArBr]{PdCl_2(o\text{-}tolyl_3P)_2} ArCH_2COCH_3 + Bu_3SnBr$$

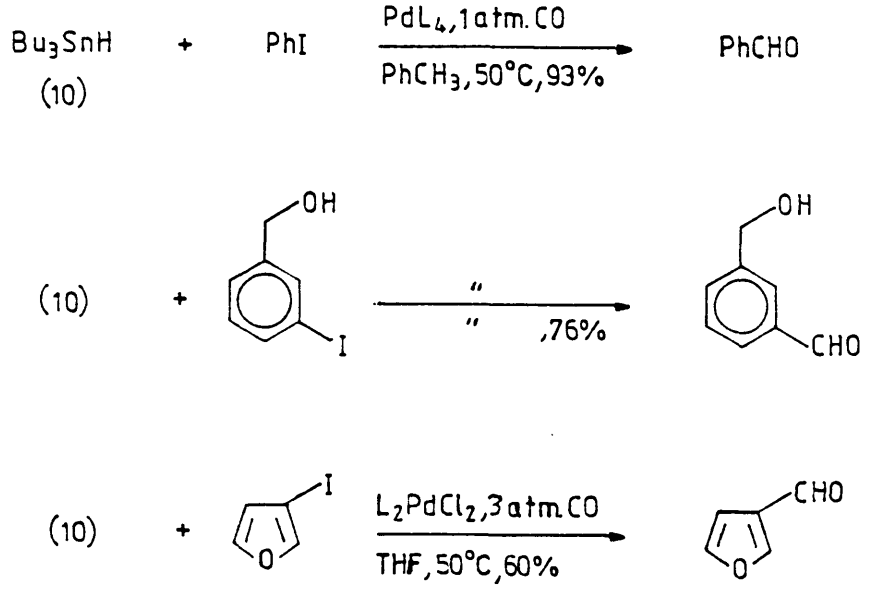
Palladium catalysed coupling of aryl bromides with cyanomethyltributyltin gave arylacetonitriles in moderate yields[42].

$$Bu_3SnCH_2CN + ArBr \xrightarrow[PhCH_3]{PdCl_2(o\text{-}tolyl_3P)_2} ArCH_2CN + Bu_3SnBr$$

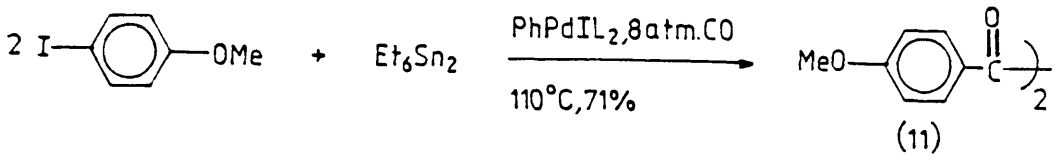
Surprisingly, aryl bromides having strong electron-withdrawing groups (e.g. acyl, cyano, nitro) cannot be applied to this reaction.

The organotributyltin methodology has been successfully applied to the coupling of many other groups with aryl halides[43], e.g. alkyl, vinyl, acetylene, etc.

A new synthetic method has been developed by Stille et al.[44] for the preparation of aldehydes from a wide variety of organic electrophiles. The palladium catalysed carbonylation reaction of the electrophile in the presence of tributyltin hydride (10) as the hydride source, yielded aldehydes under mild conditions (50°C, 1-3 atm. of CO, 2-3h). The gentle nature of the reaction allowed many functional groups to be tolerated[45].

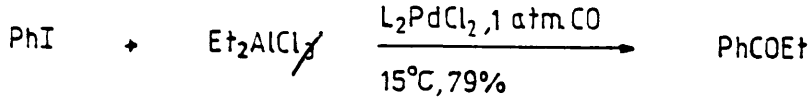


The palladium catalysed carbonylation of aryl iodides in the presence of hexaethylditin may serve as a route to symmetrical α-diketones. Such a possibility has recently been demonstrated[46] for the preparation of 4,4'-dimethoxybenzil (11).



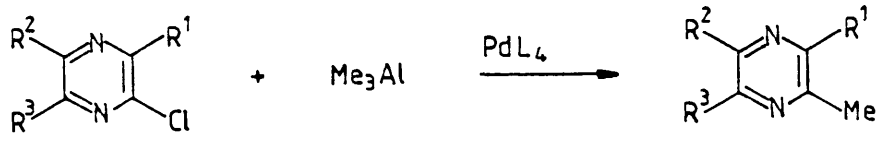
(11)

Unsymmetrical ketones have been obtained in moderate to good yields by the palladium catalysed carbonylative coupling of aryl iodides with alkylaluminium compounds[47].



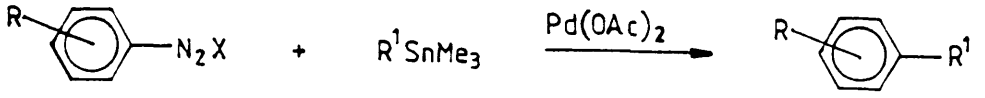
Nickel catalysts were found to be ineffective for this reaction.

Mono- and dichloropyrazines underwent the cross-coupling reaction with trimethylaluminium forming the corresponding mono- and dimethyl-pyrazines in excellent yields[48].



R^1=Cl R^2=R^3=Ph (93%)
R^1=R^2=Ph R^3=H (95%)
R^1=R^3=^{i}Bu R^2=H (97%)
R^1=R^3=^{i}Bu R^2=Cl (93%)

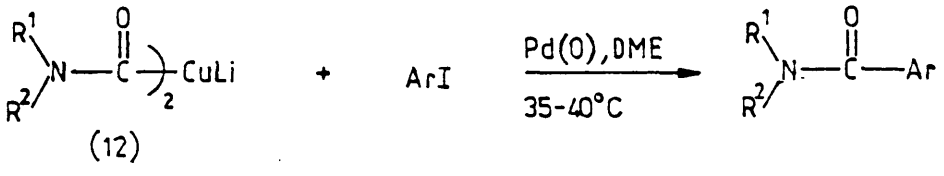
Arenediazonium salts were effectively functionalised with an alkyl or vinyl group by coupling with organotin compounds[49].



R^1=alkyl, vinyl

Good yields were obtained, irrespective of the nature of the aromatic ring substituent, including a nitro group. The reaction proceeded chemoselectively even in the presence of halogen substituents.

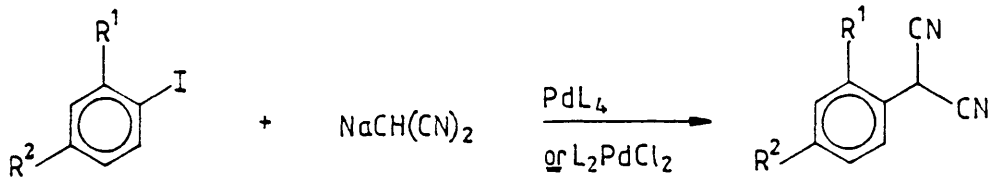
Carbamoyl cuprates of general structure (12) coupled readily with aryl iodides[50], to form aryl carboxamides.



R^1=Me R^2=Ar=Ph (71%)

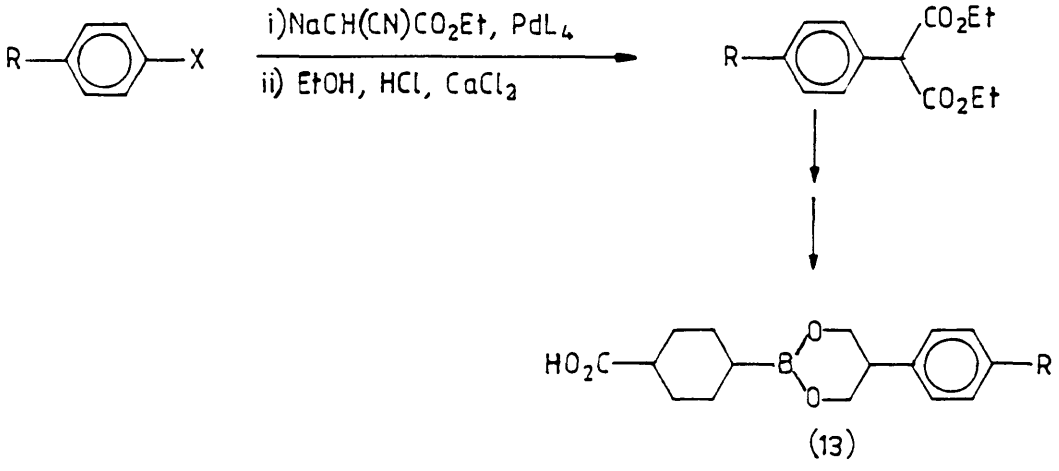
Malononitrile derivates are important intermediates in the synthesis of heterocyclic compounds. Alkylmalononitriles are easily obtained from the direct reaction of malononitrile anion with alkyl halides, whereas aryl halides do not react with the anion under the same conditions. Several synthetic routes to arylmalononitriles have appeared in the literature, but these involved complicated procedures with multiple steps, produced low yields, or were not of general applicability. However, arylmalononitriles have been prepared in good

yields by Takahashi et al.[51], using a palladium catalysed coupling reaction between aryl iodides and the malononitrile anion.



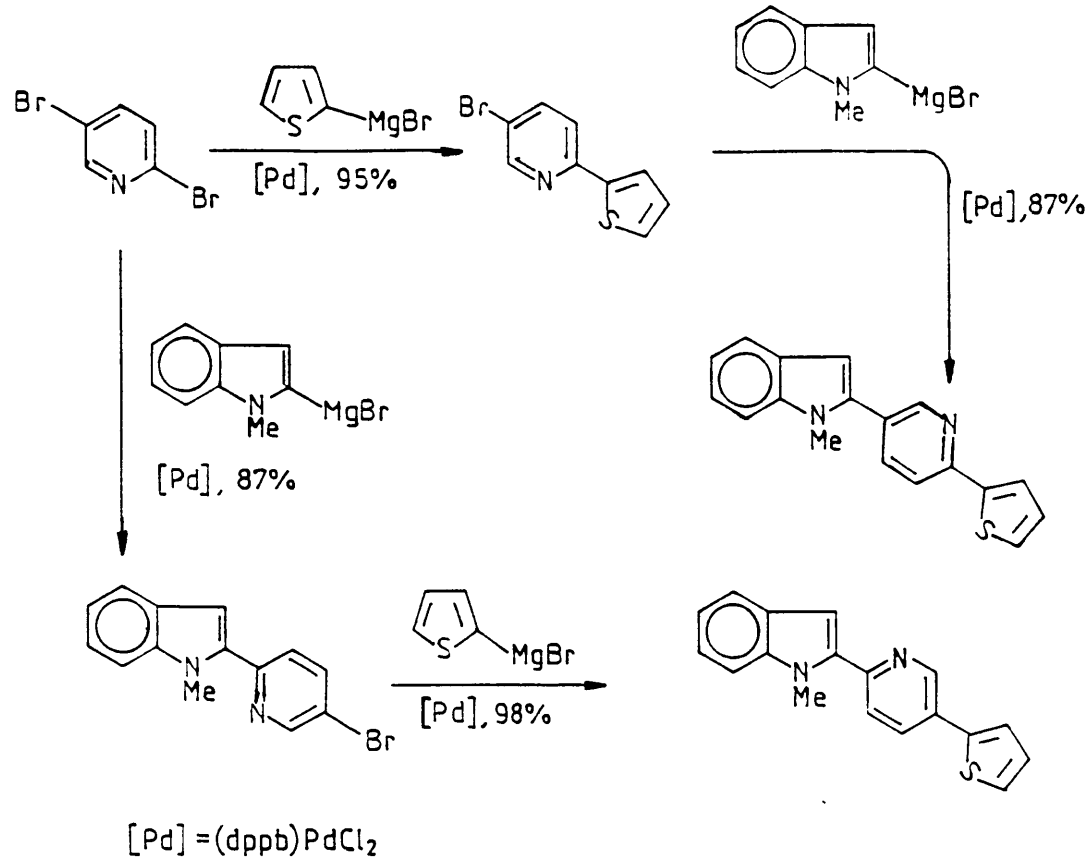
$R^1=R^2=H$ (85%)
R^1=Me R^2=H (95%)
R^1=H R^2=OMe (88%)
R^1=H R^2=Cl (86%)
R^1=H R^2=Ph (86%)

It is interesting to note that neither the nickel nor the platinum analogues were effective. The above methodology has also been used to make dioxaborinane derivatives (13), a new series of liquid crystalline compounds[52].

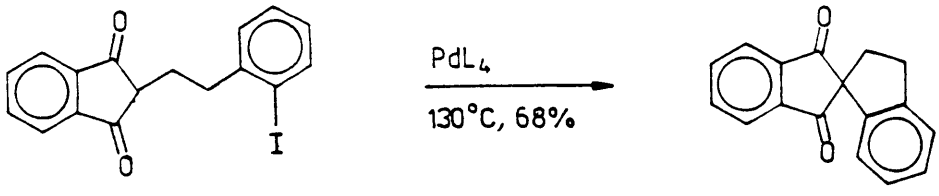


(13)

Various types of mixed heteroarene oligomers can be readily prepared from heteroarene dihalides, via stepwise coupling with heteroaryl Grignard reagents catalysed by a palladium-phosphine complex[53].



Finally, a palladium promoted intramolecular arylation of a β-diketone (14) has been used[54] to generate a spirocyclic system (15), which is a model for the antitumour agent Fredericamycin A.

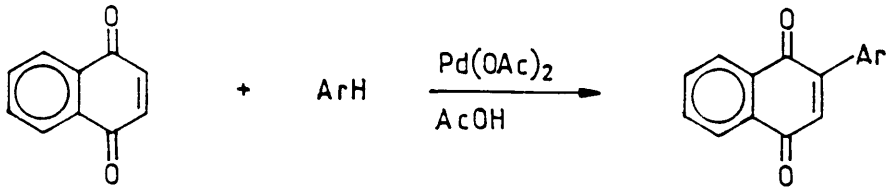


(14) (15)

1.3 VINYL COUPLING

1.3.1 Vinyl-H,TMS

Coupling reactions of olefins and aromatic heterocyles are an effective method for the preparation of important precursors of biologically and physiologically active compounds. Therefore, the oxidative coupling of olefins and aromatic heterocycles such as furans[55], pyrroles[56], pyrazoles[56], indoles[18,57] and 1-methyl-2-pyridone[55] by palladium(II)salts has been reported. For example, treatment of 1,4-naphthoquinone (16) with aromatic heterocycles in the presence of palladium(II)acetate gave the corresponding 2-heteroaryl-1,4-naphthoquinones[58].

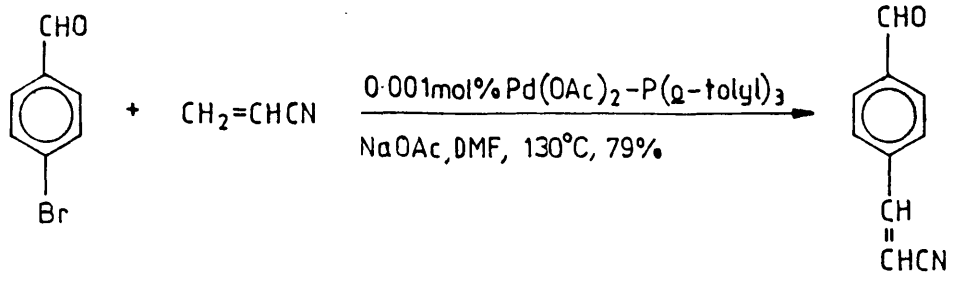


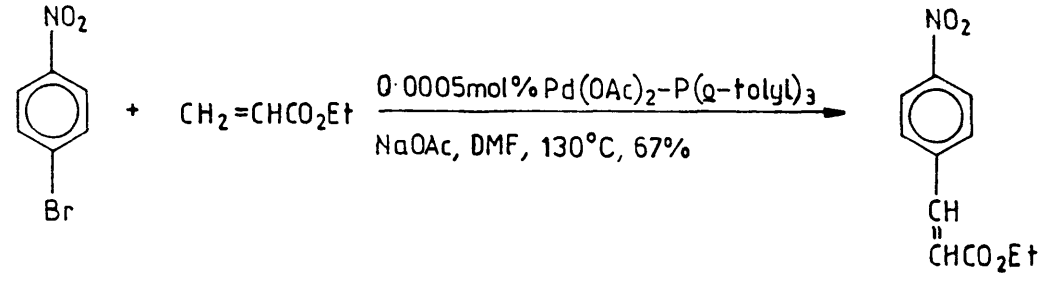
(16)

ArH =Benzene (85%)
2-formylfuran (79%)
methyl-2-furanoate (76%)
2-acetylthiophene (61%)
1,2,4,5-tetramethylbenzene (86%)
N-sulphonyl-indole (68%)

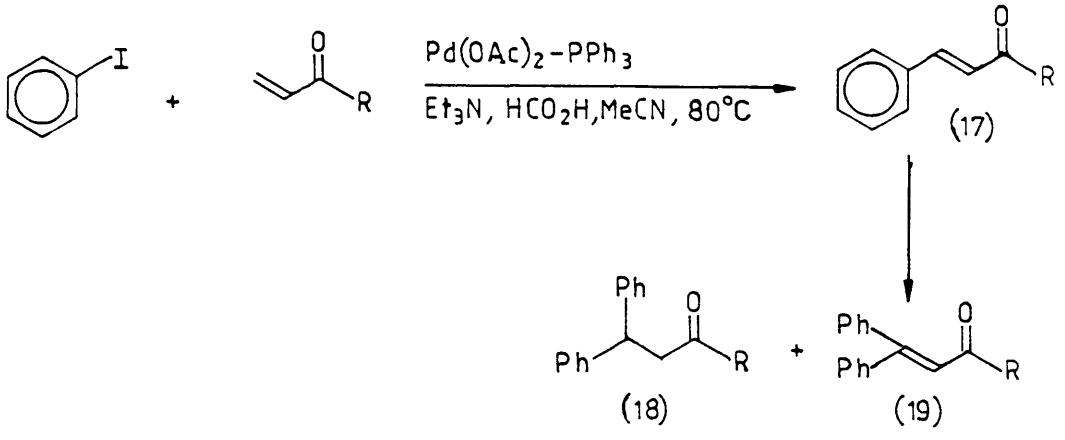
The palladium catalysed arylation of alkenes with aryl bromides or iodides has been shown to proceed in high yields[59], and at very low palladium concentrations[60], when carried out in a suitable strongly polar solvent with a carboxylate anion as base. The preferred combination was DMF with sodium acetate. The reaction was markedly dependant on the substituents on the aryl bromide, being favoured by

electron-withdrawing groups[61]. Turnover numbers of up to 134,000 have been achieved[60].



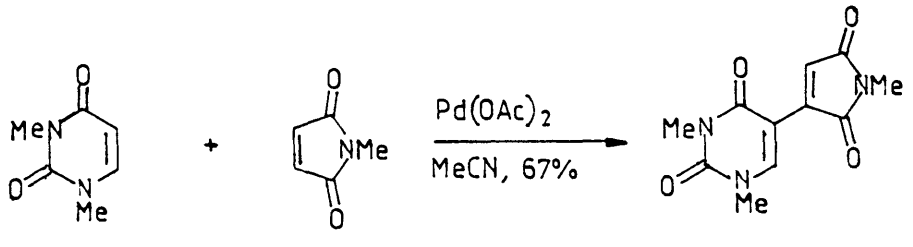


Aryl iodides have been found to react with α,β-unsaturated ketones in the presence of catalytic amounts of palladium(II)acetate, an excess of formic acid, and triethylamine, giving rise to a mixture of vinylic substitution and conjugate addition products[62,63].



The reaction appears to proceed via a palladium catalysed vinylic substitution (Heck reaction)[64] on the α,β-unsaturated carbonyl compound, followed by an *in situ* conjugate addition type reaction on the β-substituted-α,β-unsaturated carbonyl compounds (17) to give β,β-diaryl ketones and aldehydes (18). Unsaturated carbonyl compounds (19), derived from double vinylic substitution, were isolated in variable yields (15-75%), enhanced by the presence of free amino and hydroxy groups on the starting aryl iodide[65]. Competition between conjugate addition and vinylic substitution appeared to be dependent on a complex balance of steric, electronic and medium factors.

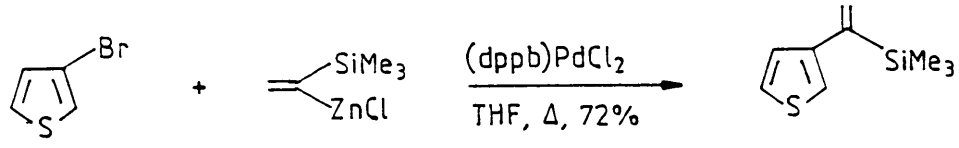
Some 5-vinyluracils are of importance as anti-cancer and antiviral agents, and increased interest is being shown in the palladium catalysed coupling reaction as an effective method for their synthesis from uracils. Previous investigations have dealt with the reaction of uracils which bear mercury[66] or halogens[67] at the 5-position. Recently, Itahara *et al.* have described the oxidative coupling of a uracil derivative with a maleimide in the presence of palladium(II)acetate[68].



This direct palladation of uracils (and uridines) is of interest in connection with the possibility of metallation of double bonds in pyrimidine bases in nucleic acids, since nickel compounds are known to be carcinogens and platinum compounds are important cancerocidal substances.

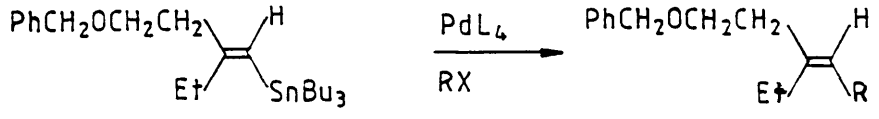
1.3.2 Vinyl-Metal

By comparison with the reaction of heteroaryl Grignard reagents with halovinylsilanes (Section 1.2.2), silyl-substituted vinylmetallic reagents coupled with heteroaryl halides in the presence of $(dppb)PdCl_2$, to produce heteroarene-substituted vinylsilanes[37].



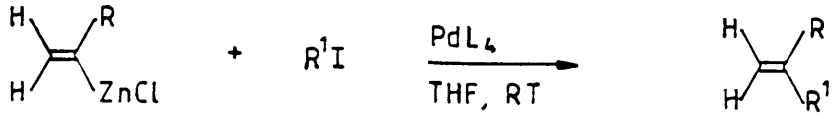
Although this route gives slightly lower yields, it has the advantage of being able to introduce silylfunctionalised vinyl groups regioselectively onto heteroarenes, metallic reagents of which are relatively unstable.

Trisubstituted alkenes have been prepared in a stereoselective manner by the coupling of vinyl stannanes and organic halides[69].



RX = $PhCH_2Br$ (81%)
PhCOCl (62%)

In addition, alkenylmetals of zinc or aluminium containing α-alkoxy, α-alkylthio, or α-trialkylsilyl substituents, reacted readily with aryl or alkenyl halides in the presence of a palladium catalyst to produce arylated alkenes or conjugated dienes, respectively, the stereospecificity of the reactions being ≥98%[70].



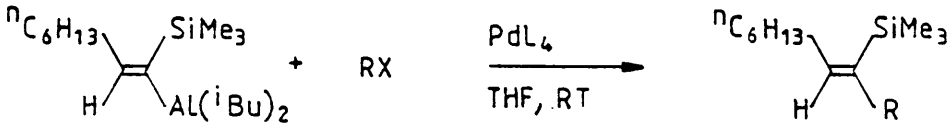
R =OEt R^1=Ph (80%)

4-ClC_6H_4 (65%)

(E)-1-heptenyl (74%)

R =SEt R^1=Ph (70%)

(E)-1-heptenyl (81%)

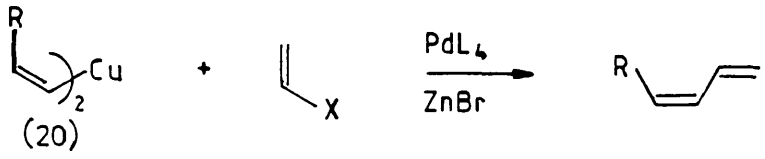


RX =vinylbromide (74%)

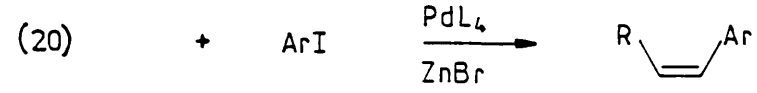
(E)-1-heptenyliodide (68%)

The number of examples reported was fairly small, nevertheless, the method itself provides a convenient and selective entry into stereodefined and heterofunctionalised conjugated dienes, that are potentially attractive as reagents for selective syntheses of cyclohexenes via the Diels-Alder reaction.

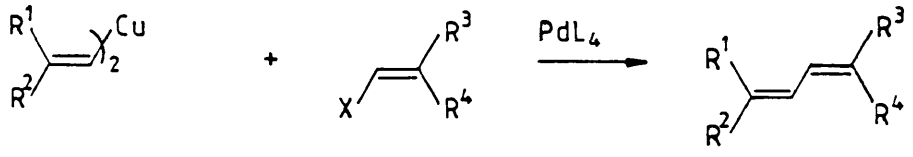
Conjugated dienes (and styrenes) have also been prepared by coupling alkenyl cuprates with alkenyl (and aryl) halides[71]. For example, (Z)-dialkenylcuprates (20) obtained by carbometallation of acetylenes, coupled easily with alkenyl halides and iodoarenes in the presence of zinc bromide and a catalytic amount of PdL_4 to afford high yields of conjugated dienes and styrenes, with very high stereoselectivity.



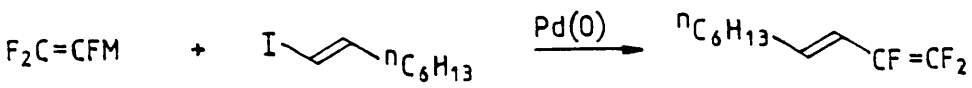
(20)



Such pure dienes are often encountered in insect sex pheromones. Polysubstituted conjugated dienes can be synthesised in the same way[72], with high yields and excellent stereoisomeric purity.

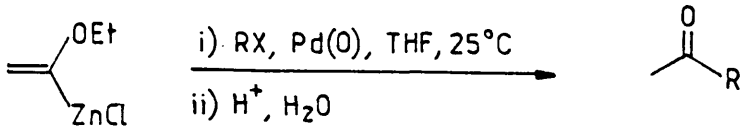


Recently[73], stereoselectively fluorinated conjugated dienes have been prepared by palladium catalysed cross-coupling reactions.



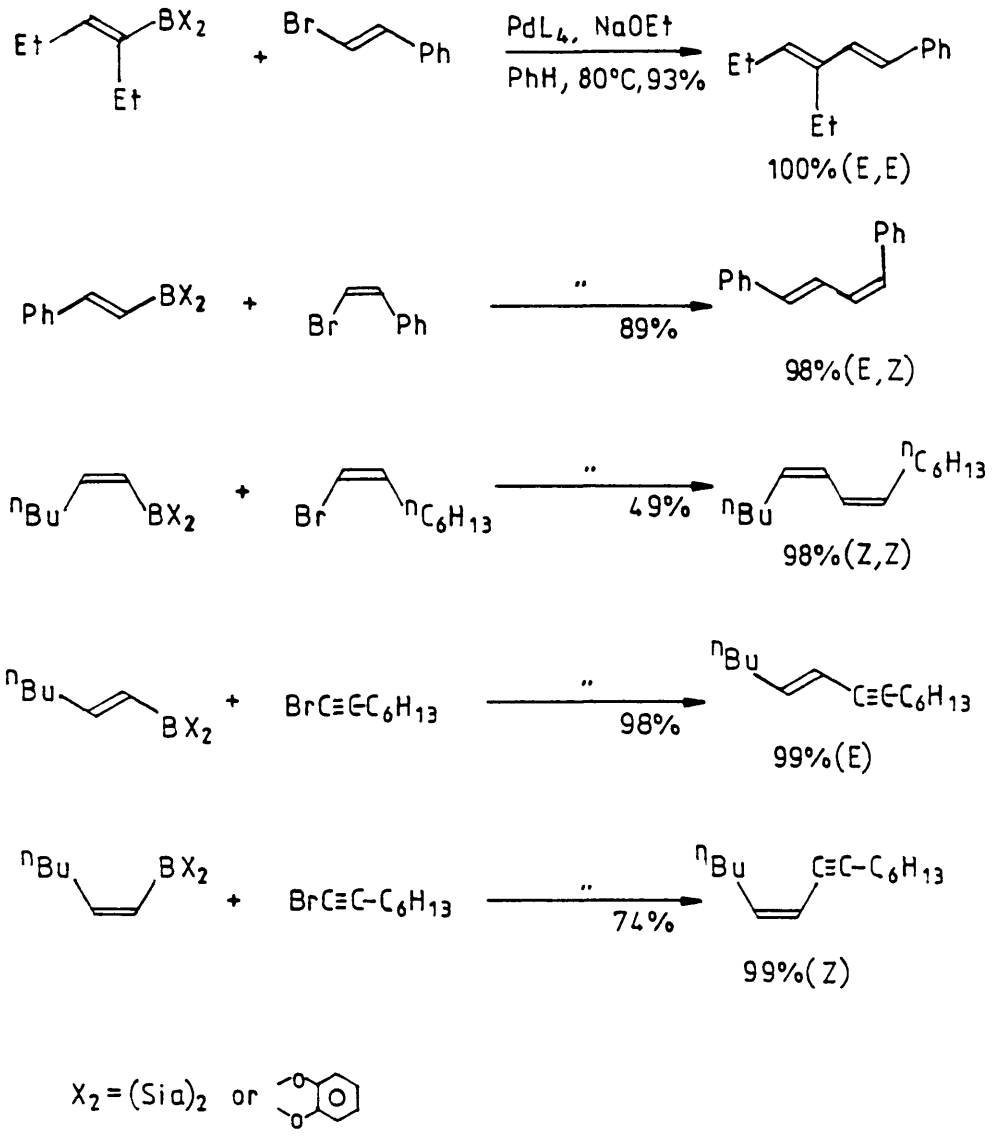
M=Li,ZnCl

Zinc salts of enol ether anions have been coupled to aryl and alkenyl halides by using palladium catalysts, effecting a direct acetylation of the organic halides[74].



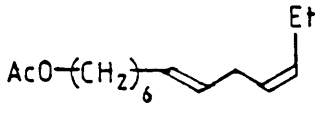
RX =phenyliodide (76%)
3-iodotoluene (82%)
2-iodomethylbenzoate (77%)
(E)-1-bromo-2-phenylethene (84%)
(Z)-1-bromo-2-phenylethene (66%)

The palladium catalysed cross-coupling reaction of haloalkenes and haloalkynes with 1-alkenyldisiamylboranes or 1-alkenyl-1,3,2-benzodioxaboroles in the presence of bases such as sodium alkoxides, has been demonstrated to proceed readily and stereo- and regio-specifically, to give conjugated alkadienes or alkenynes in high yields[75]. The configurations of both the haloalkenes and 1-alkenylboranes were retained during the reaction, thus providing versatile and reliable procedures for the syntheses of stereodefined conjugated (E,E)-, (E,Z)-, (Z,E)-, and (Z,Z)-alkadienes and enynes under mild conditions.

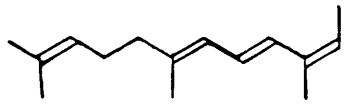


The versatility of the method has been amply demonstrated by the stereospecific synthesis of natural products bearing conjugated alkadiene or alkenyne structures, e.g. sex pheromones, such as (7E,9Z)-7,9-dodecadien-1-yl acetate (21) (European grapevine moth)[76]; acyclic sesquiterpenes, such as (2Z,4E,6E)- 3,7,11-trimethyl-2,4,6,10-dodecatetraene (22) (trans-[C_{10}] allofarnesene)[77]; the pheromone bombykol (23) and its three geometrical isomers (24-26)[78,79], and humulene (27), the major

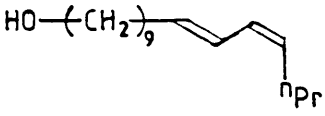
sesquiterpene of hops (synthesized via a palladium catalysed intramolecular cyclisation)[80].



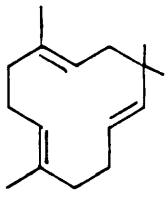
(21)



(22)



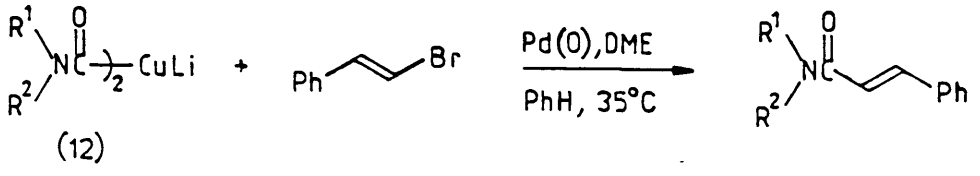
(23)=(E,Z)
(24)=(E,E)
(25)=(Z,E)
(26)=(Z,Z)



(27)

1.3.3 Vinyl-X

In analogy with the reaction of aryl halides, vinyl halides can react with carbamoyl cuprates (12) to form vinyl carboxamides[50].

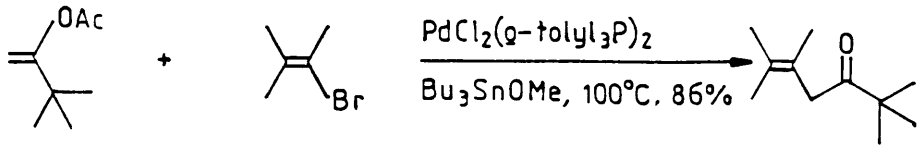


(12)

R^1=Me R^2=Ph (65%)

Recently, Migita et al. reported[81] the reaction of tributyltin enolates, prepared in situ from tributyltin methoxide and enol acetates, with 1-bromo-1-alkenes in the presence of a catalytic

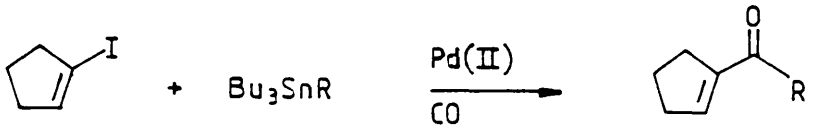
quantity of ($\underline{o}$-tolyl$_3$P)$_2$PdCl$_2$, to give the derivatives of allyl ketone in good yields.



The reaction appears to be sensitive to steric hindrance caused by substituents on the enol acetate[82]. The reaction of enol acetates bearing terminal methylene gave the 1-alkenylated ketones generally in high yields, whereas lower yields were obtained for substrates having substituents on the reaction site. The number and position of substituents on the vinyl bromide did not appear to have an important effect on the product yield.

The cross-coupling of organotin reagents with a wide variety of organic electrophiles, catalysed by palladium, provides a novel method for generating a carbon-carbon bond. Because this mild, versatile reaction is tolerant of a wide variety of functional groups on either coupling partner, is stereospecific and regioselective[83], and gives high yields of product, it is ideal for use in the synthesis of elaborate organic molecules. When the coupling reaction is carried out in the presence of carbon monoxide, instead of a direct coupling, carbon monoxide insertion takes place, linking the two coupling partners together and generating a ketone. Much work in this area has been reported by Stille $\underline{et\ al.}$ and some examples have already been described[34,38-46,49,69].

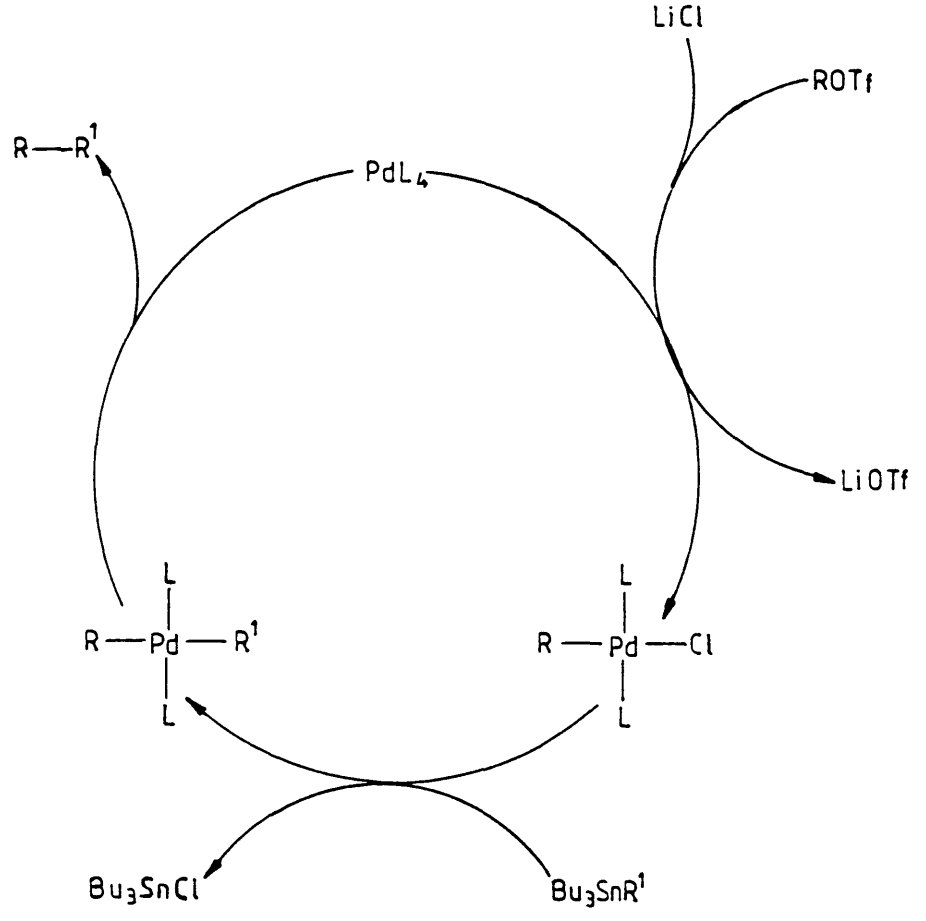
The palladium catalysed cross-coupling reaction of vinyl iodides with trimethyl-or tributylvinylstannanes, in the presence of carbon monoxide, gave unsymmetrical divinyl ketones in good yields[84]. The reaction conditions were neutral, and mild enough (40-50°C, 3atm. CO) that other functional groups in either coupling partner could be brought unaltered into the coupled product. The (E)-geometry in both partners was retained, and the (Z)-geometry in the vinyltin reagent was maintained during the coupling reaction. However, under the usual reaction conditions, the coupled product underwent slow (Z) to (E)-isomerisation. Both $PhCH_2PdClL_2$ and L_2PdCl_2 were equally effective, each being reduced <u>in situ</u> by the tin reagent, to yield the active palladium(0)catalyst[85].



R = $CH_2=CH_2$ (90%)
(E)-CH=CHPh (60%)
(Z)-CH=CHPh (63%)

Vinyl trifluoromethanesulphonates (vinyl triflates) have been shown to be excellent electrophiles for use in cross-coupling reactions with acetylenic, vinyl and alkyl tin reagents[33]. In the presence of lithium chloride, the reactions took place in high yields under mild reaction conditions, (however benzyl and phenyl tin reagents gave poor yields, for reasons which were not readily apparent)[86]. The reaction required the addition of lithium chloride or another suitable salt (e.g. LiBr, CsF, $ZnCl_2$) in order to prevent the formation of a noncatalytic palladium species and the concomitant removal of the

palladium from the catalytic cycle. In the presence of lithium chloride a vinylpalladium(II)chloride complex is generated, which can then undergo transmetallation to afford coupled products and regenerate a palladium(0)species (Scheme 3).

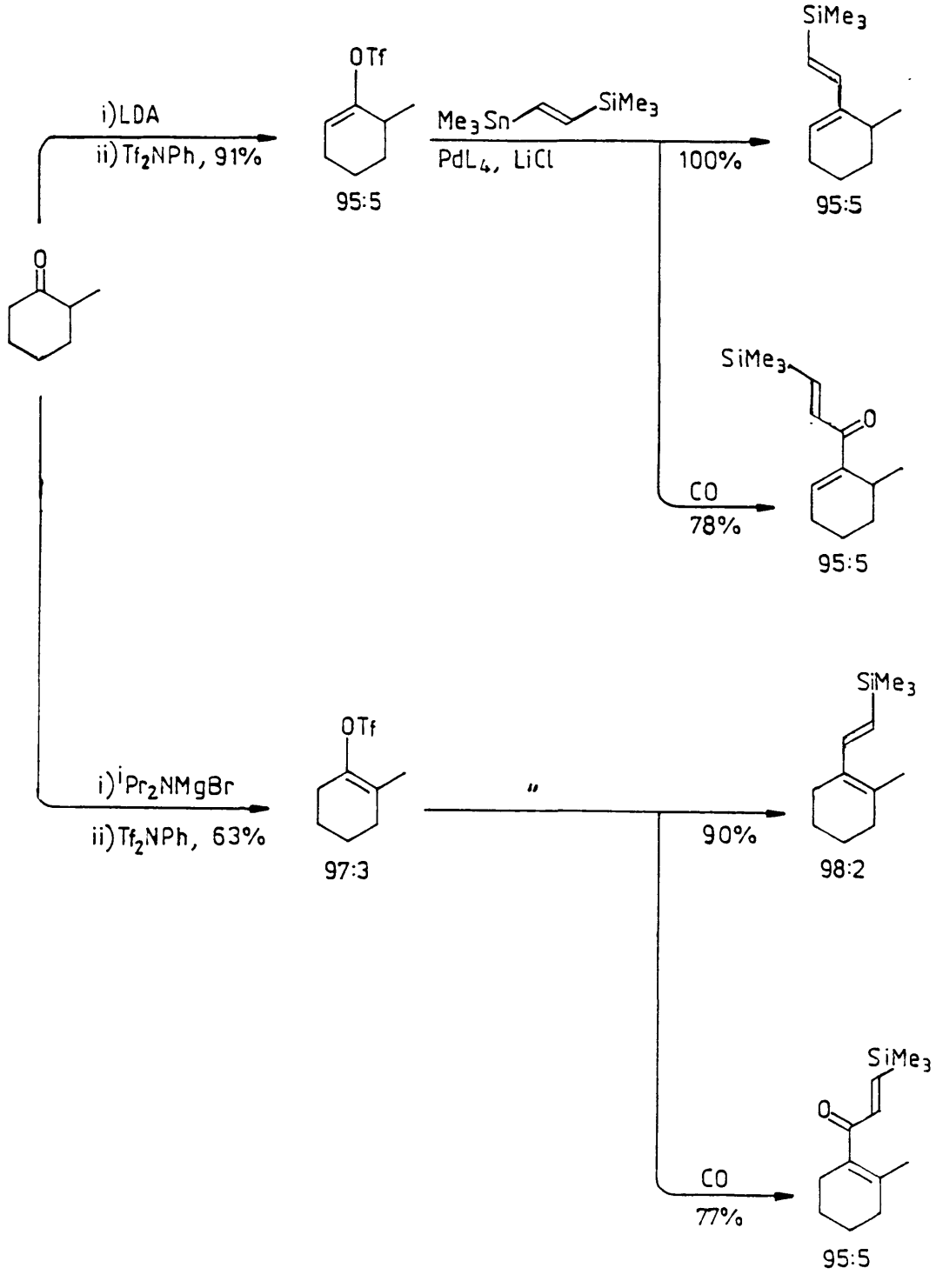


R^1: $CH=CH_2$, $CH=CHSiMe_3$, ^nBu, Me, $CH_2CH=CH_2$, $C\equiv C\text{-}SiMe_3$

Scheme 3

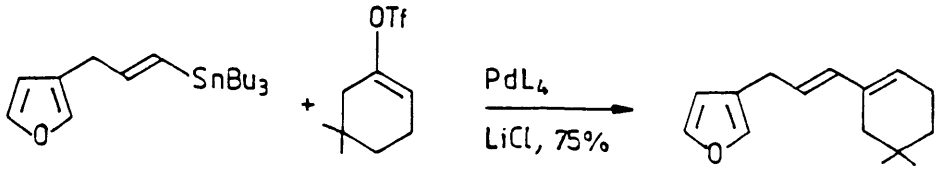
Thus, vinyl triflates couple with organostannanes in the presence of lithium chloride and palladium(0)catalysts to give a variety of olefin-substituted products. This methodology represented the first case of a transition metal catalysed reaction of a vinyl sulphonate.

In effect, this allows the conversion of the oxygen of regioselectively formed enolates into a leaving group for palladium catalysed reactions, i.e. triflates can be formed selectively from an unsymmetrical ketone by generating either the kinetic or thermodynamic enolate (Scheme 4).



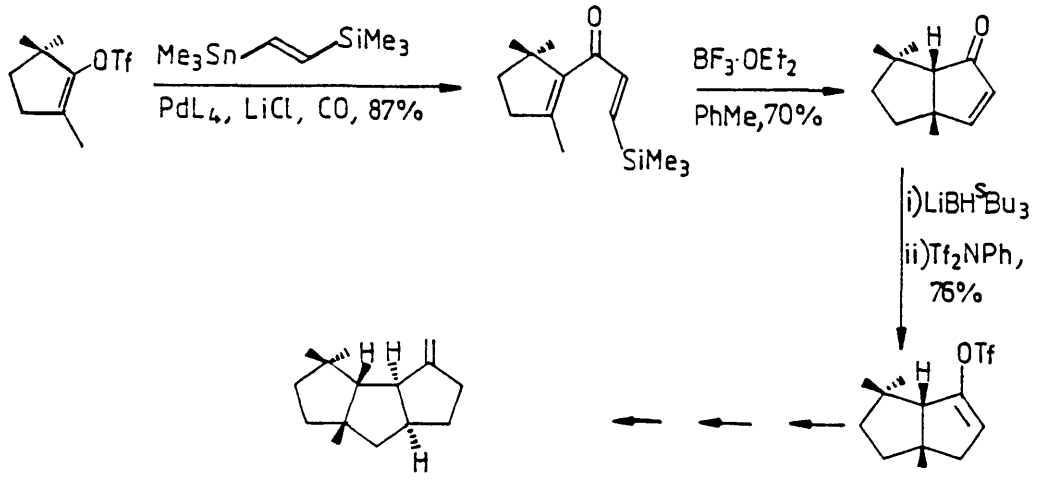
Scheme 4

This reaction allows the facile stereoselective formation of 1,3-dienes under mild conditions, and the methodology has been applied to a short synthesis of pleraplysillin-1 (28)[87].



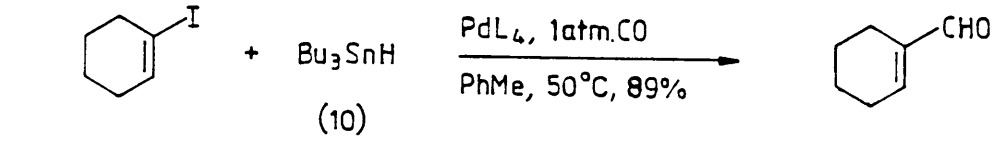
(28)

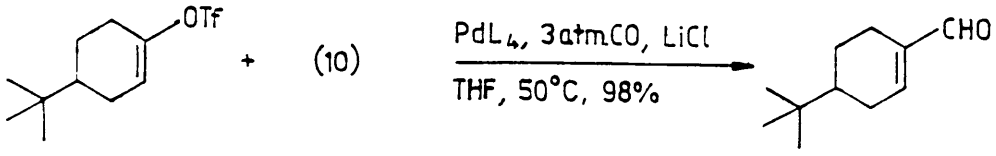
The palladium catalysed carbonylative coupling of vinyl triflates with alkyl-, vinyl-, and arylstannanes gave good yields of the cross-coupled ketone products[88]. The regioselectively formed vinyl triflates (Scheme 4) can be used to produce divinyl ketones as regioisomerically pure compounds. The (E)- and (Z)-geometry of the vinylstannane is maintained during the coupling reaction. The carbonylative coupling reaction was applied to a total synthesis of the fused five-membered-ring structure of the marine natural product (±) $\Delta^{9(12)}$-capnellene (29)[88].



(29)

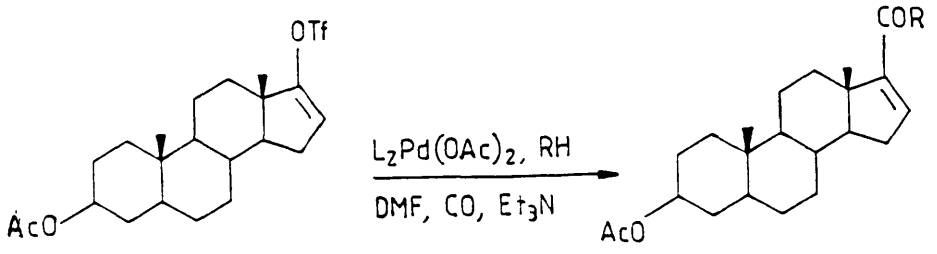
Both vinyl triflates and vinyl iodides could be formylated in the presence of tributyltin hydride (10) and PdL_4 [47]. For the preparation of α,β-unsaturated aldehydes, vinyl triflates were preferred to vinyl iodides as they offered the advantages of greater stability and regiospecific control during their preparation[87].





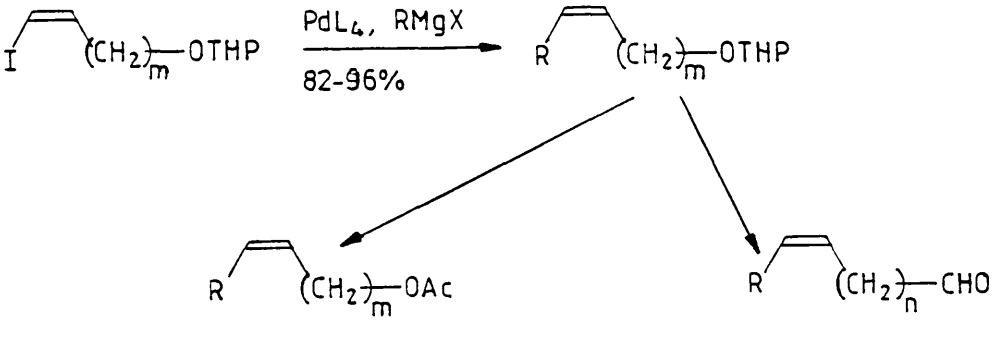
Ortar et al. reported that enol triflates reacted with olefinic compounds (in the presence of triethylamine and $2PPh_3$-$Pd[OAc]_2$) to give conjugated dienes in good yields and under mild conditions[89], and that although yields were only moderate, palladium catalysed coupling of 17-enol triflates with appropriate α,β-unsaturated esters represented a simple route to cardenolides and cardenolide analogues[90].

Synthetic methodologies which result in the nucleophilic carboxylation of a carbonyl group to a higher carboxylic acid derivative, together with elaboration of the original electrophilic centre (e.g. introduction of α,β-unsaturation) are of particular value. Ketones have been homologated to α,β-unsaturated esters or amides via their enol triflates, by a palladium catalysed reaction with carbon monoxide and alcohols or amines[91].



R =OMe (77%)
NEt_2 (91%)

The sex pheromones of Lepidoptera (moths and butterflies) present a structural uniformity : they are often straight-chain mono- or polyolefinic acetates, alcohols, or the corresponding aldehydes. These monoenic and conjugated or unconjugated dienic sex pheromone components have recently been synthesized by two highly stereo-selective methods. The first method involved the coupling of (Z)-iodoalkenes with Grignard reagents in the presence of catalytic amounts of PdL_4 (Scheme 5)[92].



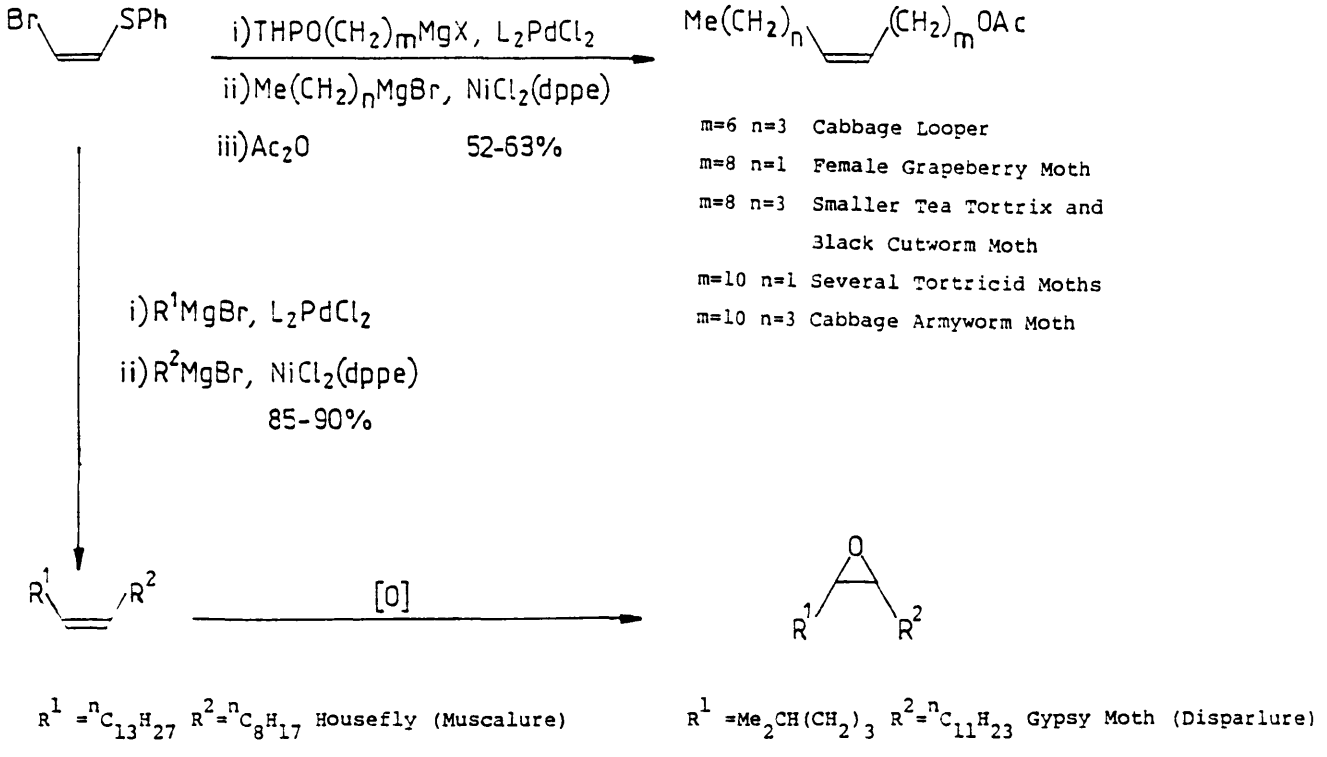
R =(Z)-EtCH=CH$(CH_2)_3$ m=6 Pink Bollworm moth
R = ^{n}Bu m=8 Summer Fruit Tortrix Moth
R = CH_2=CH m=8 Red Bollworm Moth
R =Et m=10 Fall Armyworm Moth

R =Et n=9 Navel Orange Worm Moth

Scheme 5

After removal of the oxygen-protecting THP group and acetylation or oxidation, the lepidopteran sex pheromones were obtained in stereochemically pure form.

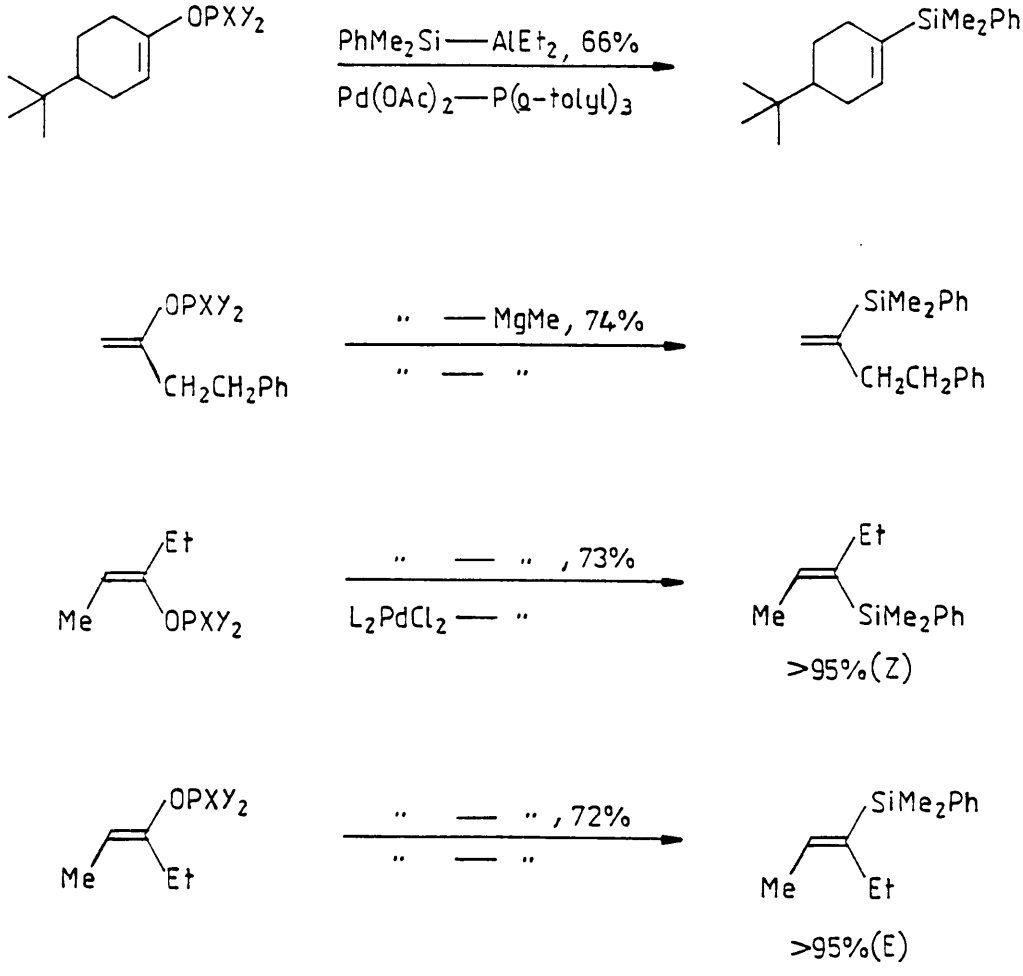
In the second method, a series of sex pheromones and structurally related olefins have been synthesised with high stereoisomeric purity (95-98%) by two sequential cross-coupling reactions, using (Z)-1-bromo-2-phenylthioethene (Scheme 6)[93].



Scheme 6

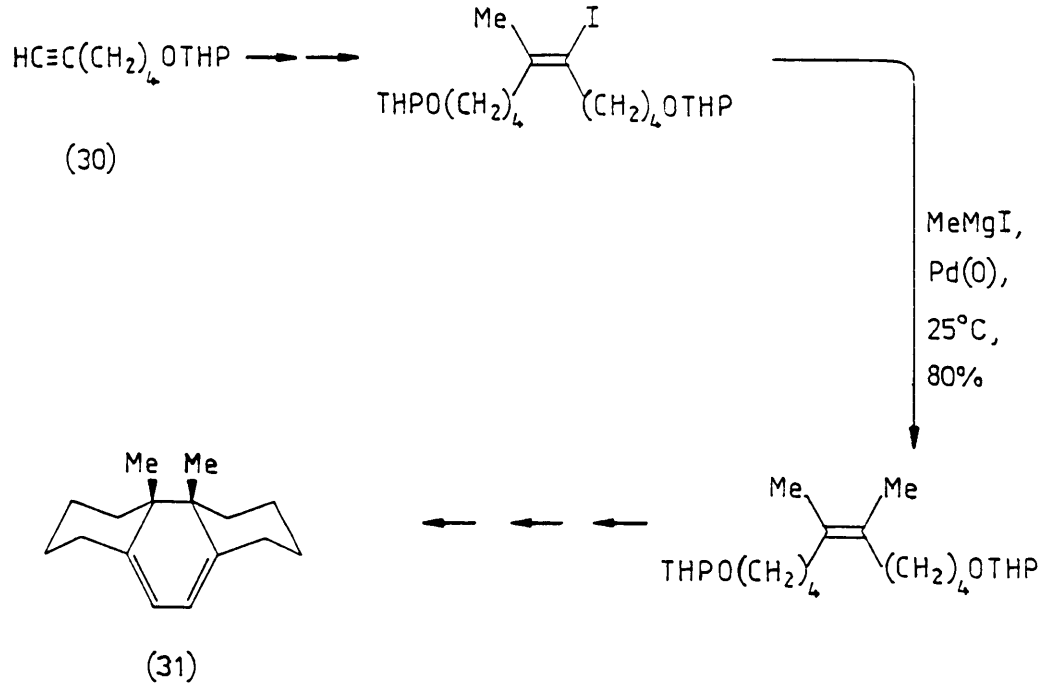
These methods have the advantages of mild reaction conditions (all performed at room temperature), good yields and high stereospecificity.

Cross-coupling of a variety of enol phosphonates with $Ph(Me)_2Si-MR_n$ (where MR_n=$AlEt_2$ or MgMe) produced vinylsilanes regio- and stereoselectively in the presence of palladium(O)catalysts[94].



X=O, Y=OPh

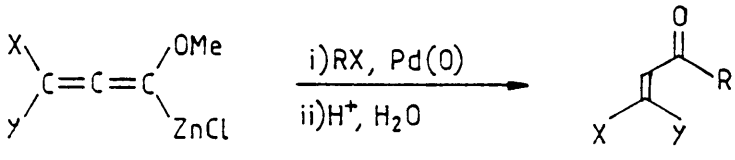
Vollhardt et al. have recently synthesised the hydrophenanthrene nucleus incorporating two adjacent quaternary centres (31) from the acetylene (30)[95].



This synthesis employed five metals (Li, Al, Zr, Mg, Co) other than palladium in various high yield steps, a powerful demonstration of the utility of both main group and transition metals in organic synthesis.

1.4 ALLENIC COUPLING

Zinc salts of allenic ethers have been coupled with aryl and alkenyl halides, in the presence of a palladium(0)catalyst, to give (on hydrolysis) α,β-unsaturated ketones, i.e. the allenic ether serves as a source of the acryloyl group[74].

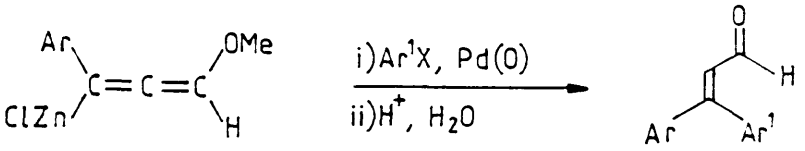


X=Y=H RX=3-Iodotoluene (84%)

X=Y=H RX=1-Iodo-1-trimethylsilylhex-1-ene (75%)

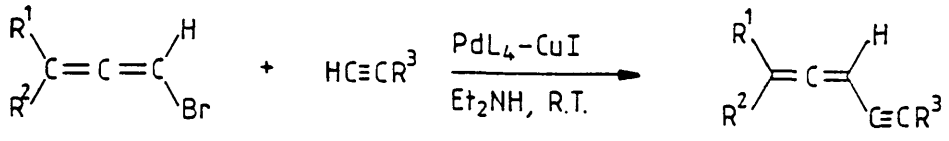
X=^{n}Bu Y=Me_3Si RX=3-Iodotoluene (74%)

In addition, allenic ethers were γ-arylated to give β,β-diaryl-α,β-unsaturated aldehydes.



Ar =Ph Ar^1=3-Iodotoluene (81%)

The synthesis of allenynes has received attention lately, as this structural unit has been found in some natural products[96]. Good yields of allenynes were obtained when allenic halides were allowed to react with terminal acetylenic compounds, in the presence of catalytic amounts of PdL_4 and copper(I)iodide, in diethylamine at room temperature.



a: $R^1=R^2$=Me	c: R^3=Ph	ac=78%
b: $R^1={}^n$Pr R^2=H	d: $^nC_6H_{13}$	bd=73%
	e: CH_2OH	ae=70%
	f: $CH(OH)^nC_3H_7$	bf=75%
	g: CMe_2NEt_2	ag=90%
	h: $SiMe_3$	bh=94%
	i: $(CH_2)_8OAc$	bi=88%

This reaction proceeded under convenient, mild and catalytic conditions, avoided the preparation of preformed organometallics, and showed good toleration of functionality.

1.5 ACETYLENIC COUPLING

Coupling reactions of terminal alkynes with aryl and vinyl halides in the presence of catalytic amounts of palladium(II)- or palladium(O)-complexes and copper(I)iodide have received considerable attention from a synthetic standpoint[97,98].

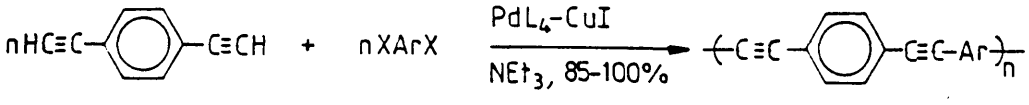
1.5.1 Acetylene-Arene

Homocoupling of arylacetylenes has been achieved by their reaction in benzene with chloroacetone (1 equiv.) and triethylamine (2 equivs.), using a mixture of PdL_4 and CuI as catalyst, to afford 1,4-diaryl-butadiynes in good yields[99].

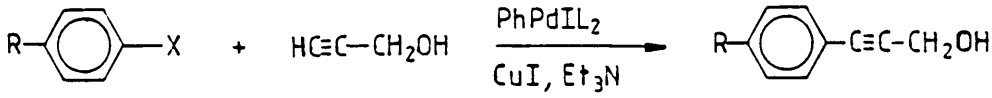
$$ArC{\equiv}CH \xrightarrow[ClCH_2COCH_3,\ Et_3N]{PdL_4\text{-}CuI,\ PhH} ArC{\equiv}C{-}C{\equiv}CAr$$

Ar =Ph (94%)
2-Thiophenyl (87%)

Both palladium(II)- and palladium(O)species catalysed poly-condensation between dihaloaromatic and diacetylenic compounds. The polymers obtained had high thermal stabilities and most of them exhibited fluorescence[100].

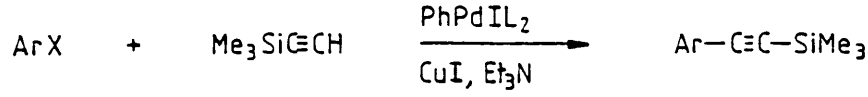


3-Arylpropargyl alcohols have been prepared by the cross-coupling of propargyl alcohols with both aryl iodides and aryl bromides[101].



R =CN X=I (97%)
R =NO_2 X=Br (95%)
R =Cl X=I (91%)
R =CO_2Me X=Br (94%)
R =$O^nC_3H_7$ X=I (90%)
R =$COCH_3$ X=Br (81%)

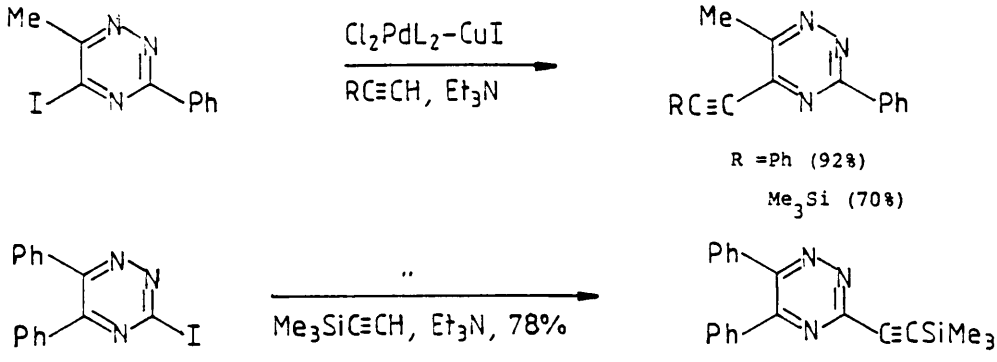
It is known[102] that the reaction of bromo- or iodoarenes with trimethylsilylacetylenes, in the presence of copper(I)iodide and a palladium(II)complex, gives trimethylsilylethynylarenes. Synthesis of ethynyl derivatives of aromatic mono- and diazines from the corresponding N-heteroaromatic halides, and trimethylsilylacetylene, has also been achieved in high yields[103].



Ar =2-Bromopyridine (100%)
4-Iodoquinoline (96%)
2,4-Dimethyl-5-bromopyridine (85%)
3-Chloro-6-methylpyridazine (84%)

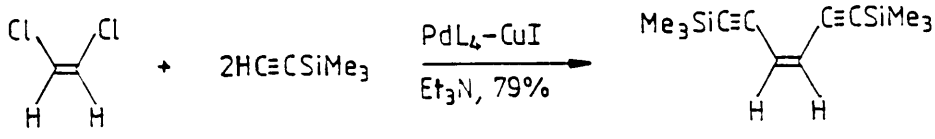
It is interesting to note that N-heteroarenes containing a chloro substituent in their active positions were sufficiently reactive for the cross-coupling, whereas, a bromo or iodo substituent was necessary for reaction at their inactive positions.

The above methodology has also been used to synthesise 2-, 6- and 8-alkynylated purines and their ribonucleosides, by the coupling of halopurines with alkynes[104-7]. In addition, naphthyridine derivatives have been prepared by the cyclisation of ethynylpyridine-carboxamides[108]; reactions of 3- and 5-iodo-as-triazines with mono-substituted acetylenes gave the corresponding alkynyl-as- triazines in good yields[109].



1.5.2 Acetylene-Alkene

Stereospecific synthesis of cis-1,6-bis(trimethylsilyl)hex-3-ene-1,5-diyne (32) was achieved via the palladium catalysed bisethynylation of (Z)-1,2-dichloroethene[110].

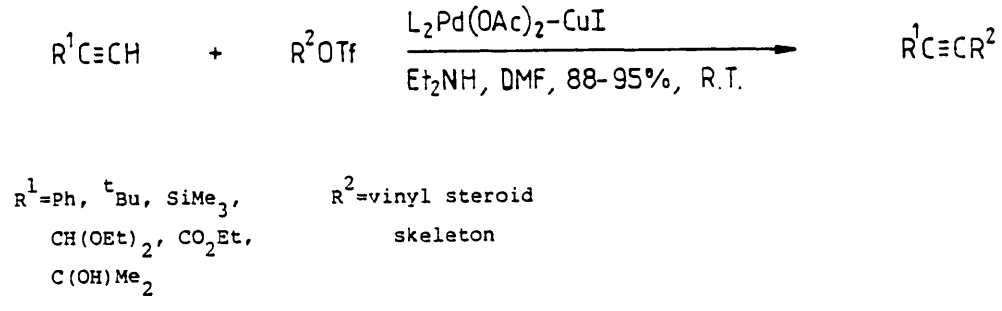


(32)

Compounds of this type have previously been synthesised by lengthy and non-stereospecific routes via nickel-catalysed Grignard reactions. Thus, this method provided an efficient route to enediynes from readily

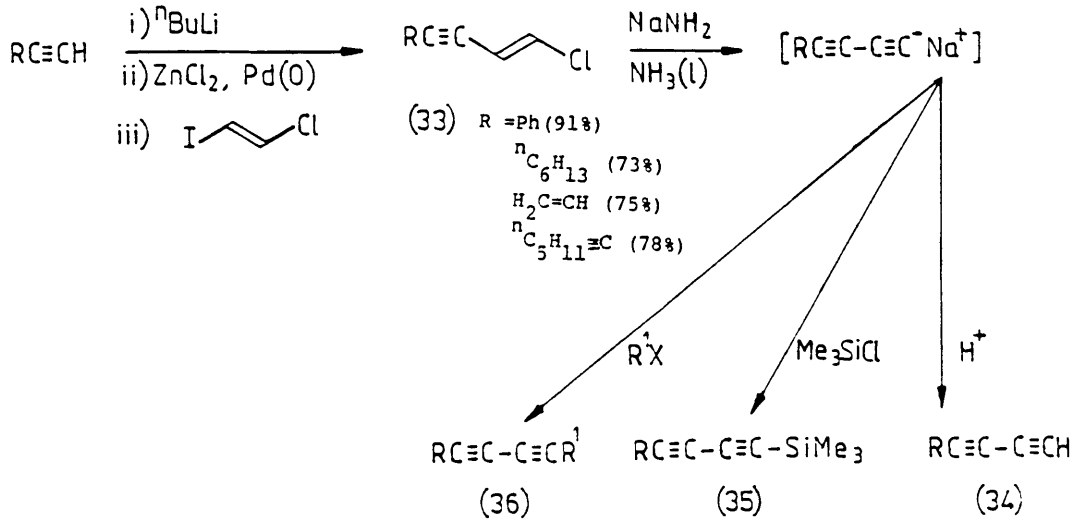
available 1,2-dichloroethenes and terminal alkynes. Partial reduction of these compounds should result in the preparation of terminally substituted trienes.

Cross-coupling of 1-alkynes with enol triflates in the presence of a base and bis(triphenylphosphine)palladium(II)acetate as catalyst, afforded conjugated enynes, a moiety incorporated in a number of natural products, in good yields[111]. The addition of copper(I)-iodide as co-catalyst allowed the reactions to proceed at room temperature.



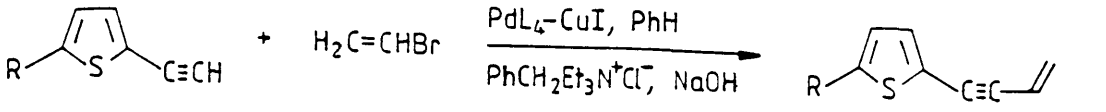
Nearly all of the alternative methods required the use of stoicheiometric amounts of an organometallic reactant and showed low compatibility with functional groups. Advantages of this method are that the starting materials are readily available, and that the coupling procedure is simple, requires mild conditions, and can be performed in the presence of a wide variety of functional groups.

(E)-1-iodo-2-chloroethylene reacted cleanly with alkynylzinc derivatives in the presence of a catalytic amount (1-5mol%) of a palladium(0)complex, to produce (E)-1-chloro-1-buten-3-yne derivatives in high yields.[112].



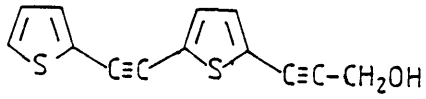
The chloroenynes (33) could be readily converted into the corresponding terminal diynes (34), silylated 1,3-diynes (35) and internal diynes (36) by known procedures.

5-(3-Buten-1-ynyl)-2,2'-bithienyl (37), a natural product which shows nematicidal and photo-induced fungicidal activity, and the related compound 2-phenyl-5-(3-buten-1- ynyl)thiophene (38) have been recently synthesised[113]. The method utilized the coupling reaction of a vinyl bromide with an acetylene, under phase-transfer conditions. Similarly, a large number of heterocyclic acetylene derivatives have been synthesised, in high yields, including the naturally occurring compounds (39) and (40)[114].

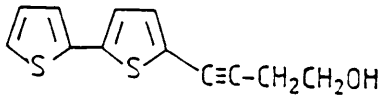


(37) R =2-Thiophenyl (93%)

(38) R =Ph (89%)



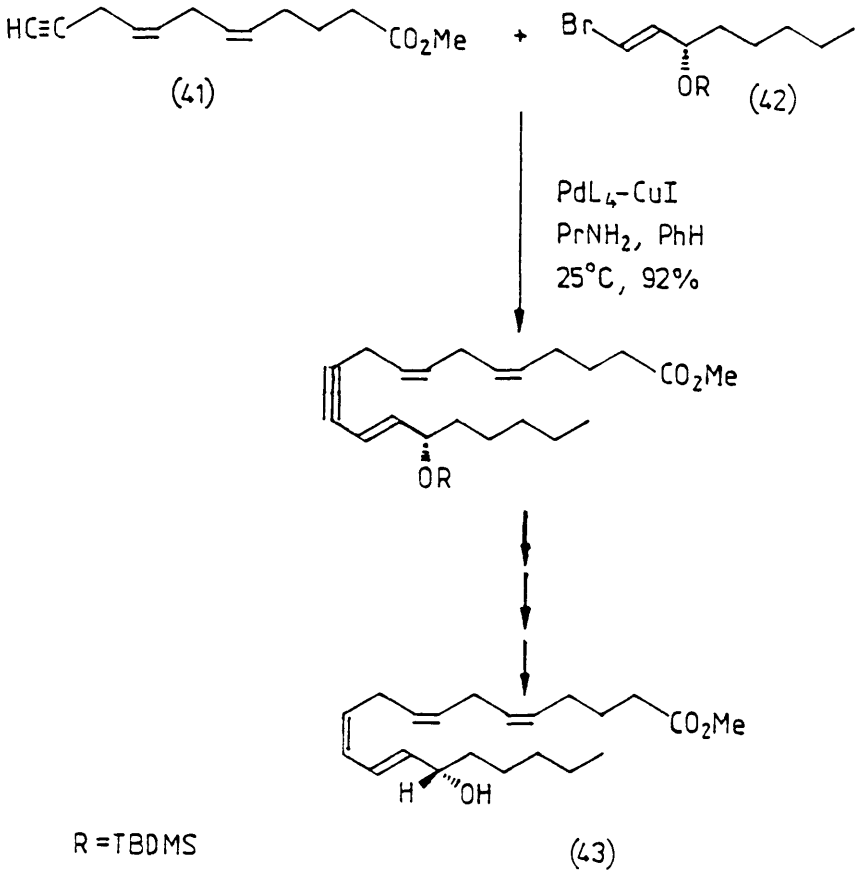
(39)



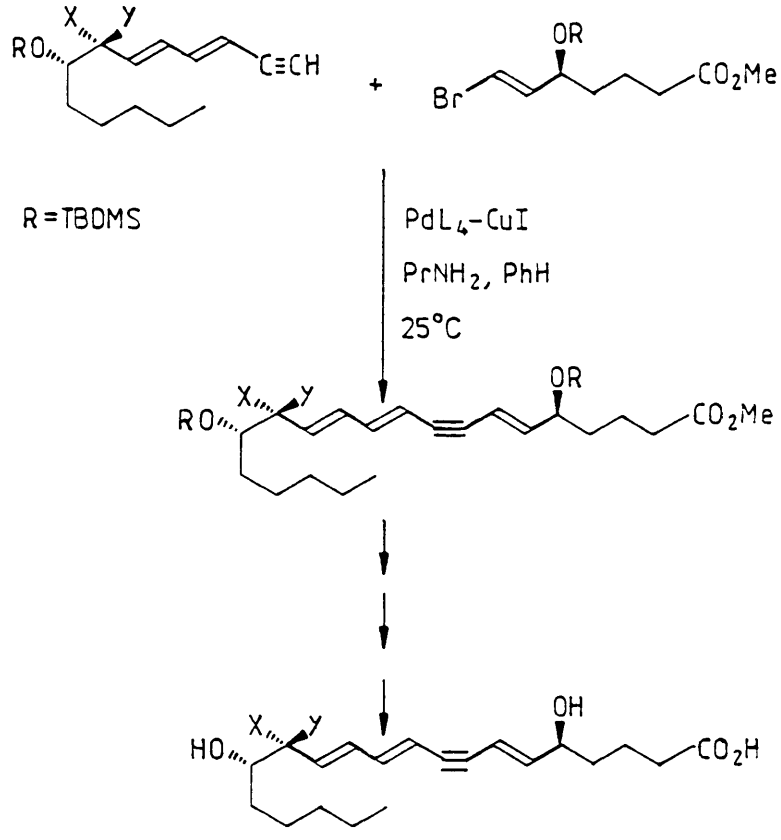
(40)

(5Z,8Z,11Z,13E)(15S)-Hydroxyeicosa-5,8,11,13-tetraenoic acid (15S-HETE)(43) is an important enzymatic product of the oxidation of arachidonic acid by human leukocytes.

Nicolaou et al. have reported the first stereocontrolled synthesis of 15S-HETE. The enantioselective route was based on their recently proposed general strategy towards linear eicosanoids employing Pd(0)-Cu(I) coupling reactions[115]. The crux of the synthesis was the coupling of the terminal acetylene (41) with the vinyl bromide (42)[116].



This methodology was also applied, by the same group, to the total syntheses of the two possible isomers of lipoxin B (44,45)[117].

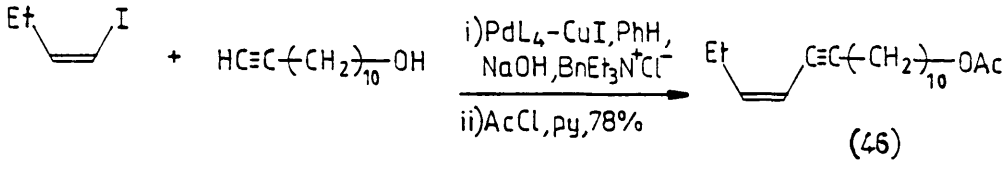


(44) X=H Y=OR (82%)

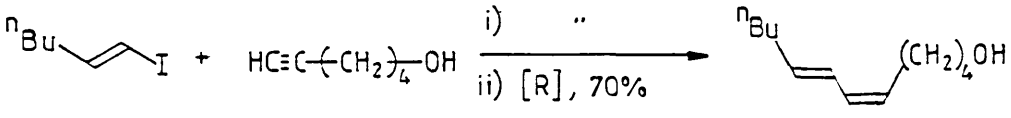
(45) X=OR Y=H (82%)

Finally, functionalised (Z)-or(E)-1,3-enynes have been stereospecifically prepared, in good yields, by the coupling reaction of ω-functionalised 1-alkynes with (Z)-or(E)-1-halo-1-alkenes, in the

presence of a catalytic amount of PdL_4 and CuI[128]. The reactions were carried out under phase-transfer conditions. This method was applied to the synthesis of (Z)-13-hexadecen-11-yn-1-yl acetate (46), the sex pheromone of the processionary moth, and of (5Z,7E)-5,7-dodecadien-1-ol(47), a sex pheromone component of both the forest tent caterpillar, and the pine moth.



(46)



(47)

1.6 ACYL COUPLING

The palladium catalysed coupling reaction of acid chlorides with organotin reagents[33,119] has been demonstrated to be an efficient reaction that gives ketones in high yields[120,121]. The reaction is quite general to both coupling partners[122,123] and can be carried out in a number of solvents, including HMPA, chloroform, dichloroethane and THF. The ketone product is formed in high yield, rapidly, under mild, neutral reaction conditions, and catalytic turnovers of 1000 have been achieved. Sterically hindered acid chlorides react normally and α,β-unsaturated acid chlorides do not undergo 1,4-addition. There is no further addition to the product

ketone, and a wide variety of functional groups can be tolerated, including nitro, nitrile, haloaryl, ester and even aldehyde groups.

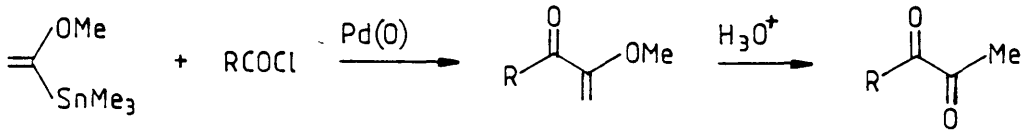
$$RCOCl + R^1SnR^2_3 \xrightarrow{Pd(0)} RCOR^1 + R^2_3SnCl$$

The tetraorganotin reagents transfer the first group rapidly, but the second group leaves about 100 times slower from R_3SnCl. Thus, with a stoicheiometric amount of tetraorganostannane, only one group is transferred. This is not a problem if it is a relatively simple organic group. However, if the group to be transferred is expensive, or difficult to synthesise, then the selective transfer of that group would be a distinct advantage. Fortunately, different groups transfer selectively from tin and the relative rates of transfer are as follows:[124] $PhC{\equiv}C > RC{\equiv}C > PhCH{=}CH$, $CH_2{=}CH > Ph > PhCH_2 > CH_3OCH_2 > CH_3 > C_4H_9$.

The catalytic cycle for the coupling reaction of acid chlorides with organotin reagents[125], is identical to that shown in Scheme 3 (Section 1.3.3), save that the ROTf is replaced by RCOCl.

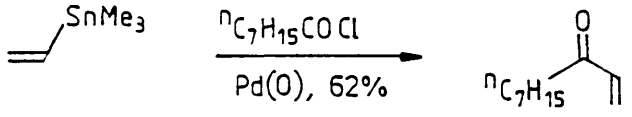
Although the uncatalysed reduction of acid chlorides to aldehydes by tributyltin hydride yielded a mixture of aldehydes and esters[126], the introduction of a palladium catalyst directed the reduction, under mild conditions, nearly exclusively to the aldehyde, in high yield even in the presence of other reducible groups (e.g. nitro, ketone, ester)[127].

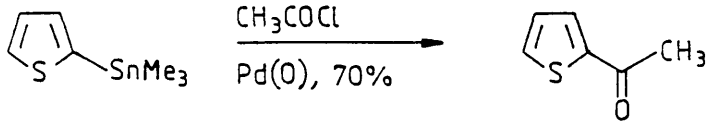
Under palladium catalysis, α-oxygenated vinyltin compounds underwent clean cross-coupling with acid chlorides to give α-oxygenated enones, which were easily converted into unsymmetrical 1,2-diketones[128].



R =n-alkyl
cy-alkyl
phenyl
1-furyl

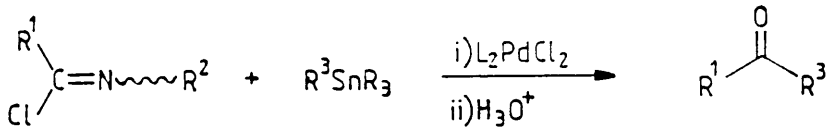
This methodology was also applied to the preparation of unsaturated ketones, from the appropriate organotin precursors[128].





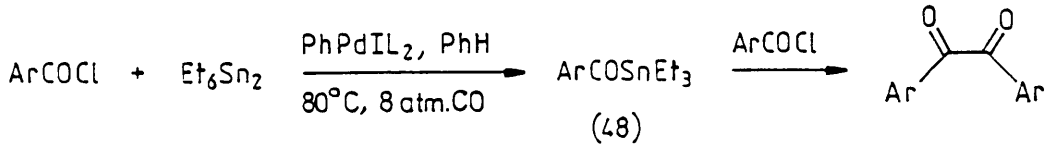
Acid chlorides can easily be converted into imidoyl chlorides. Unfortunately, the alkylation (or arylation) of imidoyl chlorides with cuprate reagents gives poor yields. Although Grignard reagents can be used, the imines once formed can react further, and many functional groups are not tolerated. However, like acid chlorides, imidoyl chlorides undergo oxidative addition to a palladium complex, and they were successfully transformed into ketimines, when treated with organotin compounds in the presence of palladium complex

catalysts[129]. Hydrolysis of these ketimines led to unsymmetrical ketones.



R =R^1=R^3=Ph R^2=4-$EtO_2CC_6H_4$ (70%)
R =^{n}Bu R^1=Ph R^2=4-MeC_6H_4 R^3= PhCH=CH (70%)
R =^{n}Bu R^1=Et R^2=Ph R^3= PhC≡C (69%)
R =^{n}Bu R^1=Ph R^2=4-MeC_6H_4 R^3= PhC≡C (84%)

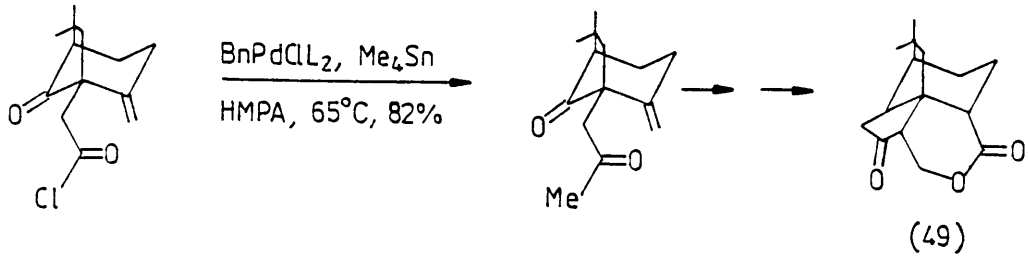
Symmetrical 1,2-diketones have been made from aroyl chlorides in a palladium catalysed coupling reaction which evidently involved conversion of half the acid chloride into an acyltin reagent, which then coupled with the remaining acid chloride (Scheme 7)[130]. Decarbonylation of the intermediate aroylpalladium complexes was minimised by running the reaction under CO (8 atm).



Ar =4-$MeOC_6H_4$ (76%)

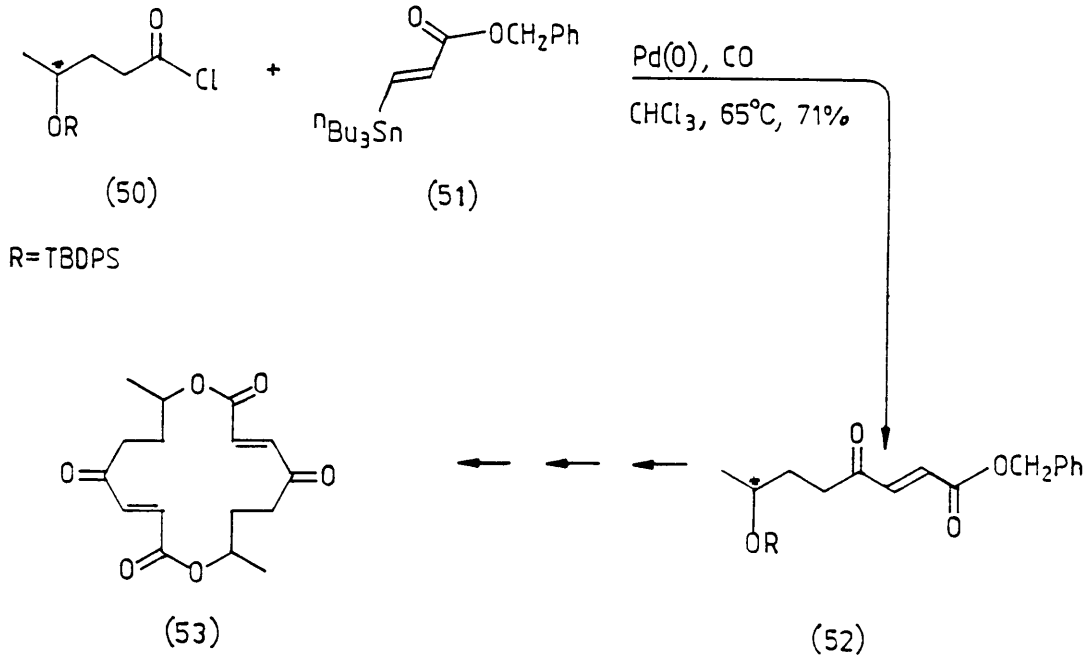
Scheme 7

The conversion of an acid chloride into a ketone has been used in a number of syntheses of more complicated organic molecules, for example, in the synthesis of (±)-quadrone (49)[131].



(49)

The palladium catalysed coupling of an organotin reagent bearing acrylate functionality, with an acid chloride, serves as a method to introduce both a ketone and an acrylate group into a carbon framework[132]; thus, the coupling reaction of the acid chloride (50) with the substituted vinyltin reagent (51) gave the ketone (52), which is a key intermediate in the synthesis of the macrolide antibiotic pyrenophorin (53) (Scheme 8)[133].



(50)

R=TBDPS

(51)

(52)

(53)

Scheme 8

1.7 ALKYL COUPLING

Yoshida et al. have recently reported two methods for the preparation of ketones from alkyl halides. In the first method, unsymmetrical ketones were prepared in excellent yields by the palladium catalysed coupling reaction of alkyl iodides and acid chlorides, mediated by zinc-copper couple[134].

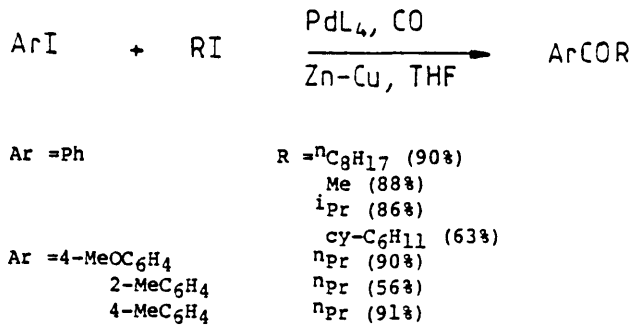
$$RCOCl + R^1I \xrightarrow[Zn\text{-}Cu,\ DMF]{PdL_4,\ PhH} RCOR^1$$

R = Ph, 2-MeC_6H_4, 4-$MeOC_6H_4$, Et, CH_2=CH

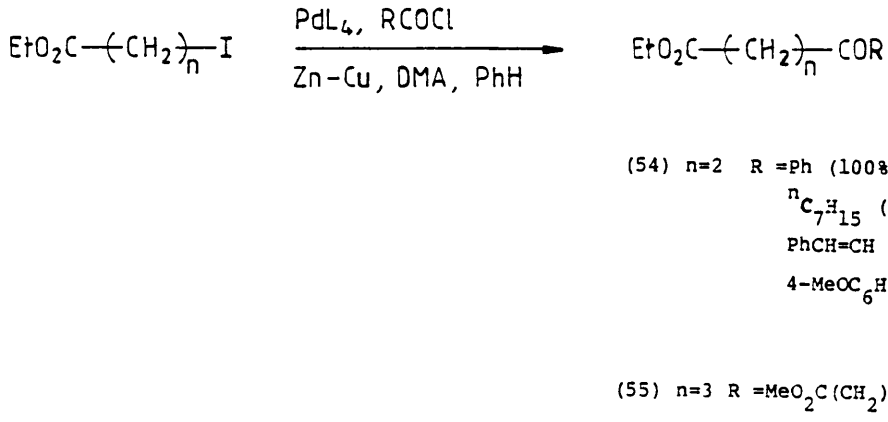
R^1 = Me, ^nPr, $^nC_8H_{17}$, $EtC{\equiv}C(CH_2)_2$

This reaction may have some advantages over the organotin method developed by Stille[33], which has been successfully applied to the synthesis of unsaturated ketones (Section 1.6), but appears to be uneconomical for the preparation of saturated ketones as only a part (one or two) of the alkyl groups of the tetraalkyltins is utilised in the reaction.

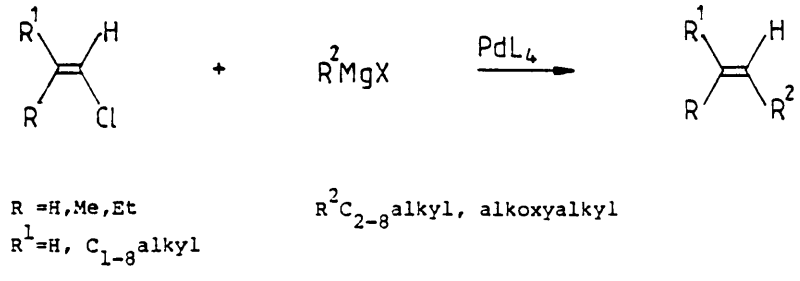
In the second method, aryl alkyl ketones were selectively prepared by the reaction of alkyl iodides and aryl iodides, in the presence of a stoicheiometric amount of zinc-copper couple and a catalytic amount of a palladium(0)complex, under an atmospheric pressure of carbon monoxide[135].



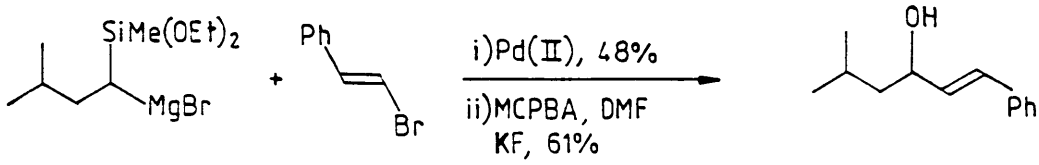
The acid chloride methodology has been used to prepare both γ-(54) and δ-ketoesters (55), in very high yields[136].



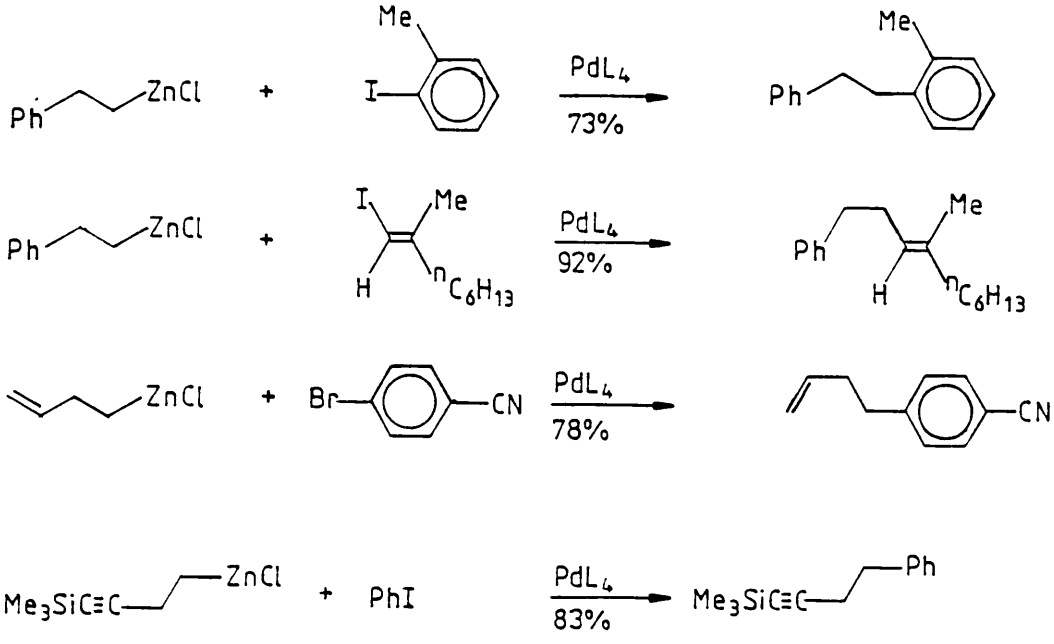
Both (E)-and (Z)-alkenes have been prepared by the palladium catalysed coupling of Grignard reagents with vinyl chlorides[137].



Carbanions α to alkoxysilyl (or aminosilyl) groups have acted as nucleophilic α-hydroxylating agents for organic halides, via the palladium catalysed coupling reaction, followed by oxidative cleavage of the carbon-silicon bond[138].

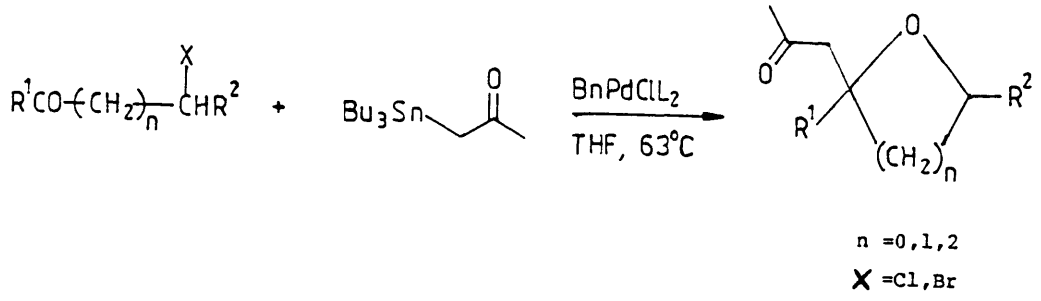


The palladium catalysed homobenzyl-aryl, homobenzyl-alkenyl, homoallyl-aryl and homopropargyl-aryl cross-coupling reactions provided the desired coupled products in high yields[139]. There was minor formation (<5%) of the dimers of the aryl or alkenyl halides.

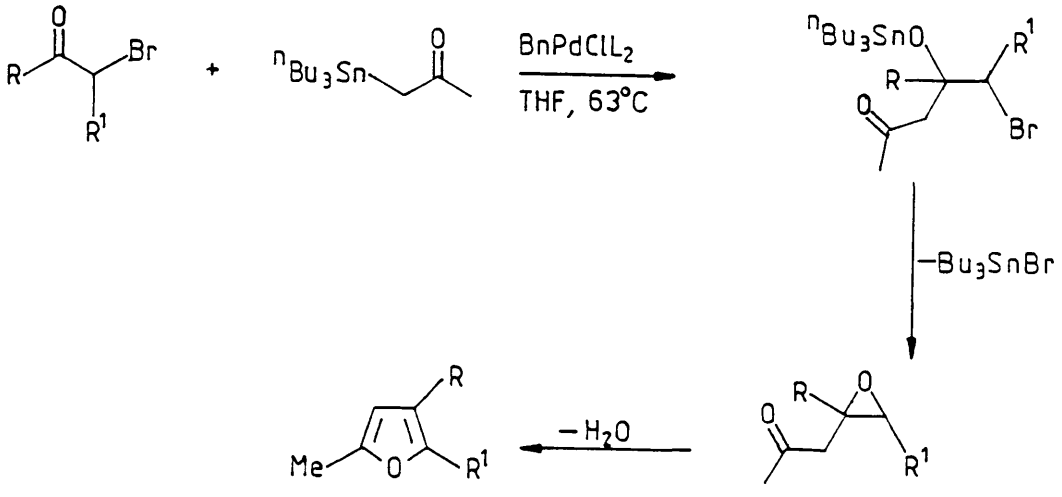


The palladium catalysed reaction of a variety of halo-ketones or halo-aldehydes with acetonyltin reagents gave cyclic ethers in good yields and under mild reaction conditions[140]. Carbonyl compounds

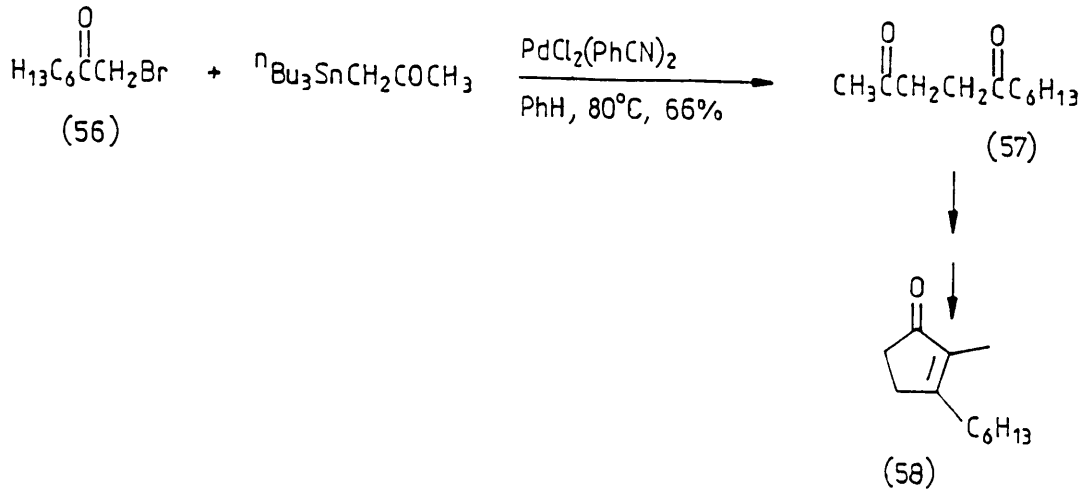
containing α-,β- or γ-halogens gave oxiranes, oxetanes and tetrahydrofurans, respectively.



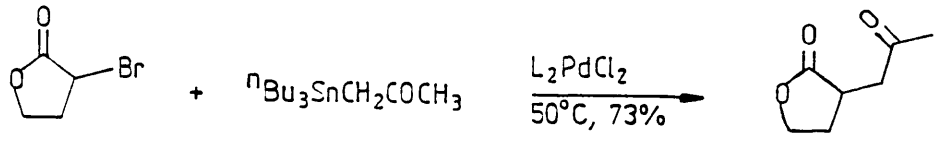
The acetonyloxiranes underwent thermal rearrangements with dehydration to yield substituted furans.



When a palladium catalyst that did not contain phosphine ligands was used, 1,4-diketones were formed, apparently via an initial oxidative addition step at the α-halo position[141]. As an example, the coupling reaction of 1-bromo-2-octanone (56) with acetonyltributyl-stannane gave the 1,4-diketone (57), a key intermediate in the synthesis of dihydrojasmone (58).



α-bromo-γ-butyrolactones underwent palladium catalysed coupling with acetonyltin reagents to give good yields of α-acetonyl-γ-butyrolactones[142].



1.8 CONCLUSIONS

In this review, an attempt has been made to provide a flavour of the many and varied aspects of chemical research where the palladium catalysed cross-coupling reaction plays a major part. The emphasis has been on catalytic reactions (however, useful stoicheiometric reactions have also been included), and on recent advances in the field of cross-coupling.

The organic reactions in which palladium, its salts and complexes are involved, apart from coupling reactions include double bond

isomerisations, molecular rearrangements, oxidations, allylic substitutions and eliminations, dimerisations and oligomerisations, carbonylations, cyclopropanations and reductions. Clearly, palladium is a very remarkable reagent in that it catalyses such a wide variety of organic reactions.

Of all these transformations, perhaps the most remarkable is the cross-coupling reaction, for its ability to bring together and unite reagents bearing a wide variety of functional groups, often in a catalytic manner, under mild conditions and in high yields.

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CHAPTER 2: RESULTS AND DISCUSSION

2.1 INTRODUCTION

Transition metal catalysed cross-coupling, first reported in 1972 in the reaction of Grignard reagents and organolithiums with aryl and vinyl halides[1,2], has subsequently been extended to include organic derivatives of zinc[3], aluminium[4], zirconium[5], tin[6], copper[7], mercury[8] and various other metals (e.g. cadmium, boron, titanium)[9].

The palladium catalysed cross-coupling reaction between an organic halide and an organo-main group metal is a powerful and widely used method for carbon-carbon bond formation[10,11].

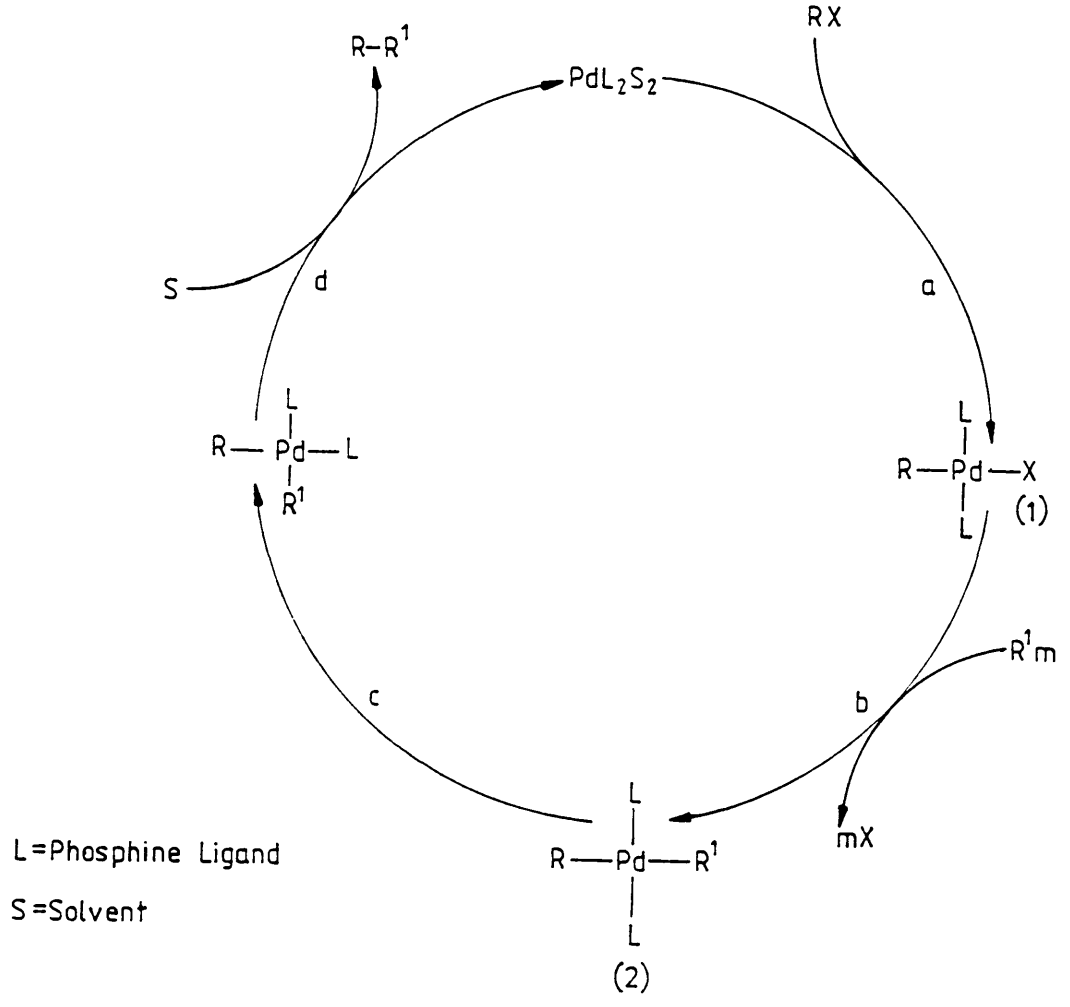
Organomagnesium compounds are most frequently employed in these reactions[12], although in a number of cases organozinc and organotin compounds have turned out to be more suitable.

The research to be reported herein falls into four sections. Firstly, a study of β-elimination in the cross-coupling reaction of an aryl halide, with an alkyl Grignard reagent, in the presence of a variety of palladium catalysts was undertaken. Secondly, variations in the Grignard reagent were studied. Thirdly, coupling reactions involving the oxidative addition of an alkyl iodide were attempted. Finally, the preparation and utilisation of a modified palladium(II)catalyst was investigated.

All compounds were isolated and characterised spectroscopically (see the experimental for a detailed analysis).

2.2 MECHANISM

The generally accepted mechanism for the cross-coupling process (Scheme 1) consists of four steps, (a) oxidative addition, (b) metathesis (transmetallation), (c) <u>trans</u> to <u>cis</u> isomerisation, and (d) reductive elimination.



Scheme 1

2.2.1 Oxidative addition

Most organic reactions that are catalysed by transition metals occur by a series of steps. An important reaction of this type is the oxidative addition of an organic substrate to the transition

metal[13]. In this reaction, the increase in the oxidation state of the metal is usually accompanied by an increase in the co-ordination number[14]. The propensity to undergo oxidative addition is characteristic of group 8 metal complexes of the d^8 and d^{10} electronic configurations[15].

A number of factors determine the ability of transition metals to undergo oxidative addition. The transition metal must be in a low valent state, behaving as a nucleophile. Unlike the group 1 and 2 metals that readily react in bulk, group 8 metals must be in the atomic state, usually through complexation by ligands. Generally, the reactivity toward oxidative addition increases in going from right to left across the periodic table, in going down a given group in the table (although there are exceptions), and in decreasing the initial oxidation number. The co-ordination number of the metal and the type of ligand involved, are also important[16].

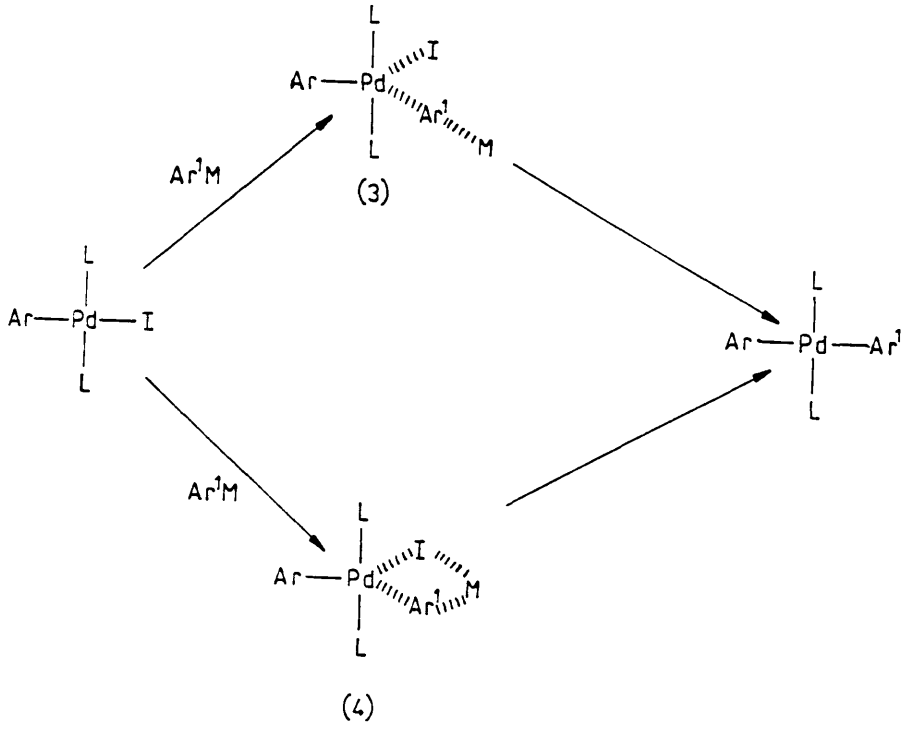
In order for oxidative addition to take place, prior generation of a vacant site may occur to give a coordinatively unsaturated species. For example, the complexes $M(PPh_3)_4$ ($M=Ni^o,Pd^o,Pt^o$) having the d^{10} configuration are coordinatively saturated and undergo dissociation in solution to form compounds which are reactive toward oxidative addition. The phosphine ligands are σ-donors (lone-pair donation) which increase the electron density on the metal. This makes the metal a good nucleophile and increases the tendency for the phosphines to dissociate[13].

However, there is evidence that steric effects are as important as electronic effects (if not more so) in determining the dissociation of

phosphine ligands from transition metal complexes. The larger the cone angle of the ligand, the greater is the tendency for dissociation.

2.2.2 Metathesis

Recently, Widdowson et al.[17] have proposed a five coordinate transition state to explain the dependance on steric factors of the synthesis of unsymmetrical biaryls (Scheme 2).



Scheme 2

Two limiting pathways are envisaged. Both involve distorted bipyramidal transition states, either the S_E2(open) process to give (3), or the S_E2(cyclic) mechanism to give (4). This theory is supported by the work of Cross, concerning the ligand substitution reactions of square-planar molecules[18]. There is general agreement that these reactions are associative and involve nucleophilic attack

of the entering ligand at the metal, the five-coordinate adduct passing through trigonal-bipyramidal and square-pyramidal stages.

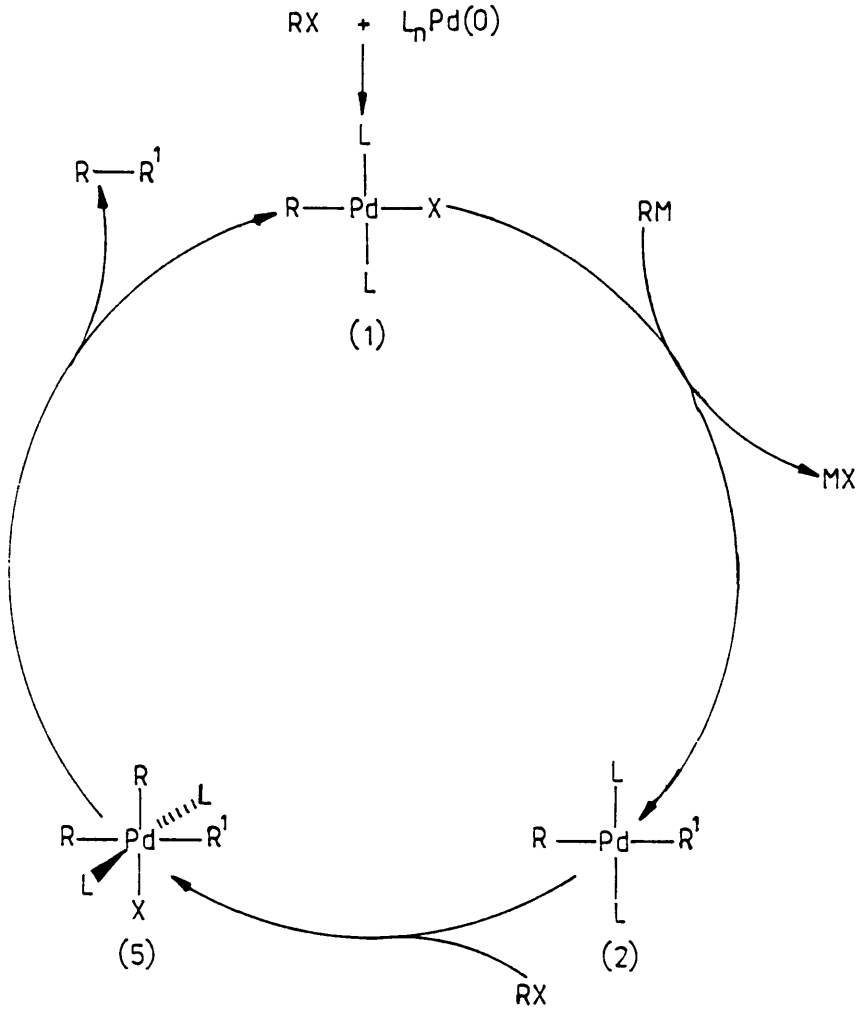
Stille[19] has proposed an associative mechanism where the key step is the oxidative addition of a second aryl halide molecule, to form a distorted, octahedral transition state (Section 2.2.3).

Both mechanisms explain their respective results. This implies either that more than one mechanism may be operating, or that a definitive solution has yet to be found.

2.2.3 Isomerisation

In order for a concerted 1,1-reductive elimination to take place (Section 2.2.4), the organic moieties must occupy adjacent positions in the palladium complex. However, the geometry of the product of oxidative addition (1), leads to the transmetallation product (2) in which the organic groups are *trans* to each other. There are a number of conceivable pathways by which the two organic groups in a *trans* complex could gain positions adjacent to one another prior to coupling.

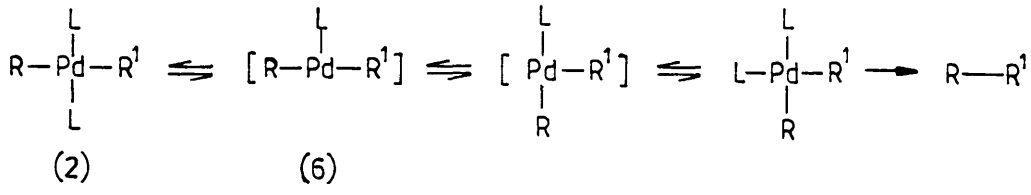
Stille *et al.*[19,20] have proposed that another molecule of the organic halide can oxidatively add to the palladium(II) complex (2), to form a palladium(IV) complex (5) (Scheme 3), in which the organic groups to be coupled are adjacent.



Scheme 3

This mechanism explains how a palladium complex containing adjacent organic groups can be realised, and explains the presence of homocoupled products (R-R). However, the palladium(IV) complex would be expected to yield approximately equal amounts of homocoupled and cross-coupled products, a conclusion which is not supported experimentally.

Yamamoto et al.[21,22] have suggested that after dissociation of a phosphine ligand (dissociative mechanism) from (2), the three co-ordinate intermediate (6) can rearrange, followed by recoordination of a phosphine, to produce the cis square-planar complex (Scheme 4).



(2) (6)

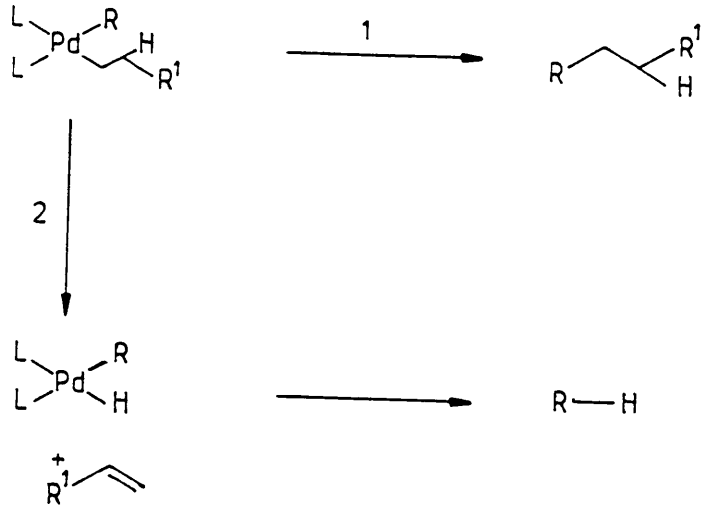
Scheme 4

Several groups have suggested an associative mechanism for the trans to cis isomerisation, i.e. formation of a five coordinate complex, which after rearrangement and dissociation of a phosphine ligand, yields the cis square-planar complex[21].

This mechanism involves the formation of a penta-coordinate trialkyl palladate intermediate, which, due to the facile isomerisation of trigonal bipyramidal species, would imply a tendency to homocoupled products similar to the octahedral complex (5).

2.2.4 Reductive elimination

The final step of the cross-coupling reaction requires the elimination of the organic partners from the transition metal complex[23]. This reductive elimination can take more than one pathway. The two important paths for the palladium catalysed coupling, are 1,1-reductive elimination (path 1)[19,24], and β-elimination (path 2)[25] (Scheme 5).



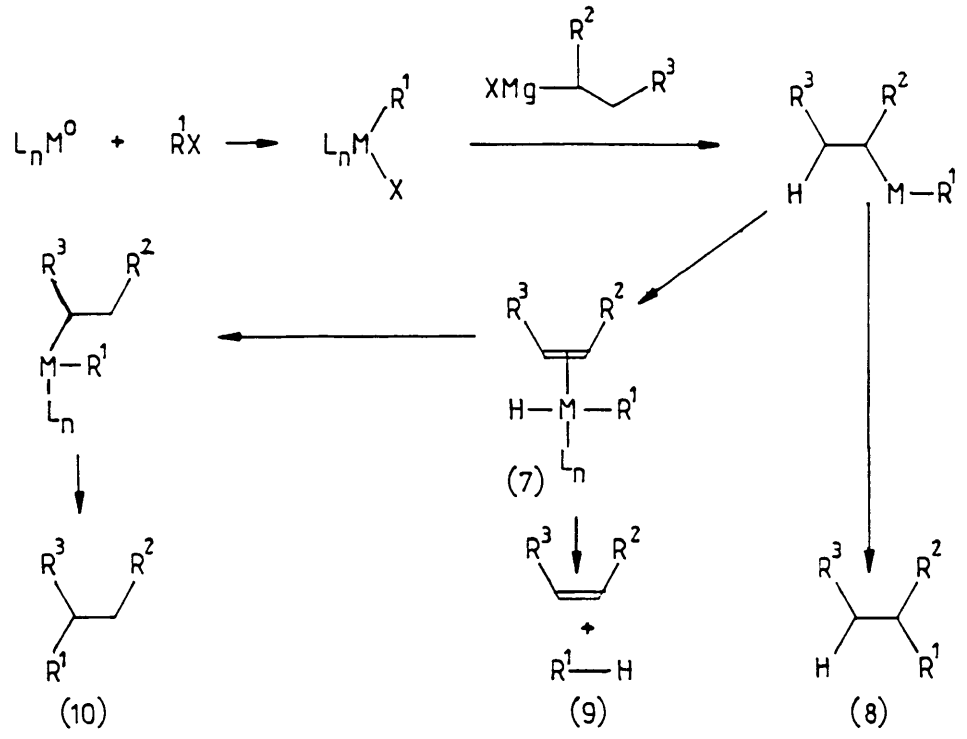
Scheme 5

In the 1,1-reductive elimination reaction, the formal oxidation state and the coordination number of the metal are reduced by two; bond breaking is accompanied by bond making. Theoretical studies have shown that reductive carbon-carbon, and carbon-hydrogen coupling from a palladium(II)complex, is facile, intramolecular and consistent with a concerted process[26,27].

2.3 BETA ELIMINATION

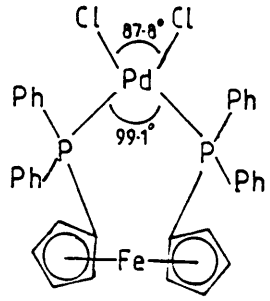
2.3.1 Introduction

While organometallic reagents with methyl, aryl, alkenyl, benzyl, or alkynyl groups had been successfully used in cross-coupling reactions, those with alkyl groups containing β-hydrogens had not given satisfactory results[28-30]. This was because the formation of the expected cross-coupled products (8) was accompanied by β-hydride elimination of the σ-alkylmetal moiety. This gave a hydrido-olefin complex (7) which led to isomerisation of the alkyl group (10) and/or reduction of the starting halide (9) (Scheme 6)[31].



Scheme 6

Selective cross-coupling, free from side reactions, would be realised by the development of a catalyst that could make the reductive elimination of the coupling product much faster than β-elimination. The identity of the phosphine-palladium complex was found to be a crucial factor in maximising the selectivity for these cross-coupling reactions with alkyl groups[11]. Bidentate phosphines were known to stabilise the σ-alkyl moiety against β-hydride elimination, by inhibiting the creation of coordinative unsaturation in the alkyl-palladium species through their chelating ability. Recently[32], it has been reported that dichloro-(1,1'- bis[diphenylphosphino]-ferrocene)palladium(II) ($PdCl_2$[dppf]) (11), is an effective catalyst for the cross-coupling reaction, both in terms of activity and selectivity.



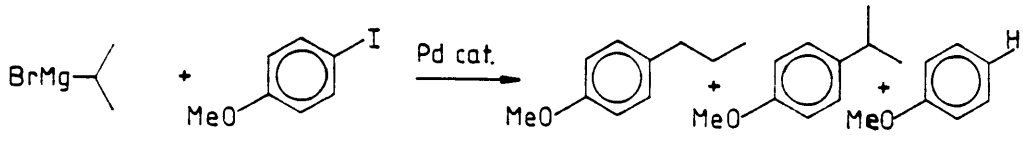
(11)

The most conspicuous feature of this molecule is the large P-Pd-P bond angle of 99.1°, and a small Cl-Pd-Cl angle of 87.8° [32]. The opening up of the P-Pd-P angle is due to the bulk of the dppf moiety, where the two cyclopentadienyl rings are in a staggered conformation.

In order to test the claims of $PdCl_2$(dppf), a standard cross-coupling reaction was chosen, wherein the only variable was the catalyst.

2.3.2 Standard coupling reaction/catalyst variation

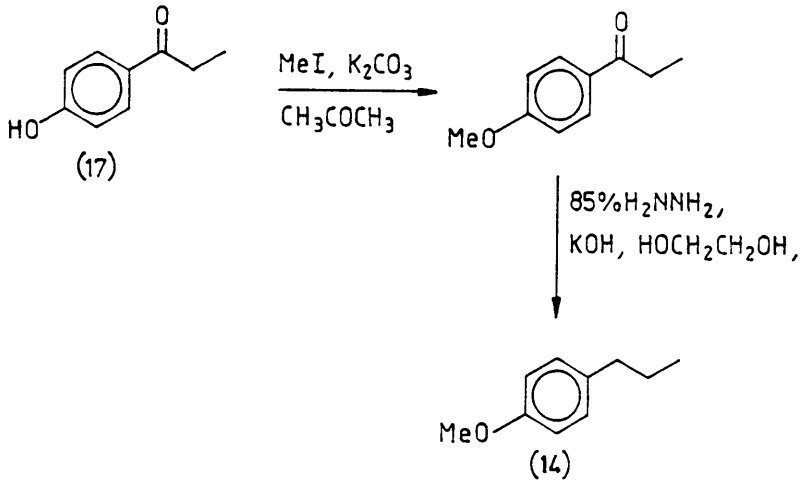
The Grignard reagent of 2-bromopropane (12) was coupled with 4-iodoanisole (13) in the presence of a variety of palladium catalysts (Scheme 7), and the yields of 4-^{n}propylanisole (14), 4-isopropylanisole (15) and anisole (16) were determined.



(12) (13) (14) (15) (16)

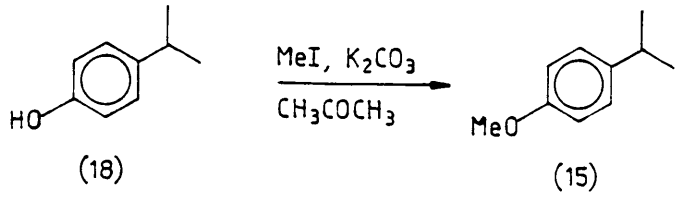
Scheme 7

The reactions were to be analysed by gas liquid chromatography (G.L.C.). The anisole (16) was readily available, and the 4-^{n}propylanisole (14) was prepared[33] by the methylation and subsequent Wolff-Kishner reduction of 4-hydroxypropiophenone (17) (Scheme 8).



Scheme 8

4-Isopropylphenol (18) was methylated in good yield (71%), to give 4-isopropylanisole (15) (Scheme 9).



Scheme 9

Four palladium catalysts were selected for this comparison study; tetrakis(triphenylphosphine)palladium(0) (PdL_4) (19), which was easily prepared in 91% yield, from palladium(II)chloride and triphenylphosphine (Scheme 10)[34], and bis(triphenylphosphine)-(1,2-bis[diphenylphosphino]ethane)palladium(II) (PdL_2[dppe]), dichloro(1,2-bis[diphenylphosphino]ethane)palladium(II) ($PdCl_2$-[dppe])[35], and dichlorobis(triphenylphosphine)palladium(II) ($PdCl_2L_2$)[36], which were all prepared *in situ.*

$$2PdCl_2 + 8PPh_3 + 5H_2NNH_2.H_2O \longrightarrow 2Pd(PPh_3)_4 + 4H_2NNH_2.HCl + 5H_2O + N_2$$

Scheme 10

All of the coupling reactions were carried out in THF, at reflux, under nitrogen, for 16 hours.

The results are summarised in Table 1.

Table 1

Catalyst	Extent(%)	4-IC_6H_4OMe(%)	4-$^{i}PrC_6H_4OMe$	4-$^{n}PrC_6H_4OMe$(%)	C_6H_5OMe(%)
PdL_4	68	32	28	17	55
PdL_2(dppe)	28	72	21	18	61
$PdCl_2$(dppe)	24	76	0	0	100
$PdCl_2L_2$	63	37	24	14	62

Although the reaction solutions were refluxed for 16 hours, the results did not change significantly over a time range of 4-24 hours. Each value was an average of at least five repeat experiments, and the yields of the three products are expressed as a percentage of the total product yield (Extent of reaction). Taking into account the ratios of coupled product, rearranged product, quenched product and extent of reaction, the order of efficiency of the palladium catalysts for the standard coupling reaction was PdL_4, $PdCl_2L_2$> $PdL_2(dppe) \gg PdCl_2(dppe)$. In solution, both PdL_4 and $PdCl_2L_2$ are considered to generate the catalytically active species "PdL_2", therefore the similarity in their results was not surprising. The results obtained for the $PdL_2(dppe)$ implied that the active catalyst in the reaction mixture was PdL_4. However, the lower value for Extent of reaction pointed to the presence of a catalytically inactive species. Disproportionation of the $PdL_2(dppe)$ (Scheme 11) explained both observations, provided that the catalytic turnover is limited.

$$2PdL_2(dppe) \longrightarrow PdL_4 + Pd(dppe)_2$$

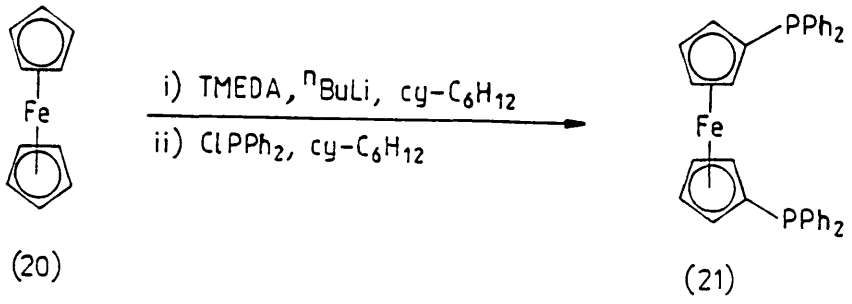
Scheme 11

As expected the $PdCl_2(dppe)$ was inactive in the coupling reactions. The amount of palladium catalyst used was varied between 2 and 10 mol%, however, the results obtained were unaffected.

2.3.3 Standard coupling reaction/$PdCl_2(dppf)$

Having investigated the efficiencies of the comparison catalysts, the preparation and catalytic activity study of $PdCl_2(dppf)$ was

undertaken. The dppf (21) was prepared by dilithiation of ferrocene (20), followed by addition of chlorodiphenylphosphine (Scheme 12).



(20) (21)

Scheme 12

Separation of the product (21) from the unreacted starting material (20), mono-lithiated products and unrequired dilithiated products, by fractional crystallisation, proved to be rather inefficient, and the optimum yield obtained was 37%.

On stirring the dppf with chlorobis(benzonitrile)palladium(II) ($PdCl_2[PhCN]_2$) (22) in benzene, at room temperature, for 12 hours, $PdCl_2$(dppf) was precipitated in a 94% yield, after recrystallisation from chloroform (Scheme 13)[32].

$$PdCl_2(PhCN)_2 + dppf \xrightarrow[12h,\ 94\%]{C_6H_6,\ R.T.} PdCl_2(dppf)$$

Scheme 13

The $PdCl_2$(dppf) was then used as a catalyst in the standard cross-coupling reaction. The effects of temperature, catalyst

concentration, solvent and time on the performance of the catalyst were investigated (Table 2). Aliquots of the reaction mixture were taken at regular intervals, to be analysed by G.L.C.

Table 2

Run	Temp (^{o}C)	Solvent	Time(h)	Cat.	Yield,%[a]			
				mol.%	Extent	C_6H_5OMe	4-$^{i}PrC_6H_4OMe$	4-$^{n}PrC_6H_4OMe$
1	67	THF	16	5[b]	54	32	56	12
2	RT	THF	16	5[b]	53	40	47	13
3	RT	THF/C_6H_6	0.5	10[c]	100	31	50	19
4	-78→ RT	THF/Et_2O	0.167	5	94	27	67	6
5	-78→ RT	Et_2O	1.5	5	99	31	60	9
6(i)	-78→-23	THF/Et_2O	3	5	30	78	20	2
6(ii)	-23→ RT	THF/Et_2O	16	5	99	45	50	5
7	-78→ +2	THF/Et_2O	3	5	88	22	76	2
8	-78→ +2	THF/Et_2O	3	0	66	46	0	0
9	-78→ +2	THF/Et_2O	3	100	99	25	75	0
10[d]	-78→ +2	THF/Et_2O	3	5	99	14	83	1
11[d,e]	-78→ +2	THF/Et_2O	3	5	99	14	79	0

a. Determined by GLC using an internal standard
b. $^{i}C_3H_7Br$:Mg 1:1
c. $^{i}C_3H_7Br$:Mg 1:2
d. Transfer through filter paper
e. Isolated yield

The dramatic increases in Extent for Runs 3 to 11 illustrated the importance of having an excess of magnesium filings, thereby maximising the formation of the Grignard reagent. The concentration of the rearranged product (14) appeared to be sensitive to the temperature of the reaction, i.e. the lower the temperature, the lower the yield of (14). However, if the temperature was too low, the reaction rate became prohibitively slow (Run 6). As expected, the $PdCl_2$(dppf) was acting catalytically (Run 9).

The amount of anisole (16) produced in all reactions was higher than expected, in fact, anisole was formed even in the absence of any catalyst (Run 8). There were two possible explanations. The first involved transmetallation of the alkyl Grignard reagent with the aryl iodide, and subsequent proton quenching during the work-up. When a graph was plotted showing the variation in product distribution with time (Figure 1), it was noticed that the concentration of anisole rose rapidly in the early stages of the reaction, but quickly reached a constant value.

Cross-coupling of 4-iodoanisole and 2-bromopropane, in the presence of $PdCl_2(dppf)$.

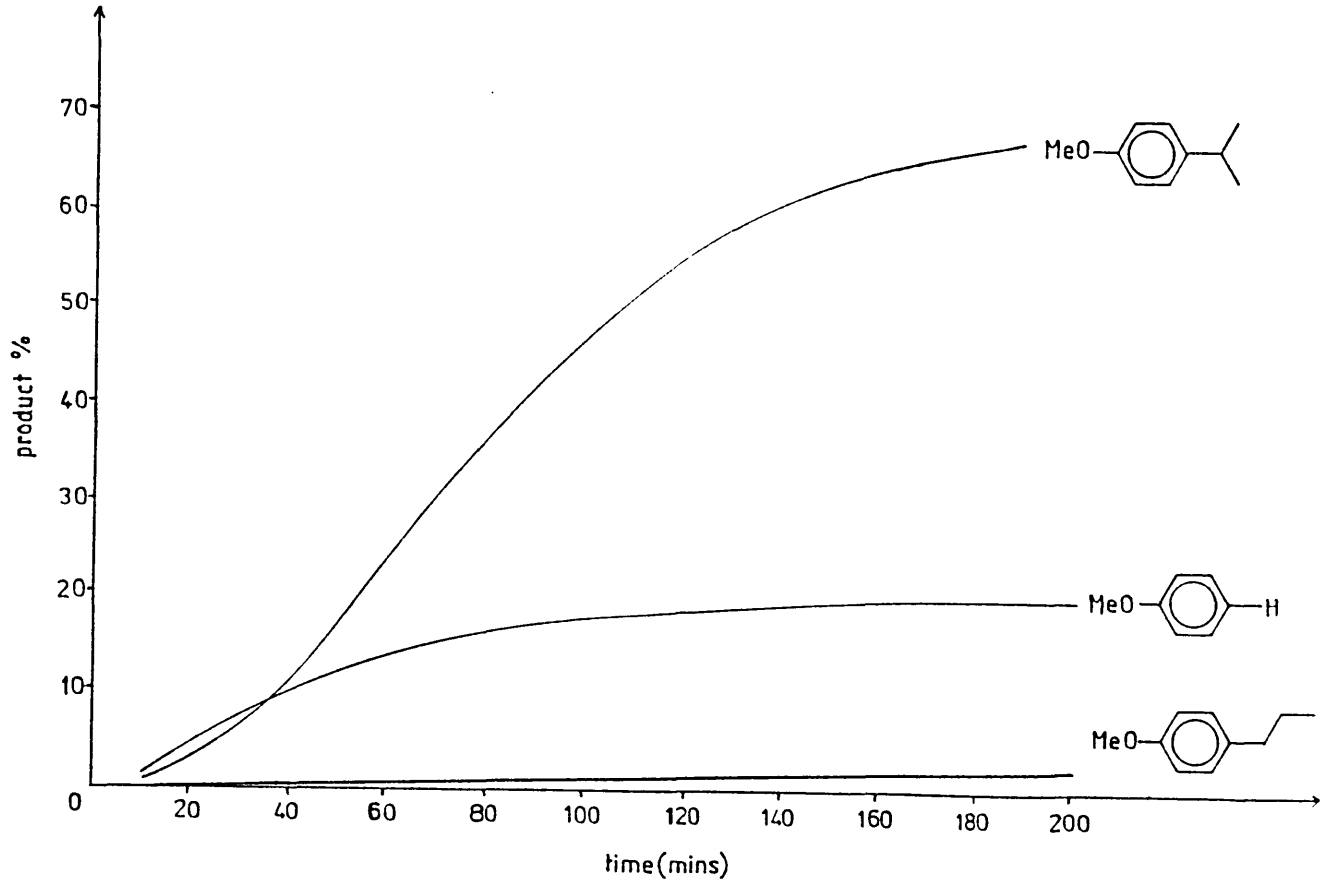


Figure 1.

It was postulated that the appearance of anisole could also be explained by small particles of magnesium being transferred through the filter stick, with the Grignard solution, into the vessel containing the aryl iodide and the catalyst. Thus a quantity of anisyl Grignard reagent would be formed, and quenched on work-up, as for the transmetallation. In order to test this hypothesis, the filter stick was covered with a piece of filter paper (Run 10). Although the production of anisole was greatly reduced, the fact that approximately 15% was being formed, indicated that both processes were taking place. The double filter was used in all subsequent reactions.

The substrate used as a standard, 2-bromopropane, was specifically selected as a good test of the various palladium catalysts, due to its high number of β-hydrogens.

The results obtained illustrate that under the appropriate reaction conditions, the use of $PdCl_2$(dppf) as a catalyst in the cross-coupling reaction, virtually removes the problem of β-elimination.

2.4 ALKYL HALIDES - GRIGNARD VARIATION

2.4.1 Introduction

Having established the deterrent ability of the $PdCl_2$(dppf) catalyst toward β-elimination, the effect of changing the steric bulk of the Grignard reagent was investigated. To this end, the 2-bromopropane was replaced by a primary, a cyclic secondary, a tertiary and a neopentyl halide. In addition, attempts were made to couple the 4-iodoanisole with a steroidal halide, and with a protected keto halide.

2.4.2 Steric studies

The alkyl halides were converted to their respective Grignard reagents and were then added to 4-iodoanisole in the presence of a catalytic amount of $PdCl_2(dppf)$.

Table 3

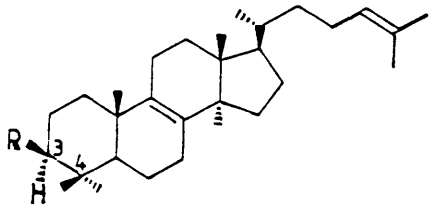
Alkyl Halide	%Coupled Product
Me_2CHBr	79
$Me_2CH(CH_2)_2Br$	94
cy-$C_6H_{11}Br$	96
Me_3CBr	-
Me_3CCH_2Br	87

The only unsuccessful reaction was that of the t-butylbromide. As the t-butylmagnesium bromide had formed (an aliquot was quenched with benzophenone), the failure to couple was probably due to the steric bulk of the t-butyl substrate in the transition state. This implied a penta-coordinate transition state (see section 2.2.2) for the replacement of the halide by the alkyl anion.

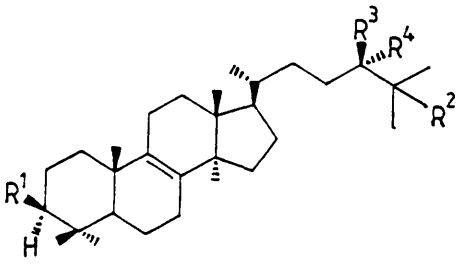
Previously, the coupling of sec-butyl groups with aryl halides had been reported[32]. The results shown in Table 3, illustrated that primary, neopentyl and cyclohexyl halides could also be coupled to aryl iodides in high yields.

2.4.3 Steroid coupling

In order to study the cross-coupling of a bulky substrate, containing β-hydrogens, attempts were made to synthesise lanosteryl bromide (29). The commercially available starting material was, in fact, a 60:40 mixture of lanosterol (23) and dihydrolanosterol (24).



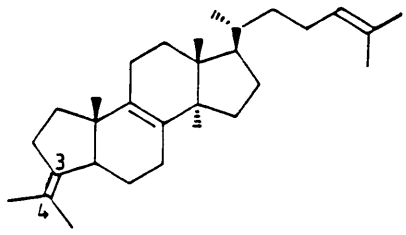
R =OH (23)
R =OAc (25)
R =Br (29)



R^1 =OH R^2=R^3=R^4=H (24)
R^1 =OAC R^2=R^3=R^4=H (26)
R^1 =OAC R^2=R^3 =Br R^4 =H (27)
R^1 =OAC R^2=R^4 =Br R^3 =H (28)

In order to obtain a clean starting material[37], commercial lanosterol was acetylated to give a mixture of the acetates (25) and (26), and brominated to give compounds (27) and (28) as crystalline solids, free of any dihydrolanosterol impurity. Debromination with zinc dust yielded acetate (25), which was hydrolysed to lanosterol (23).

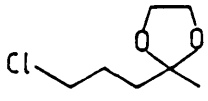
The method chosen for the conversion of the alcohol (23) to the bromide (29) was the triphenylphosphine/carbon tetrabromide system, in order to avoid the formation of a carbonium ion at C-3, which would have induced a neopentyl rearrangement. However, the only detected product was indeed the rearranged product, the triene (30). Reaction of alcohol (23) with mesyl chloride and triethylamine in dichloromethane gave the mesylate, and subsequent treatment with lithium bromide in THF also yielded only compound (30).



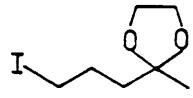
(30)

2.4.4 Ketal coupling

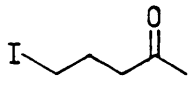
The major drawback to the use of Grignard reagents in organic chemistry in general, and the cross-coupling reaction in particular, is their lack of toleration towards many functional groups. Therefore, the ethylene ketal (31) of 1-chloro-4-pentanone (34) was selected, in order to investigate the tolerance of the cross-coupling reaction to functional groups on the alkyl moiety.



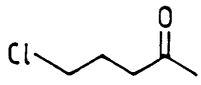
(31)



(32)



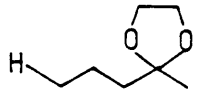
(33)



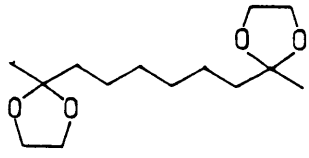
(34)

It was found that under a wide variety of conditions (variation of the solvent, temperature, initiator, time), the ketal (31) was recovered unchanged. It seemed likely that the reason for the lack of reaction was the known sluggish nature of chloro Grignard reagent formation. Therefore, it was decided to try to convert the chloro ketal (31) to the iodo ketal (32), by adding (31) to a warm solution of sodium

iodide in acetone (Finkelstein reaction)[38]. Despite the use of pre-dried (over K_2CO_3) and degassed acetone, the reaction mixture contained only 1-iodo-4-pentanone (33) and 1-chloro-4-pentanone (34), (25:1). When the reaction was followed by G.L.C., it was found that the iodo ketal (32) was formed and destroyed in the early stages of the reaction ($t \leqslant 90$ minutes). The iodo ketone (33) was reprotected to form the iodo ketal (32), which reacted readily with magnesium, in THF, at reflux, room temperature, and even at $0^{o}C$. However, on quenching the reaction (with aqueous NH_4Cl), the isolated product was not 2-pentanone ethylene ketal (35), but the diethylene ketal of 2,9-decanedione (36), i.e. the Grignard reagent had homocoupled.

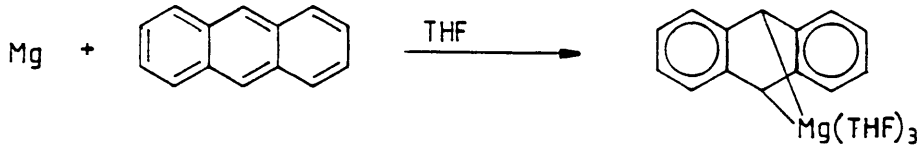


(35)



(36)

It has recently been reported[39-41] that in THF, magnesium forms a 1:1 adduct with anthracene (Scheme 14).



Scheme 14

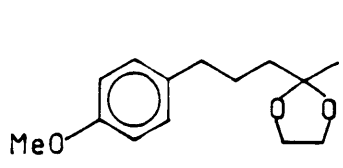
This species acts as a source of magnesium atoms. Therefore, a catalytic amount of anthracene in the Grignard reaction vessel, was

expected to increase the reactivity of the magnesium turnings to such an extent that the Grignard reagent of the chloro ketal (31) would be formed. No reaction ensued. Neither the addition of methyl iodide as an initiator, nor subjecting the solution to ultrasound had any discernible effect.

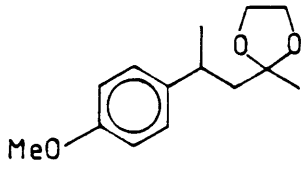
Finally, the reaction was repeated, replacing the previously used magnesium turnings by the more reactive magnesium powder. On quenching, the product detected was 2-pentanone ethylene ketal (35).

In order to maximise the efficiency of Grignard formation, a series of experiments were undertaken in which small variations were applied to the method. The reactions were quenched with benzophenone and the most satisfactory combination of conditions was employed.

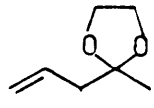
The chloro ketal Grignard reagent was allowed to react with 4-iodo-anisole (13) in the presence of a catalytic quantity of $PdCl_2$(dppf) to give the cross-coupled product, 1-(4-methoxyphenyl)- 4-pentanone ethylene ketal (37) in 89% yield (also isolated was 6% of the starting 4-iodoanisole).



(37)



(38)



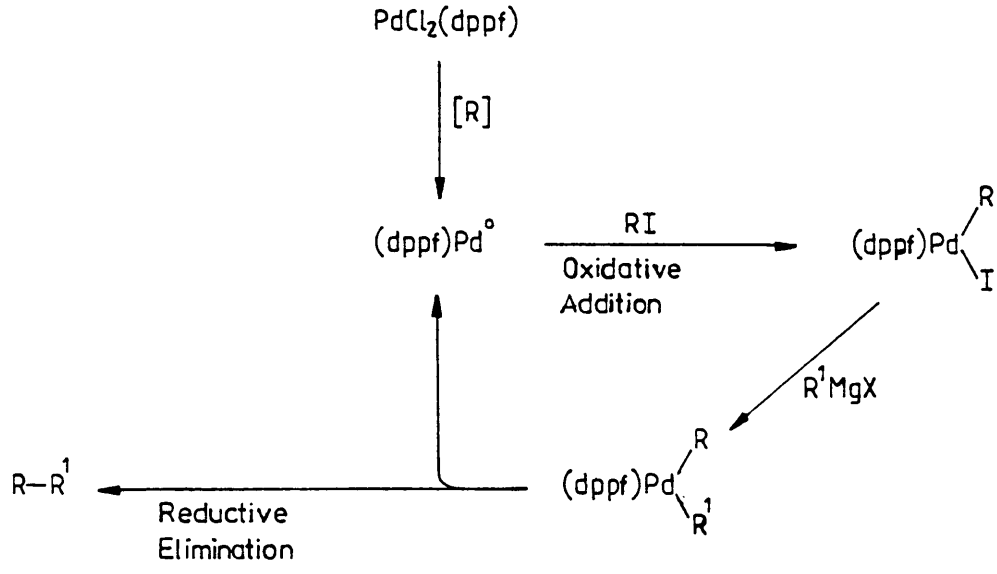
(39)

The final point of note, was the absence of compounds (38) and (39), once again indicating that the use of $PdCl_2$(dppf) had removed the threat of β-elimination.

2.5 ALKYL HALIDES - OXIDATIVE ADDITION

2.5.1 Introduction

The idea behind this section of the research, was prompted by two previously reported observations. Firstly, that as well as aryl iodides, methyl iodide could oxidatively add to palladium(O)-species[42]. Secondly, that in the presence of a palladium(II)-catalyst and hydrazine, an alkyl halide would reductively homo-couple[43]. These results suggested that the scope of alkyl halide oxidative addition, and subsequent reductive coupling should be investigated (Scheme 15).



[R] = reducing agent
R = alkyl
R^1 = aryl, alkyl

Scheme 15

~~The questions to be answered were a) would the alkyl iodides oxidatively add, b) would the intermediate β-eliminate, c) could the~~

The questions to be answered were a) would the alkyl iodides oxidatively add, b) would the intermediate β-eliminate, c) could the intermediate transmetallate and then reductively eliminate to yield cross-coupled products, and d) what range of RI could be used?

2.5.2 Reductive coupling

The reductive coupling of aryl halides has been widely reported[44-6] (Scheme 16).

$$2RX + Pd \longrightarrow RR + PdX_2$$

$$PdX_2 + H_2N.NH_2 \longrightarrow Pd + N_2 + H_2 + 2HX$$

Scheme 16

Nakajima et al.[43] reductively coupled 1-iodoalkanes, in the presence of a catalytic amount of palladium(II)chloride, to give the corresponding dimers in variable yields (the yield of the coupled product decreased with the decrease in the number of carbon atoms in the 1-iodoalkanes).

The above procedure was repeated using 1-bromohexadecane (cetyl bromide) (40), and the product mixture was analysed for the starting material, dotriacontane (41), hexadecane (42) and 1-hexadecene (43). The values obtained (expressed as percentages) were as follows:-

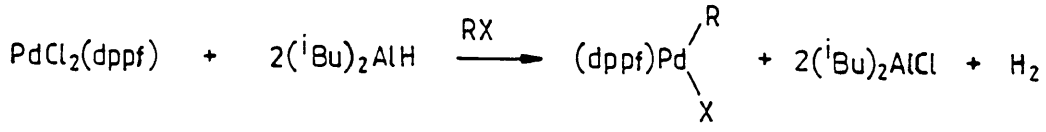
$C_{16}H_{33}Br$ (40)	:	$C_{32}H_{66}$ (41)	:	$C_{16}H_{34}$ (42)	:	$C_{16}H_{32}$ (43)
1	:	55	:	31	:	7

These results compared favourably with the literature values for the reductive coupling of 1-iodohexadecane (44) possibly due to the

increased strength of the C-Br bond diminishing the amount of olefin formed.

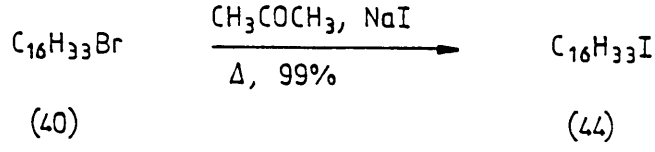
2.5.3 Cross-coupling

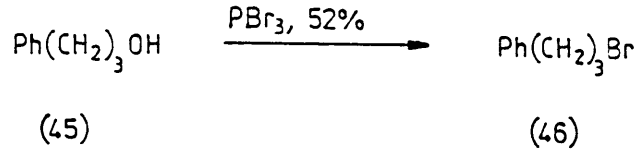
Prior reduction of the $PdCl_2(dppf)$ with 2 equivalents of diisobutyl-aluminiumhydride (DIBALH)[48-9] in THF as solvent (Scheme 17), was found to promote the oxidative addition of the alkyl halides.



Scheme 17

The 1-iodohexadecane (44) was prepared from the bromide (40) by reaction with sodium iodide in acetone, in very high yield. Reaction of phosphorus tribromide with hydrocinnamyl- alcohol (45), yielded 1-bromo-3-phenylpropane (46) (Scheme 18)[50].





Scheme 18

The results of the aryl-alkyl and alkyl-alkyl cross-coupling reactions are summarised in Table 4[47].

Table 4

Run	Reactants		Cat. mol.%	T °C	t h	Products (%)[a]		
	R'MgBr	RI				RR'	RI	R'R'[b]
1	4-$MeOC_6H_4MgBr$	MeI	2	0	16	74	-	4
2	4-$MeOC_6H_4MgBr$	MeI	2	21[d]	36	88	-	9
3	4-$MeOC_6H_4MgBr$	n-$C_{16}H_{33}I$	2	21	16	-	81[e]	28
4	4-$MeOC_6H_4MgBr$	n-$C_{16}H_{33}I$	2	67[f]	16	53	18	5
5	4-$MeOC_6H_4MgBr$	n-$C_{16}H_{33}I$	0	67	16	-	97[g]	5
6	$Ph(CH_2)_3MgBr$	EtI	5	21	16	87	-	-
7	$Ph(CH_2)_3MgBr$	EtI	10	21	16	88	-	-
8	$Ph(CH_2)_3MgBr$	n-$C_6H_{13}I$	5	67	16	91	-	-
9	$Ph(CH_2)_3MgBr$	n-$C_{16}H_{33}I$	5	67	16	80	6	-
10	$Ph(CH_2)_3MgBr$	n-$C_{16}H_{33}I$	0	67	16	-	87	-
11	n-$C_6H_{13}MgBr$	n-$C_6H_{13}I$	5	67	16	77	9	-
12	n-$C_6H_{13}MgBr$	n-$C_6H_{13}I$	5[h]	67	16	62	21	-
13	n-$C_6H_{13}MgBr$	n-$C_6H_{13}I$	0	67	16	-	82	-
14	n-$C_6H_{13}MgBr$	-	5	67	16	-	-	-
15	n-$C_6H_{13}MgBr$	cy-$C_6H_{11}I$	5	67	16	69	16	-
16	n-$C_6H_{13}MgBr$	cy-$C_6H_{11}I$	5[h]	67	16	58	29	-
17	cy-$C_6H_{11}MgBr$	n-$C_6H_{13}I$	5	67	16	63	19	-
18	cy-$C_6H_{11}MgBr$	cy-$C_6H_{11}I$	5	67	16	37	53	-
19	cy-$C_6H_{11}MgBr$	-	5	67	16	-	-	-
20	$Me_2CHMgBr$	cy-$C_6H_{11}I$	5	21	16	47	31	-
21	n-$C_6H_{13}MgBr$	Me_3CCH_2I	5	67	16	54	-	-
22	n-$C_6H_{13}MgBr$	$Cl(CH_2)_3I$	5	67	16	54	-	-

a. Isolated yields of major products, relative yields determined by G.L.C. analysis, no olefins from β-elimination reactions were detectable.

b. This arises by homo-coupling when Grignard reagent formation is incomplete.

c. No detectable yield.

d. Ambient temperature.

e. Also detected: 4-bromoanisole (37%).

f. Refluxing THF solution.

g. Also detected: anisole (83%), the product of proton quenching of unreacted Grignard reagent.

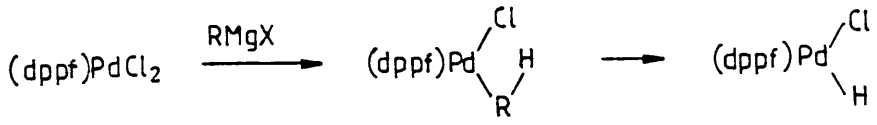
h. No addition of DIBALH.

Runs 1 and 2 demonstrated that a catalysed coupling could occur in the reverse sense (i.e. alkyl iodide/aryl Grignard), in high yield. For a longer chain alkyl iodide (Runs 3-4), elevated temperatures were necessary. However, the cross-coupling did occur in moderate yield (53%), and most importantly, no hexadecene derived from β-elimination was observed.

When the aryl Grignard reagent was replaced by a primary alkylmagnesium (Runs 6-9), the yields improved to 80-90% although increasing the catalyst concentration to 10mol% (Run 7) produced no significant improvement. The coupling of n-hexylmagnesium bromide and n-hexyliodide (Run 11) proceeded in good yield (72%). As expected, with no catalyst present, only the unreacted alkyl iodide was recovered (Runs 5,10,13). The use of the more sterically demanding cyclohexyl iodide (Run 15) or cyclohexylmagnesium bromide (Run 17) gave slightly reduced coupling yields (69% and 63% respectively), and the cyclohexyl-cyclohexyl coupling (Run 18) was lower still (37%). The higher yields for alkyl over aryl, and primary over secondary coupling, showed again that the formation of the diorganopalladium intermediates was susceptible to steric inhibition as required by a penta-coordinated transition state (Section 2.2.2).

In the cases where the product could have arisen from the homocoupling of the Grignard reagent (Runs 11-13,18), it was found that in the absence of added iodide (Runs 14,19), only starting material was recovered. Yields of cross-coupling products for reactions carried out in the absence of DIBALH (Runs 12,16) were consistently lower, implying that addition of the DIBALH saved the loss of approximately

10% of the Grignard reagent from reducing the palladium(II) to palladium(0) (Scheme 19).



Scheme 19

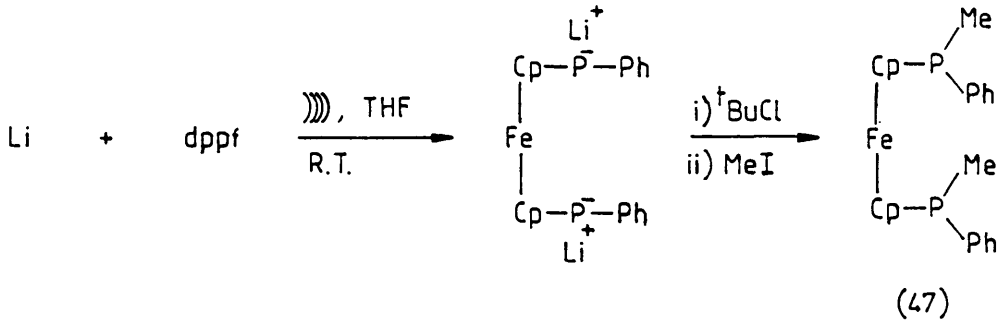
2.6 CATALYST DEVELOPMENT

2.6.1 Introduction

In order to improve the yields of the non-primary couplings, it was necessary to synthesise a less bulky bidentate ligand than dppf. The catalyst chosen was a simple variation on the dppf, 1,1'-bis(methylphenylphosphino)ferrocene (mppf) (47).

2.6.2 Preparation

Initial attempts at preparing the mppf were based on using lithium metal and ultrasound to dephenylate dppf, followed by addition of t-butylchloride and methyl iodide (Scheme 20).

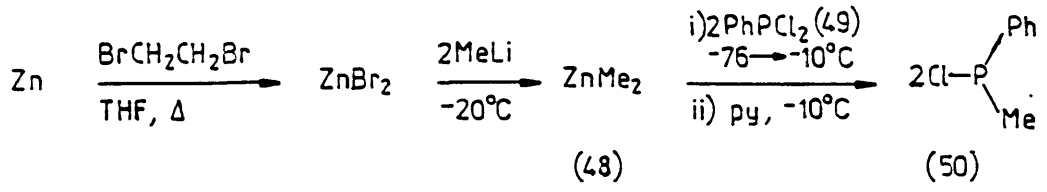


(47)

Scheme 20

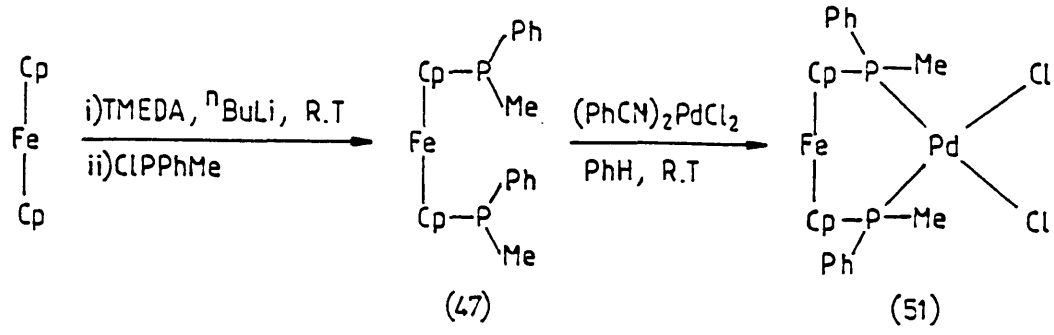
When the same reaction conditions had been applied to triphenylphosphine, diphenylmethylphosphine had been obtained in 87% yield. However, using dppf, only unreacted starting material was recovered, despite trying temperature variations, an argon atmosphere, removal of unreacted lithium (by anaerobic filtration) before the addition of the t-butyl chloride, and adding the methyl iodide at $0^{o}C$.

The mppf was finally prepared by adaptation of the methodology used to synthesise dppf[51]. Preparation of dimethylzinc (48), and subsequent reaction with dichlorophenylphosphine (49), produced chloromethylphenylphosphine (50) (Scheme 21).



Scheme 21

Dilithiation of ferrocene, followed by addition of the phosphine (50), yielded mppf (47), which was added, without purification to a stirred solution of $PdCl_2(PhCN)_2$ (22) in benzene, producing, after recrystallisation, the new palladium compound $PdCl_2$(mppf) (51) (Scheme 22).



(47) (51)

Scheme 22

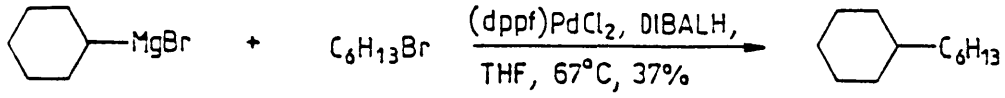
2.6.3 Reactions

The $PdCl_2$(mppf) was used as a replacement catalyst for the $PdCl_2$ (dppf), in a selection of reactions from Table 4. The results (Table 5) show that, as expected, the less-hindered catalyst improved the coupling yields of hindered substrates by up to 15%, while still preventing β-elimination.

Table 5

Run	Reactants		Cat. mol.%	T °C	t h	Products (%)		
	R'MgBr	RI				RR'	RI	R'R'
1	n-C_6H_{13}MgBr	cy-C_6H_{11}I	5	67	16	75	18	-
2	cy-C_6H_{11}MgBr	n-C_6H_{13}I	5	67	16	73	17	-
3	cy-C_6H_{11}MgBr	cy-C_6H_{11}I	5	67	16	48	44	-
4	Me_2CHMgBr	cy-C_6H_{11}I	5	21	16	61	32	-

Finally, an attempt was made to couple an organometallic reagent with an alkyl bromide (Scheme 23).



Scheme 23

Although the yield of the coupled product was only 37% (51% of the unreacted alkyl bromide was recovered), results show that alkyl bromides will undergo oxidative addition to a palladium(0)species. This could further increase the scope and utility of that wide-ranging methodology, the palladium catalysed cross-coupling reaction.

2.7 CONCLUSIONS

2.7.1 General

In a series of standard cross-coupling reactions, it was found that $PdCl_2$(dppf) was a catalyst capable of making the reductive elimination of the coupled products much faster than the normally competing β-elimination. From this investigation and others, it appears that the selectivity and the catalytic activity of palladium complexes with bidentate phosphine ligands is superior to those with monodentate ligands, and is strongly dependent upon the molecular framework of the two diphenylphosphino groups in the ligand. The phosphine ligand that forms a complex having a large P-Pd-P and a small Cl-Pd-Cl angle, accelerates reductive elimination of the diorganopalladium intermediate.

The activity of $PdCl_2$(dppf) has been demonstrated recently by the alkylation of allyl alcohols with Grignard reagents[52-53], cross-coupling of aryl Grignard reagents with a 2-methylthio-oxazoline[54], cross-coupling of an alkenylborane with an alkenyl bromide[55], and reaction of organic halides with carbon monoxide and terminal acetylenes[56].

Alkyl iodides have been found to successfully oxidatively add to a "(dppf)Pd^0" species generated <u>in situ</u> from the action of the reducing agent DIBALH on the complex $PdCl_2$(dppf). Coupling of the alkyl iodides with alkyl Grignard reagents under these conditions, led to a new methodology for unsymmetrical sp^3-sp^3 coupling, a process which is not readily achieved by conventional organic synthetic methods.

Yields for secondary-primary and secondary-secondary coupling reactions were significantly improved by employing a less sterically demanding bidentate ligand, in the synthesis of a new palladium catalyst, $PdCl_2$(mppf).

2.7.2 <u>Why palladium catalysed cross-coupling?</u>

There are relatively few basic reaction types that generate a new carbon-carbon bond without adjacent functionality, although this is one of the most critical operations in the synthesis of organic molecules. Transition metals, particularly nickel and palladium, have been effective in catalysing the cross-coupling of organometallic reagents with organic halides and related electrophiles[57-62].

Although there have been advances in the copper(I) catalysed cross-coupling reaction in recent years, many problems still persist[63]. For example, the copper-promoted coupling of two different alkenyl or aryl groups is very slow and often involves extensive homocoupling, and the reaction of alkynylcoppers with organic halides is so slow that drastic reaction conditions are required.

Palladium complexes are not only effective catalysts, but also, in many cases have a superiority over the nickel analogues, in catalytic activity, selectivity of product formation, and capability of use of a wide range of organometallics[59,61,64]. For example[62], palladium catalysts show greater scope than the nickel catalysts for the cross-coupling of an unsaturated organometallic (R^1M) and an unsaturated halide (R^2X) (Table 6).

Table 6

R^1 \ R^2	Aryl		Alkenyl		Alkynyl	
	Pd	Ni	Pd	Ni	Pd	Ni
Aryl	+[a]	+	+	+	+	-[b]
Alkenyl	+	+	+	-[c]	+	-[b]
Alkynyl	+	-[b]	+	-[d]	-[d]	-[b]

a) The + sign indicates satisfactory results.

b) The product yield is generally very low.

c) Stereochemical scrambling occurs.

d) Statistical mixtures of three diynes are formed in high combined yields.

2.7.3 Future developments?

All the organometallic species used during this research were Grignard reagents. In order to extend the scope of the alkyl-alkyl coupling reactions, it will be necessary to use metals which are compatible with a much wider range of functionality, e.g. Zn,Sn.

Asymmetric carbon-carbon bond-forming reactions are of great significance for the synthesis of optically active compounds, and the use of chiral transition metal catalysts for such reactions has recently attracted considerable attention[65]. Asymmetric cross-coupling of secondary alkyl Grignard reagents with alkenyl and alkynyl halides has been effected by chiral phosphine-palladium catalysts and is now recognised to provide an efficient route to the synthesis of optically active olefins[60,66], allylsilanes[67-69] and propargyl-silanes[70]. With these results in mind, it would be interesting to study the chiral phosphine-palladium catalysed cross-coupling of alkyl metals with alkyl halides.

Recently, palladium complexes with ferrocenyl thio - and selenoether ligands have been reported[71], and there appears to be a wide range of variations on the ferrocenyl unit that might be of interest. For example, replacement of all four phenyl groupls in $PdCl_2$(dppf) by methyl groups, may produce a catalyst which would allow secondary, and perhaps even tertiary alkyl substrates to couple in good yields.

CHAPTER 3: EXPERIMENTAL

3.1 GENERAL INFORMATION

Melting points were determined on a Kohfler hot-stage apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer with a polystyrene ($1602cm^{-1}$) reference.

Proton NMR were recorded at 60MHz on a Varian EM-360A spectrometer, at 90MHz on a Perkin-Elmer R32 spectrometer and at 250MHz on a Bruker WH-250 FT spectrometer, with tetramethylsilane as an internal standard. Apparent J values and multiplicities are recorded: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Gas chromatographs were run on a Varian Vista 6000 chromatograph, fitted with a chromosorb WHP 80-100 mesh column (liquid phase OV101) linked to a Varian Vista CDS 401 data handling station.

All solvents and reagents were purified by standard methods[72]. THF and diethyl ether were sodium dried and then distilled from sodium benzophenone ketyl immediately before use. Most alkyl halides (including methylene chloride) were purified by passage through a short column of neutral alumina (Brockmann grade 1) after distillation. Petroleum ether was that fraction boiling in the range $40-60^{o}C$. Solvents were routinely degassed before use, and removed under reduced pressure on a Buchi rotary evaporator.

Column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh). Samples were preadsorbed onto silica for chromatography in the

proportions 1:3:15, sample : silica for preadsorption : silica for column (w/w).

Unless otherwise stated, all reactions were carried out under anaerobic conditions achieved by the use of flame-dried apparatus, and a rigorously dried and deoxygenated nitrogen atmosphere.

Anaerobic transfer refers to the slow transfer of a solution from one vessel to another, through a steel catheter, under a positive nitrogen gas pressure.

All temperatures quoted are in degrees centigrade (^{o}C).

Mass spectra and microanalyses were performed by the respective laboratories at Imperial College.

3.2 DATA FOR SECTION 2.3

4-Methoxypropiophenone[33]

4-Hydroxypropiophenone (15.02g, 0.1mol), methyl iodide (42.58g, 18.7ml, 0.3mol) and potassium carbonate (14g, 0.1mol) were refluxed for six hours in acetone (300ml). The acetone and any excess methyl iodide were removed under reduced pressure. The residual white solid was dissolved in water and extracted with ethyl acetate. After evaporation of the ethyl acetate, the remaining yellow liquid was distilled under reduced pressure, yielding 4-methoxypropiophenone (9.4g, 62mmol, 63%), b.p.$_{14}$ 144-6^{o}C (lit.[73] 145-7^{o}C at 14mmHg), δ_H ($CDCl_3$, 90MHz) 1.1-1.3 (3H, t, J 7Hz, $CH_2\underline{CH}_3$), 2.8-3.1 (2H, q, J 7Hz, $\underline{CH}_2CH_3$), 3.9 (3H, s, O<u>Me</u>), 6.9-8.1 (4H, m, Ar<u>H</u>).

4-n-Propylanisole (14)[74]

A mixture of 4-methoxypropiophenone (8.2g, 0.05mol), potassium hydroxide (9.5g, 0.17mol, 3.2eq), 85% hydrazine (6.8ml, 3.6eq) and ethylene glycol (67.6ml) was refluxed for ten hours. The yellow solution was allowed to cool, diluted with distilled water (70ml) and then slowly poured into 6N HCl (40ml). After extraction with diethyl ether (5x50ml), drying over magnesium sulphate ($MgSO_4$) and filtration, the solvent was removed under reduced pressure. Distillation of the resulting yellow liquid, gave compound (14) (1.25g, 8.3mmol, 17%), b.p.$_{10}$ 85-6°C (lit.[75] 86.5°C at 10mmHg), δ_H ($CDCl_3$, 60MHz) 0.9 (3H, t, J 7Hz, CH_2-C$\underline{H}_3$), 1.6 (2H, m, C$\underline{H}_2$-CH_3), 2.5 (2H, t, J 8Hz, Ar-C$\underline{H}_2$), 3.7 (3H, s, O$\underline{Me}$), 7.0 (4H, m, Ar-$\underline{H}$).

4-isopropylanisole (15)

4-Isopropylphenol (13.62g, 0.1mol) was treated as for 4-hydroxypropiophenone (with the inclusion of a 2M NaOH wash of the ethyl acetate layer, in order to remove any unreacted starting material) to yield compound (15) (10.66g, 71mmol, 71%), b.p.$_{30}$ 102-3°C (lit.[76] 95-6°C at 19mmHg), δ_H($CDCl_3$, 60 MHz) 1.2 (6H, d, J 6Hz, $\underline{Me}_2$CH), 2.8 (1H, m, $Me_2C\underline{H}$), 3.7 (3H, s, O$\underline{Me}$), 7.0 (4H, m, Ar-$\underline{H}$).

Tetrakis(triphenylphosphine)palladium(0) (20)[34]

Palladium(II)chloride (1.00g, 5.64mmol), triphenylphosphine (7.39g, 28.2mmol) and dry DMSO (68ml, redistilled from CaH_2) were added to a 250ml flask equipped with a condenser and a magnetic stirrer, under an atmosphere of dry nitrogen. The solution was degassed and heated to 135°C, during which time the yellow solution became orange and

clear. The heat was removed and hydrazine hydrate (1.12g, 1.1ml, 22.4mmol) was added immediately, causing a slight effervescence. The solution was then placed in a warm water bath and the contents of the flask were allowed to come to room temperature overnight. The yellow crystals which formed, were filtered under nitrogen, washed (2x5ml of ethanol, 2x10ml of diethyl ether) and dried in vacuo. The PdL_4 (5.94g, 5.14mmol, 91%) was stored under nitrogen, at $0^{o}C$ in light free conditions, m.p. 114-5^{o}C (dec.) (lit.[34] 116^{o}C).

Preparation of other palladium catalysts[35,36]

$PdL_2(dppe) \longrightarrow PdL_4$ (leq.) + dppe (leq.)

$PdCl_2$ (dppe) $\longrightarrow PdCl_2$ (leq.) + dppe (leq.)

$PdCl_2L_2 \longrightarrow PdCl_2$ (leq.) + L (2eq.)

1,1'-Bis(diphenylphosphino)ferrocene (21)[77]

A mixture of N,N,N',N'-tetramethylethylenediamine (6.3ml, 4.82g, 41.6mmol) and a 15.20% (c.a. 1.63N) solution of n-butyllithium in hexane (25.2ml, 41.1mmol) was added with stirring, to a solution of ferrocene (3.72g, 20mmol) in dry cyclohexane (120ml), under nitrogen, in a 500ml, three-neck flask, equipped with a stirrer, nitrogen inlet and reflux condenser. The orange-red solution was stirred under nitrogen for a further 4.5 hours at room temperature (during which time the solution became cloudy, indicating the formation of a lithium-ferrocene salt), and chlorodiphenylphosphine (7.6ml, 40.8mmol) in cyclohexane (8ml) was added dropwise over a 20 minute period, with constant stirring. During this time, the temperature of the solution rose to 50^{o}C. The reaction mixture was further stirred under nitrogen for 2 hours, and then carefully quenched with distilled water (8ml). The supernatent cyclohexane layer was decanted from the

orange-yellow solid, which was washed with distilled water (3x20ml) and dissolved in hot dioxan (32ml). Cooling the dioxan solution produced an orange solid which was purified by repeated recrystallisation from 1/2 benzene/hexane, to give orange crystals of compound (21) (4.1g, 7.4mmol, 37%), m.p. 182-3°C (lit.[77] 182-4°C), $\nu_{max.}$ (nujol) 1475, 1430, 1165, 828, 745, 698 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 4.1 (4H, m, 4xP-C-CH-CH), 4.3 (4H, m, 4xP-C-CH-CH), 7.2 (20H, m, Ar-H); (Found: C, 73.45; H, 5.01. $C_{34}H_{28}FeP_2$ requires C, 73.66; H, 5.09%).

Preparation of chlorobis(benzonitrile)palladium(II) (23)[78]

Palladium(II)chloride (2g, 11.28mmol) was suspended in benzonitrile (50ml), and the mixture was warmed to 100°C for 20 minutes. While warm, the dark red solution was filtered, and the filtrate was poured into petroleum ether (300ml). The pale yellow precipitate formed was filtered, washed with additional quantities of petroleum ether and dried in vacuo, to give compound (23) (3.965g, 92%), m.p. 129-130°C (lit.[79] 131°C).

$PdCl_2$(dppf) (11)[80]

To a suspension of dichlorobis(benzonitrile)palladium(II) (0.5544g, 1.0mmol) in benzene (20ml), was added with stirring a solution of dppf (0.383g, 1.0mmol) in hot benzene (20ml). The solution was stirred for 12 hours at room temperature, and the red-brown precipitate formed was collected, dried in vacuo and recrystallised from chloroform, to yield compound (11) (0.6880g, 0.94mmol, 94%), m.p. 262-3°C (dec.) (lit.[80] 265°C), $\nu_{max.}$ (nujol) 1480, 1435, 1100, 690cm^{-1}; δ_H ($CDCl_3$, 250MHz) 4.15-4.25 (4H, m, 4xP-C-CH-CH), 4.32-4.43 (4H, m, 4xP-C-CH-CH), 7.27-7.52 (10H, m, Ar-H), 7.70-8.02 (10H, m, Ar-H).

General cross-coupling procedure

The previously purified alkyl halide (1 eq.) was added to rigorously dried magnesium turnings (1.5 eq.) in THF (20ml). The solution was refluxed until formation of the Grignard reagent was complete (2-7 hours). The Grignard reagent (1.1 eq.) was added, via a (filter paper covered) filter stick, to a well stirred solution of 4-iodoanisole (1 eq.) and the palladium catalyst (2mol%) in diethyl ether (20ml), at -78°C. The solution was allowed to come to room temperature, and was stirred, under nitrogen, for 16 hours. The products were analysed by GLC, or separated by column chromatography and purified by distillation or recrystallisation.

3.3 DATA FOR SECTION 2.4

The following three compounds were synthesised by the cross-coupling procedure outlined in the preceding section.

1-Anisyl-3-methylbutane

Colourless liquid (94%), b.p.$_6$ 105-6°C (lit.[81] 121°C at 14mmHg), δ_H ($CDCl_3$, 60MHz) 0.8 (6H, d, J 6Hz, Me_2CH), 1.4 (3H, m, Me_2CH and Me_2CH-CH_2), 2.5 (2H, t, J 8Hz, $Ar-CH_2$), 3.6 (3H, s, OMe), 6.9 (4H, m, Ar-H)

1-Cyclohexyl-4-methoxybenzene

White solid (96%), m.p. 58-9°C, δ_H ($CDCl_3$, 60MHz) 1.3-2.1 (10H, m, cy-c_5H_{10}), 2.4 (1H, m, Ar-CH), 3.8 (3H, s, OMe), 7.0 (4H, m, Ar-H); (Found: C, 81.84; H, 9.72. $C_{13}H_{18}O$ requires C, 82.06; H, 9.53%).

1-Anisyl-2,2-dimethylpropane

Colourless liquid (87%), b.p.$_{0.8}$ 60-61°C (lit.[82] 49-50°C at 0.3mmHg), δ_H ($CDCl_3$, 60MHz) 0.9 (9H, s, $\underline{Me}_3$ C), 2.4 (2H, s, Ar-C$\underline{H}_2$), 3.7 (3H, s, O$\underline{Me}$), 6.9 (4H, m, Ar-$\underline{H}$).

Isocholesteryl acetates[37]

Commercial 'lanosterol' (50g) in pyridine (50ml) and acetic anhydride (200ml) was heated on a steam bath for 3 hours, and then left to cool overnight. The solution was poured into ice-water (650ml) and the resulting yellow precipitate was filtered off and recrystallised from ethyl acetate-water, to afford the white solid isocholesteryl acetate (42.9g), m.p. 124-7°C (lit.[37] 125-130°C).

Bromination of isocholesteryl acetate[37]

A solution of isocholesteryl acetate (30g) in diethyl ether (300ml), was treated over a 30 minute period with a solution of bromine (3ml) in glacial acetic acid (162ml), the temperature being maintained between 0 and 5°C by means of an ice bath. The mixture was left overnight at room temperature, during which time a precipitate appeared. The mixture was filtered to yield a white solid, which was recrystallised from benzene-methanol to give compound (28) (1.9g), m.p. 175.5-176.5°C (lit.[37] 176-7°C), δ_H ($CDCl_3$, 250MHz) 0.71 (3H, s, 13β-C$\underline{H}_3$), 0.88 (9H, s, 4α-, 4β-, and 14α-C$\underline{H}_3$), 1.01 (3H, s, 10β-C$\underline{H}_3$), 1.85 (3H, s, 25-C$\underline{H}_3$), 2.01 and 2.07 (each 3H, s, 25-C$\underline{H}_3$ and acetate), 4.18 (1H, d, $\underline{J}$ 10Hz, 24-$\underline{H}$), 4.46 (1H, m, 3α-$\underline{H}$). The solvent was removed under reduced pressure, and recrystallisation of the resulting solid, from benzene-methanol, produced compound (29) (11.7g), m.p. 165-6°C (lit.[37] 166-7°C), the C-24 stereoisomer of compound (28).

Debromination with zinc dust[37]

Zinc dust (20g) was added, over a period of 4 hours, to a refluxing solution of the dibromides (28) and (29) (10g) in benzene-methanol (450ml; 5:1 v/v). The mixture was filtered and the residual zinc was washed thoroughly with boiling benzene. The combined filtrates were washed with water and the solvent was removed under reduced pressure. Crystallisation from benzene-methanol afforded compound (26) (4.22g, 57%), m.p. 129-30°C (lit.[37] 129-30°C), δ_H ($CDCl_3$, 250MHz) 0.68 (3H, s, 13β-C<u>H</u>$_3$), 0.84 (9H, s, 4α-, 4β-, and 14α-C<u>H</u>$_3$), 0.99 (3H, s, 10β-C<u>H</u>$_3$), 1.61 and 1.69 (each 3H, s, 25-C<u>H</u>$_3$), 2.02 (3H, s, acetate), 4.50 (1H, m, 3α-<u>H</u>), 5.05 (1H, t, <u>J</u> 6Hz, 24-<u>H</u>).

Lanosterol (24)[37]

The acetate (26) (3.5g, 7.4mmol) was hydrolysed by refluxing with 10% ethanolic potassium hydroxide (120ml) for 2 hours. The orange solution was diluted with water, extracted with diethyl ether, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Crystallisation from chloroform-methanol gave lanosterol (24) as a white solid (2.2g, 5.2mmol, 70.3%), m.p. 142-3°C (lit.[37] 140°C).

Attempted preparation of lanosteryl bromide (30)[83]

A solution of carbon tetrabromide (0.78g, 2.35mmol) in acetonitrile (3ml) was added to triphenylphosphine (3.7g, 14.08mmol) in acetonitrile (3ml), by anaerobic transfer. The solution was stirred at 45-50°C for 2 hours, and then lanosterol (1g, 2.35mmol) was added. The problem of the low solubility of lanosterol in acetonitrile was overcome by the addition of THF (10ml). The solution was stirred overnight at 50-60°C. After removal of the solvent, the

residue was repeatedly extracted with petroleum ether and the organic layer was washed with brine, dried over $MgSO_4$ and passed through a thin pad of silica, in order to remove any triphenylphosphine oxide, to yield compound (31), δ_H ($CDCl_3$, 60MHz) as for compound (26), save for loss of signals at 2.02 and 4.50, and reduction of signal at 0.84 to 3H (14α-$C\underline{H}_3$), m/z 408 ($\underline{M}^+$).

Mesylation of lanosterol

Lanosterol (2g, 4.7mmol) was dissolved in dichloromethane (75ml) and stirred, under nitrogen, in an ice bath. To this solution was added mesyl chloride (0.4ml, 0.6g, 5.2mmol) and triethylamine (0.5g, 0.75ml, 5.2mmol). The solution was allowed to warm to room temperature and the reaction was followed by T.L.C. The products were extracted using dichloromethane and water, and the organic layer was washed with dilute sodium bicarbonate solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting solid was purified by column chromatography to yield lanosteryl mesylate, δ_H ($CDCl_3$, 90MHz) as for compound (26), save that the acetate signal at 2.02 was replaced by one at 3.0 (3H, s, $-OSO_2C\underline{H}_3$), m/z 504 ($\underline{M}^+$), 489, 409.

Refluxing the mesylate (2g, 4mmol) with lithium bromide (0.38g, 4.4mmol, 1.leq.) in THF (40ml) for 16 hours, produced triene (31) only.

Preparation of 1-iodo-4-pentanone (34)[84]

1-Chloro-4-pentanone ethylene ketal (32) (3.0ml, 3.292g, 20mmol) was added to sodium iodide (7.5g, 50 mmol, 2.5eq.) in pre-dried (over K_2CO_3) and degassed acetone (40ml), and the solution was refluxed for 36 hours. The acetone was removed under reduced pressure, and the residue was extracted with diethyl ether/water. The diethyl ether

layer was washed with 0.1N sodium thiosulphate, dried over $MgSO_4$ and distilled, yielding compound (34) (2.313g, 10.9mmol, 55%), b.p.$_3$ 57°C (lit.[84] 94°C at 14mmHg), $\nu_{max.}$ (neat) 1715cm^{-1} (C=O); δ_H ($CDCl_3$, 60MHz) 1.80-2.05 (2H, m, I-CH_2-$\underline{CH}_2$), 2.15 (3H, s, $\underline{Me}$CO), 2.55 (2H, t, $\underline{J}$ 7Hz, MeCO-$\underline{CH}_2$), 3.20 (2H, t, $\underline{J}$ 7Hz, I-$\underline{CH}_2$).

Preparation of 1-iodo-4-pentanone ethylene ketal (33)[84]

1-Iodo-4-pentanone (6.4g, 30mmol) in benzene (75ml) was treated with ethylene glycol (5ml, 90mmol) and p-toluenesulphonic acid (0.57g, 3mmol) at reflux, for 12 hours. The dark red solution was cooled, diluted with 5% sodium hydrogen carbonate (120ml) and extracted with diethyl ether. The combined ethereal extracts were washed with 0.1N sodium thiosulphate (40ml), dried over $MgSO_4$ and the solvent was removed. Distillation produced a colourless liquid, compound (33) (7.3g, 28.5mmol, 95%), b.p.$_3$ 68°C (lit.[84] 76°C at 5mmHg), $\nu_{max.}$ (neat) 1455cm^{-1} (C-O); δ_H ($CDCl_3$, 60MHz) 1.3 (3H, s, $\underline{Me}$C), 1.8 (4H, m, I-CH_2-$\underline{CH}_2$-$\underline{CH}_2$), 3.2 (2H, t, $\underline{J}$ 7Hz, I-$\underline{CH}_2$), 3.9 (4H, s, O-$\underline{CH}_2$-$\underline{CH}_2$-O).

Attempted cross-coupling using ketal (33)

The general cross-coupling procedure was followed, except that the alkyl halide used was the ketal (33). The Grignard reagent formed readily, but after 30 minutes (at THF reflux, room temperature or 0°C), a precipitate appeared. This was found to be the homocoupled product 2,9-decanedione bis(ethylene ketal) (37) (1.55g, 6.0mmol, 92%), $\nu_{max.}$ (nujol) 1450cm^{-1} (C-O); δ_H ($CDCl_3$, 60MHz) 1.2-1.6 (14H, m, 2x$\underline{Me}$C and [$\underline{CH}_2$]$_4$), 1.8 (4H, t, $\underline{J}$ 8Hz, 2x$\underline{CH}_2$ [CH_2]$_4$), 3.9 (4H, s, O-$\underline{CH}_2$-$\underline{CH}_2$-O); $\underline{m/z}$ 258 ($\underline{M}^+$), 243, 87.

Cross-Coupling of 1-chloro-4-pentanone ethylene ketal (32) with 4-iodoanisole (13)

The general cross-coupling procedure (section 3.2) was repeated, using the ketal (32) and the aryl halide (13). The previously used magnesium turnings were replaced by magnesium powder (0.5mesh). Distillation of the product yielded the colourless liquid 1-(4-methoxyphenyl)-4-pentanone ethylene ketal (38) (89%), b.p.$_4$ 217-8°C, $\nu_{max.}$ (neat) 1600cm^{-1} (C=C); δ_H ($CDCl_3$,250MHz) 1.30 (3H, s, MeC), 1.66-1.70 (4H, m, Ar-CH_2-CH_2-CH_2), 2.53-2.59 (2H, t, J 7.8Hz, Ar-CH_2), 3.78 (3H, s, OMe), 3.88-3.94 (4H, m, O-CH_2-CH_2-O), 6.80-7.11 (4H, m, Ar-H); m/z 236 (M^+), 221, 135, 134, 121, 91, 87, 77; (Found: C, 70.89; H, 8.73. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

3.4 DATA FOR SECTION 2.5

Reductive coupling of 1-bromohexadecane (41)[43]

A mixture of 1-bromohexadecane (7.65ml, 7.63g, 25mmol), sodium hydroxide (7.52g, 188mmol) and palladium(II)chloride (0.44g, 2.5mmol) in methanol (16ml) containing 98% $H_2NNH_2.H_2O$ (1.1ml, 1.13g, 22.5mmol), was refluxed with stirring, under nitrogen, for 6 hours. The residual metal was filtered and washed with hexane, and subsequently with water. The organic layer was separated from the aqueous layer, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Careful distillation of the reaction mixture yielded three colourless liquids.

1-Hexadecene (44) (0.4g, 1.8mmol, 7%), b.p.$_6$ 138-9°C (lit.[85] 284°C at 760mmHg), δ_H ($CDCl_3$, 60MHz) 0.9 (3H, m, CH_3-CH_2),

1.3 (24H, br.s., ($C\underline{H}_2$)$_{12}$), 2.0-2.1 (2H, m, $C\underline{H}_2$-CH=CH_2), 4.9-5.0 (2H, m, CH=$C\underline{H}_2$), 5.7-6.0 (1H, m, $C\underline{H}$=CH_2); $\underline{m/z}$ 224 ($\underline{M}^+$).

Hexadecane (43) (1.75g, 7.7mmol, 31%), b.p.$_6$ 166-8°C (lit.[86] 287°C at 160mmHg), δ_H ($CDCl_3$, 60MHz) 0.9 (6H, m, 2x$C\underline{H}_3$), 1.25 (28H, br.s, ($C\underline{H}_2$)$_{14}$); $\underline{m/z}$ 226 ($\underline{M}^+$).

1-Bromohexadecane (41) (0.08g, 0.26mmol, 1%), b.p.$_6$ 176-8°C (lit.[87] 193-6°C at 14mmHg), δ_H ($CDCl_3$, 60MHz) 0.9 (3H, m, $C\underline{H}_3$-CH_2), 1.3 (28H, br.s, ($C\underline{H}_2$)$_{14}$), 3.5 (2H, t, $\underline{J}$ 6Hz, $C\underline{H}_2$-Br); $\underline{m/z}$ 306 ($\underline{M}^+$), 304.

Recrystallisation of the residue from diethyl ether gave dotriacontane (42) (6.2g, 13.8mmol, 55%) m.p. 73-4°C (lit.[88] 74-5°C), δ_H ($CDCl_3$, 60MHz) 0.9 (6H,s, 2x$C\underline{H}_3$), 1.25 (60H, br.s, ($C\underline{H}_2$)$_{30}$); $\underline{m/z}$ 450 ($\underline{M}^+$).

1-Iodohexadecane (45)[38]

1-Bromohexadecane (6.1ml, 6.1g, 20mmol) was added to sodium iodide (7.5g, 50mmol, 2.5eq.) in acetone (40ml) and the solution was refluxed for 16 hours. The sodium bromide was filtered off, and the acetone was removed under pressure. The product was isolated by the same procedure used in the preparation of compound (33) (Section 3.3), to yield compound (45) (7.01g, 19.9mmol, 99%), b.p.$_3$ 176-7°C (lit.[89] 211°C at 15mmHg), δ_H ($CDCl_3$, 60MHz) 0.9 (3H, m, $C\underline{H}_3$), 1.3 (28H, br.s, ($C\underline{H}_2$)$_{14}$), 3.2 (2H, t, $\underline{J}$ 7Hz, $C\underline{H}_2$-I); $\underline{m/z}$ 352 ($\underline{M}^+$).

1-Bromo-3-phenylpropane (47)[50]

Hydrocinnamylalcohol (10ml, 10g, 74mmol) was placed in a 25ml round-bottomed flask equipped with a stirrer, and the flask was placed in an ice-salt bath. Phosphorous tribromide (2.6ml, 7.5g, 27.7mmol) was added slowly (over a period of 1 hour), in order to keep the solution temperature below $0^{o}C$. The cooling bath was removed and stirring was continued for 16 hours while the reaction mixture reached room temperature. The reaction was quenched with distilled water, extracted with petroleum ether, dried over $MgSO_4$, filtered through a thin silica pad and the solvent was removed under reduced pressure. Distillation of the crude product yielded compound (47) (7.63g, 38mmol, 52%), b.p.$_{760}$ 218-9^{o}C (lit.[90] 219-220^{o}C at 760mmHg), δ_H ($CDCl_3$, 60MHz) 1.9-2.1 (2H, m, CH_2-C$\underline{H}_2$-CH_2), 2.6 (2H, t, $\underline{J}$ 6Hz, Ar-C$\underline{H}_2$), 3.2 (2H, t, $\underline{J}$ 7Hz, C$\underline{H}_2$-Br), 7.0-7.2 (5H, m, Ar-$\underline{H}$).

Modified cross-coupling procedure

The purified alkyl or aryl bromide (1eq.) was added to rigorously dried magnesium powder (1.5eq.) in THF (20ml). The solution was refluxed until formation of the Grignard reagent was complete (2-7 hours). The Grignard reagent was anaerobically transferred, through the modified filter stick, described earlier, to a well stirred solution of the alkyl halide (1eq.), $PdCl_2$ (dppf) (a mol%) and DIBALH (2.3xamol%), in THF (20ml). Previously, the DIBALH had been added to a solution of the halide and the catalyst. When the solution had been stirred at the required temperature for a specified length of time, the reaction mixture was quenched with 2.8M aq.NH_4Cl. Diethyl ether was added, followed by a small amount (0.5ml) of 2M HCl and the solution was extracted with distilled water and brine. The organic layer was washed with $NaHCO_3$. The ethereal extracts were combined,

dried over $MgSO_4$, filtered and the solvent was removed under reduced pressue. Petroleum ether was added and the solution was filtered through an alumina pad. The solvent was removed once again and the products were separated and purified. The following compounds were similarly synthesised.

1-Methoxy-4-methylbenzene

Colourless liquid, b.p.$_{760}$ 175-6°C (lit.[91] 174-5°C at 760mmHg), δ_H ($CDCl_3$, 60MHz) 2.3 (3H, s, Ar-Me), 3.8 (3H, s, OMe), 6.9-7.1 (4H, m, Ar-H); m/z 122 (M^+), 107, 92.

1-Hexadecyl-4-methoxybenzene

White solid (from ethanol), m.p. 41.5-42°C, $\nu_{max.}$ (nujol) 1610, 1510, 1380, 1300, 1175, 1040cm^{-1}; δ_H ($CDCl_3$, 250MHz) 0.85-0.90 (3H, t, J 6.6Hz, CH_3-CH_2), 1.25 (26H, m, $(CH_2)_{13}$), 1.55 (2H, m, Ar-CH_2-CH_2), 2.50-2.57 (2H, t, J 7.7Hz, Ar-CH_2-CH_2), 3.78 (3H, s, OMe), 6.80-7.25 (4H, m, Ar-H); m/z 332 (M^+), 121; (Found: C, 83.26; H, 12.29. $C_{23}H_{40}O$ requires C, 83.07; H, 12.12%).

1-Phenylpentane

Colourless liquid, b.p.$_{760}$ 203-4°C (lit.[92] 205°C at 760mmHg), δ_H ($CDCl_3$, 250MHz) 0.85-0.90 (3H, t, J 6.8Hz, CH_3-CH_2), 1.2-1.3 (4H, m, $(CH_2)_2$), 1.55 (2H, m, Ar-CH_2-CH_2), 2.55-2.60 (2H, t, J 7.9Hz, Ar-CH_2-CH_2), 7.2-7.3 (5H, m, Ar-H); m/z 148 (M^+).

1-Phenylnonane

Colourless liquid, b.p.$_5$ 126-7°C (lit.[93] 282°C at 760mmHg), δ_H ($CDCl_3$, 250MHz) 0.85-0.90 (3H, t, J 6.7Hz, CH_3-CH_2), 1.25-1.35 (12H, m, $(CH_2)_6$), 1.55-1.65 (2H, m, Ar-CH_2-CH_2),

2.57-2.62 (2H, m, J 7.7Hz, Ar-C$\underline{H}_2$-CH$_2$), 7.15-7.30 (5H, m, Ar-$\underline{H}$); m/z 204 ($\underline{M}^+$), 175, 133, 119, 105, 92, 91.

1-Phenylnonadecane

Colourless liquid, b.p.$_{0.2}$ 155°C (lit.[94] 419°C at 760mmHg), δ_H (CDCl$_3$, 250MHz) 0.85-0.90 (3H, t, J 6.6Hz, C$\underline{H}_3$-CH$_2$), 1.25-1.30 (32H, m, (C$\underline{H}_2$)$_{16}$), 1.6 (2H, m, Ar-CH$_2$-C$\underline{H}_2$), 2.6 (2H, t, J 7.7Hz, Ar-C$\underline{H}_2$-CH$_2$), 7.15-7.25 (5H, m, Ar-$\underline{H}$); m/z 344 ($\underline{M}^+$).

n-Dodecane

Colourless liquid, b.p.$_{10}$ 90-1°C (lit.[95] 214°C at 760mmHg), m/z 170 ($\underline{M}^+$).

1-Cyclohexylhexane

Colourless liquid, b.p.$_{760}$ 218-9°C (lit.[92] 88-90°C at 15mmHg), m/z 168 ($\underline{M}^+$), 111, 97, 84, 82, 57; (Found: C, 85.81; H, 14.19. $C_{12}H_{24}$ requires C, 85.63; H, 14.37%).

Bicyclohexyl

Colourless liquid, b.p.$_{760}$ 228-9°C (lit.[96] 99-100°C at 9mmHg), m/z 166 ($\underline{M}^+$), 125, 111, 99, 97, 85, 83, 82.

1-Cyclohexyl-1-methylethane

Colourless liquid, b.p.$_{760}$ 151-3°C (lit.[97] 155°C at 760mmHg), δ_H (CDCl$_3$, 60MHz) 0.8-0.9 (6H, d, J 6Hz, $\underline{Me}_2$CH), 1.0-1.2 (10H, m, cy-C$_5\underline{H}_{10}$), 1.6-1.8 (1H, m, Me$_2$C$\underline{H}$); m/z 126 ($\underline{M}^+$), 111, 83.

1-Chlorononane

Colourless liquid, b.p.$_{760}$ 202-3°C (lit.[98] 202°C at 760mmHg),

δ_H ($CDCl_3$, 90MHz) 0.8-1.0 (3H, t, J 7Hz, $C\underline{H}_3CH_2$), 1.2-1.4 (14H, m, $(C\underline{H}_2)_7$), 3.4-3.6 (2H, t, J 7Hz, $ClC\underline{H}_2$); m/z 154 ($\underline{M}^+$), 162.

2,2-Dimethylnonane

Colourless liquid, b.p.$_{760}$ 174-6°C (lit.[99] 177°C at 760mmHg), δ_H ($CDCl_3$, 60MHz) 0.8 (9H, s, $\underline{Me}_3C$), 0.9-1.0 (3H, t, J 7Hz, $C\underline{H}_3$-CH_2), 1.1-1.2 (12H, m, $(C\underline{H}_2)_6$); m/z 156 ($\underline{M}^+$).

3.5 DATA FOR SECTION 2.6

Diphenylmethylphosphine

THF (8ml) was added to triphenylphosphine (2.623g, 10mmol) and finely chopped lithium wire (0.278g, 40mmol) under an argon atmosphere, in a 50ml flask. The contents were stirred for 3 hours at room temperature, during which time the solution became dark red. After the addition of t-butylchloride (1.1ml, 0.926g, 10mmol), the solution was stirred at 50°C for 30 minutes and methyl iodide (0.62ml, 1.419g, 10mmol) was added, which caused the red colour to disappear. The resulting colourless solution was filtered, to remove any unreacted lithium, and concentrated under reduced pressure. Distillation yielded diphenylmethylphosphine as a colourless liquid (1.742g, 8.7mmol, 87%), b.p.$_6$ 132-3°C (lit.[100] 284°C at 760mmHg), δ_H ($CDCl_3$, 60MHz) 1.5-1.6 (3H, d, J 8Hz, Me), 7.1-7.3 (10H, m, Ar-H).

When the same reaction conditions were applied to dppf (22), only unreacted starting material was recovered, despite the additional usage of an ultrasound sonicator[101-102].

Chloromethylphenylphosphine (51)[103]

To zinc powder (6.02g, 92mmol, 100 mesh) in a 250ml three-neck flask, was added THF (66ml) and 1,2-dibromoethane (8ml, 17.3g, 92mmol). The solution was stirred for 2 hours, at reflux, under nitrogen, during which time the greater part of the zinc was consumed. The resulting grey solution was cooled to -20°C and methyllithium (118ml, 4.05g, 0.184mol, 2eq.) was slowly added. During this time, the solution temperature was maintained at about -20°C. The organozinc was added dropwise, through a filter stick, to dichlorophenylphosphine (50) (25ml, 33g, 0.184mol) in ether (93ml), stirring at -76°C. The cloudy solution was slowly allowed to warm to -10°C. Pyridine (88ml) was added and the stirring was continued at -10°C for 16 hours. The precipitate was filtered, washed with benzene and the filtrate was concentrated under reduced pressure. The resulting red oil was twice distilled under vacuum, producing a yellow liquid, which on further distillation yielded chloromethylphenylphosphine (51) as a colourless liquid (3.3g, 21mmol, 12%), which became yellow unless stored at 0°C, b.p.$_5$ 65-6°C (lit.[104] 106-110°C at 30mmHg), δ_H ($CDCl_3$, 60MHz) 1.7-1.9 (3H, d, J 10Hz, Me), 7.2-7.8 (5H, m, Ar-H).

1,1-Bis(methylphenylphosphino)ferrocene (mppf) (48)

Chloromethylphenylphosphine (2g, 12.78mmol) was utilised to prepare mppf (48), following the procedure used to synthesise dppf (section 3.2). The product obtained was a mixture of mppf and ferrocene (21), m/z 430 (M^+), 415, 308, 293, 186.

$PdCl_2$(mppf) (52)

The mixture obtained above (2.86g) was added to a stirred suspension

of $PdCl_2(PhCN)_2$ (0.554g, 1.44mmol) in benzene (60ml). The solution was stirred for 12 hours at room temperature, and the precipitate formed was collected, dried *in vacuo* and recrystallised from chloroform, to yield compound (52) (1.191g, 1.96mmol, 31% from ClPPhMe), m.p. 245-7°C (dec.), δ_H ($CDCl_3$, 250MHz) 2.35-2.40 (6H, d, *J* 11Hz, 2x*Me*), 4.00-4.15 (4H, m, 4xP-C-CH-C*H*), 4.40-4.50 (4H, m, 4xP-C-C*H*-CH), 7.35-7.60 (10H, m, Ar-*H*); *m/z* (in $HOCH_2CH_2SCH_2CH_2OH$) 697 (M^+), 661, 617, 575, 540, 523.

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