CYCLOPALLADATED AROMATICS

IN

ORGANIC SYNTHESIS

A thesis presented by

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ABSTRACT

In the first part of this thesis a review is presented which covers recent developments in organic synthesis using palladated aromatics. The review is divided into two major parts. The first of these discusses reactions of palladated aromatics derived from aryl halides, aryldiazonium salts, aryl metal compounds and arenes, while the second is concerned with the reactions of ortho-palladated aromatics.

In the second part of this thesis the results and discussion are presented. The preparation and characterisation of some new ortho-palladated aromatic benzaldimine complexes and their reactions with olefins are described. Reaction of di-μ-chlorobis[(N-t-butyliminomethyl)aryl]-1,N-dipalladium (II) complexes (A) with styrene in trifluoroacetic acid-acetic acid mixtures yielded a synthesis of 2-formylstilbenes, which were converted to N-methyl-3-phenyl-1(2H)-isoquinolones via a mercury (II) mediated cyclisation of the N-methyl imine derivatives of the 2-formylstilbenes. Reaction of the complexes (A) with methyl acrylate in refluxing toluene in the presence of triethylamine produced methyl 2-(N-t-butyliminomethyl)-cinnamates. Reaction of acrylonitrile with complexes (A) yielded 2-(N-t-butyliminomethyl)-cinnamonitriles which, upon in situ thermolysis, were found to undergo an electrocyclic ring closure to produce the corresponding isoquinolines. However, substituents on the aromatic ring of the complexes (A) showed a pronounced effect upon the reaction with acrylonitrile, which was not seen for styrene or methyl acrylate. Olefins which are π rich, such as n-butyl vinyl ether and vinyl acetate were found not to react with the complexes (A).

The third and final part of this thesis is the experimental, where the methods of preparation employed and spectral data of the compounds concerned are listed.

ACKNOWLEDGEMENTS

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REVIEW

RECENT DEVELOPMENTS IN ORGANIC SYNTHESIS USING PALLADATED AROMATICS

INTRODUCTION

The literature contains many reviews of organopalladium chemistry.[1-18] The survey presented here looks at the more recent aspects of the reactions of palladium carbon sigma bonded species, and their application to organic synthesis.

Aryl palladium carbon sigma bonds may be formed by a number of processes. Part 1 is divided into four main sections 1.A. - 1.D., divisions being based upon the aromatic species (aryl halides, 1.A.; aryldiazonium salts, 1.B.; aryl metal compounds, 1.C.; and arenes, 1.D.) from which the aryl palladium intermediates are derived. Further subdivisions within the main sections are based upon the substrates with which the aryl palladium intermediates react. Part 2 deals with the reactions of cyclopalladated complexes and is subdivided in a similar manner to sections 1.A.-1.D.

The reactions may be stoichiometric in palladium, or they may be made catalytic by the addition of an appropriate oxidant and/or reductant, or they may be truly catalytic requiring no additives.

PART 1 FORMATION AND CLEAVAGE OF ARYL PALLADIUM SIGMA BONDS

1.A. Reactions of Aryl Halides in the Presence of Palladium

Generally, the first step in the reaction of palladium with aromatic halides is the oxidative addition of zerovalent palladium to the carbon halogen bond (eqn.1).

$$\underset{1}{ArX} + \text{"Pd°"} \longrightarrow \underset{2}{ArPdX} \qquad (1)$$

X = halogen.

The precise nature of the mechanism is uncertain, however general orders of reactivity are known, for chlorobenzenes, $p\text{-}NO_2C_6H_4Cl > p\text{-}NCC_6H_4Cl > p\text{-}PhCOC_6H_4Cl > C_6H_5Cl$,[3,19] and likewise for both bromo[20] and iodobenzenes.[21] This ordering is the same as that found for nucleophilic aromatic substitution reactions, these reactions however require powerful nucleophiles and/or forcing conditions. Also, in the oxidative addition reactions with palladium, the order of reactivity for halo benzenes was found to be PhI>PhBr>PhCl,[3,19] which is the reverse of that found for nucleophilic aromatic substitutions. These facts point to an electron transfer process (Scheme 1) which is in good agreement with both the orders of reactivity.

Scheme 1

$$ArX + Pd° \longrightarrow [ArX^{\cdot-}Pd^{I}]$$

$$[ArX^{\cdot-}Pd^{I}] \xrightarrow{FAST} [Ar\cdot Pd^{I}X]$$

$$[Ar\cdot Pd^{I}X] \xrightarrow{FAST} [ArPd^{II}X]$$

X = halogen.

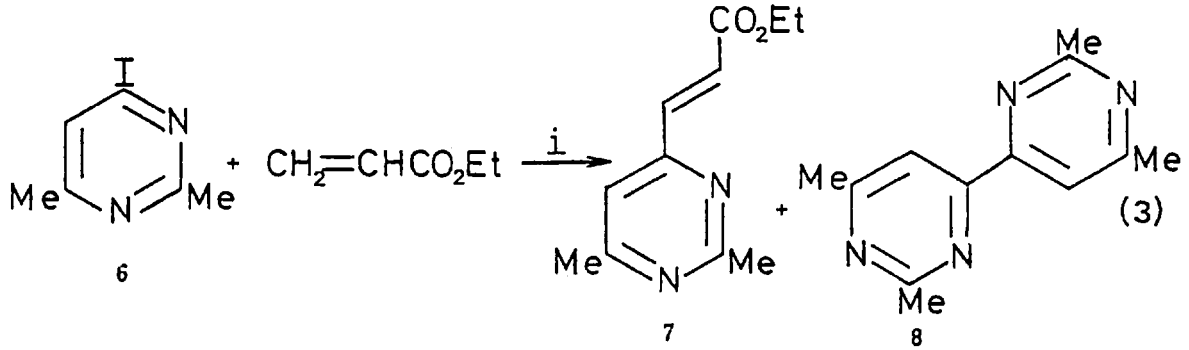
In the reactions of a number of substituted iodobenzenes with palladium (0), in tetrahydrofuran, the lack of any of the normal by-products of radical reactions, i.e. biaryls from homocoupling, and reduced products ArH formed by hydrogen abstraction from solvents led to the suggestion that the mechanism is nonradical, and an interaction between the halogen and palladium preceded an attack by palladium onto the aromatic ring.[21] Alternatively, the reaction may be partially or wholly concerted. The precise mechanistic path or pathways for both oxidative addition and the reverse reaction, reductive elimination, depend on the conditions of reaction, nature of the organic substrate and of course the ligands bound to the metal itself.[22,23]

1.A.(i) Homocoupling

The aryl palladium species 2 in the absence of any other reagents can react further on heating to produce the homocoupling product (eqn.2).

$$\underset{3}{Pd^{\circ}} + PhI + PEt_3 \xrightarrow{\Delta} \underset{4}{PdI_2(PEt_3)_2} + \underset{5}{Ph\text{-}Ph} \qquad (2)$$

The formation of the homocoupling product can present a problem, as shown in the reaction of the iodopyrimidine 6 with ethylacrylate (eqn.3).

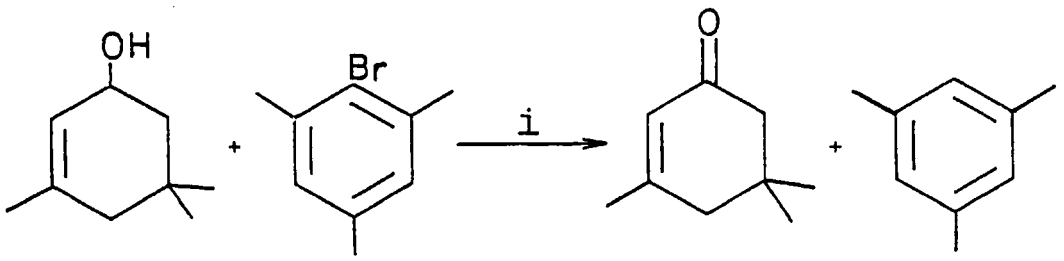


i, $Pd(OAc)_2$; Et_3N; 68hr; 100°. 49% 11%

On addition of triphenylphosphine to the above reaction (eqn.3) the starting material 6 was recovered, with only a small amount of 7. However, by using palladium black or palladium on charcoal, only the desired product 7 was obtained. Biaryls have also been prepared by the reductive coupling of aromatic iodides over a palladium amalgam catalyst.[26]

1.A.(ii) Reduction

Although often aryl halides may be conveniently reduced using heterogeneous palladium catalysis and molecular hydrogen, homogeneous reduction without hydrogen gas offers a valuable alternative. In some cases the reduction of aryl halide is only a means of providing palladium (II) in a catalytic cycle, such as in the catalytic oxidation of secondary alcohols [27,28] (eqn.4).



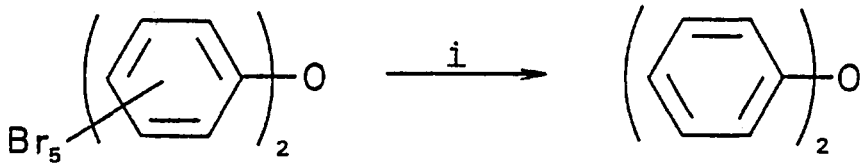
(4)[27]

9 10 11 12

65%

i, $Pd(OAc)_2$; K_2CO_3; DMF; 7.5hr; 100°.

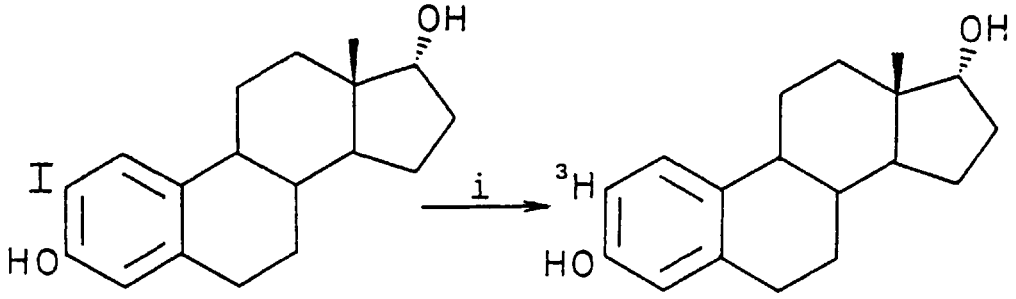
However, with this reduction it may be possible to carry out both oxidation and reduction steps in remote parts of a molecule in "one reaction". Palladium has been used for catalytic dehalogenation [29,30] (eqn.5), and more usefully, as shown (eqn.6), for the regiospecific labelling of estradiol.[31]



(5)[29]

13 14

i, $Pd(OAc)_2$; PPh_3; NaOH; ROH; 5hr; 82°; 100%.



(6)[31]

15 16

i, $PdCl_2$; NaB^3H_4; MeOH; ^3H_2O; 40 mins; 0°.

1.A.(iii) Nucleophiles

Using palladium catalysts, aryl halides can effectively undergo nucleophilic aromatic substitution reactions under mild conditions. Mechanistically this can be viewed (Scheme 2) in three stages: oxidative addition producing the palladated aromatic (eqn.7); exchange of halide ligand (X) for the incoming nucleophile (Y) (eqn.8); reductive elimination to form the new C-Y bond and release of zero-valent palladium for the continuation of the catalytic cycle.

Scheme 2

$$ArX + Pd^{\circ}(L)_2 \longrightarrow ArPd^{II}X(L)_2 \quad (7)$$

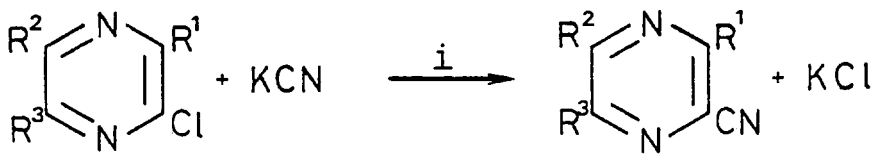
$$ArPd^{II}X(L)_2 \xrightarrow[+Y^-]{-X^-} ArPd^{II}Y(L)_2 \quad (8)$$

$$ArPd^{II}Y(L)_2 \longrightarrow ArY + Pd^{\circ}(L)_2 \quad (9)$$

X = halogen.

Y = nucleophile.

With cyanide ion as the nucleophile, aryl halides were converted to the corresponding nitriles in the presence of palladium [32,33] (eqn.10).



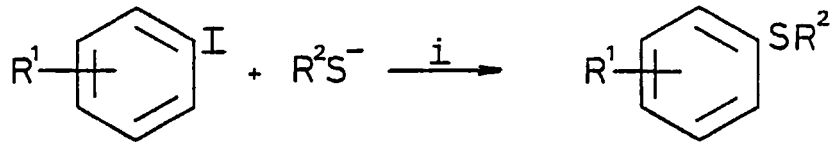
(10)[32]

17 18

R^1, R^2, R^3 = H, alkyl, or phenyl.

i, $Pd(PPh_3)_4$; DMF; 16 - 98%.

Using thiolate anions a synthesis of unsymmetrical sulphides was obtained[34,35] (eqn.11).



(11)[34]

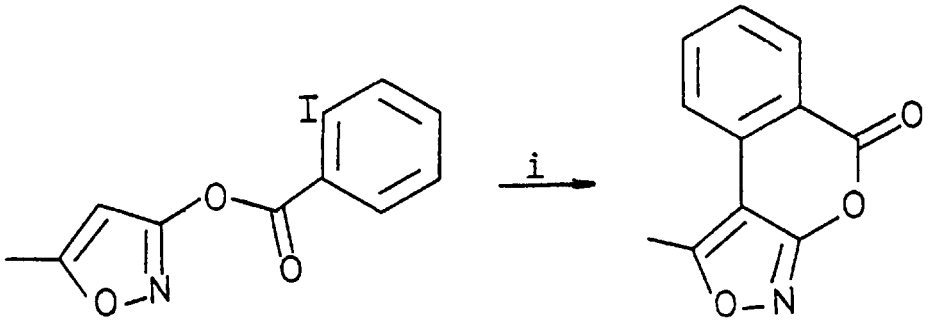
19 20

R^1 = o-, m-, p-Me; o-, m-, p-MeO; or p-Cl

R^2 = t-Bu, n-Bu, Et, or Ph.

i, $Pd(PPh_3)_4$; 0 - 100%

Fused ring systems are formed by intramolecular nucleophilic attack of aromatics onto aryl halides[36,37] (eqn.12).

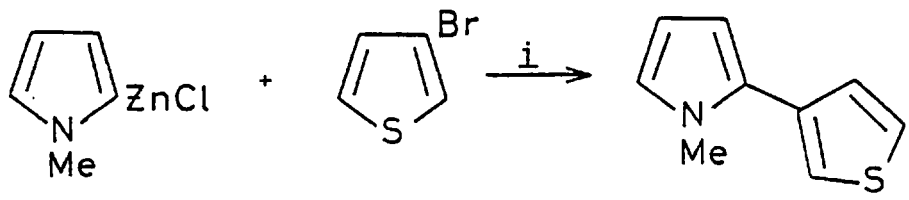


(12)[37]

21 22

i, $Pd(OAc)_2$, 10%; PPh_3, 20%; $NaHCO_3$, 1 eq; HMPT; 6hr; 70-75°; 45%.

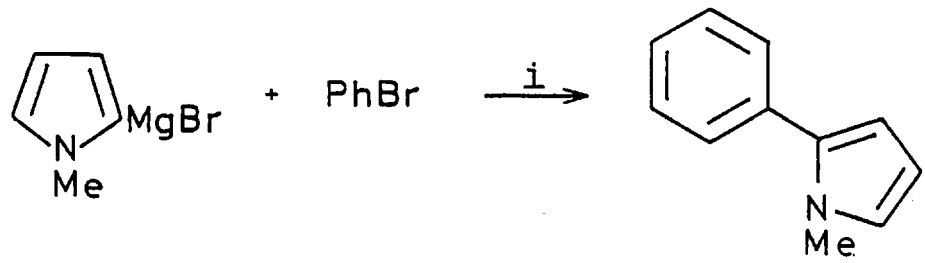
Coupling of aryl halides with aryl magnesium or zinc reagents in the presence of palladium catalysts provides a highly selective synthesis of biaryls[38-41] (e.g. eqns. 13 & 14).



23 24 25

73%

(13)[38]



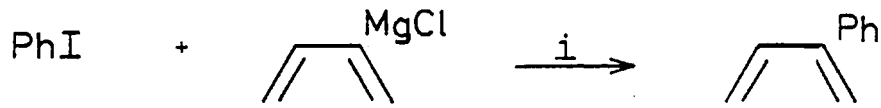
26 27

87%

(14)[38]

i, $PdCl_2$(1,4-bisdiphenylphosphino)-butane; THF; reflux.

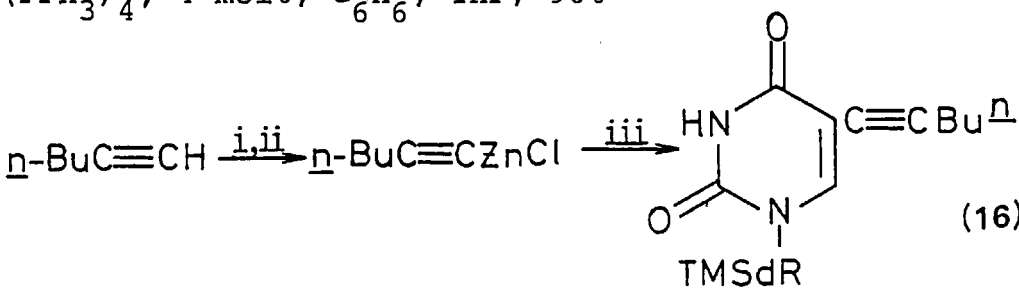
Aryl iodides were also coupled to vinyl Grignards,[42] and zinc acetylides[43] in good yields(e.g. eqns. 15 & 16).



28 29 30

(15)[42]

i, $Pd(PPh_3)_4$, 4 mol%; C_6H_6; THF; 90%



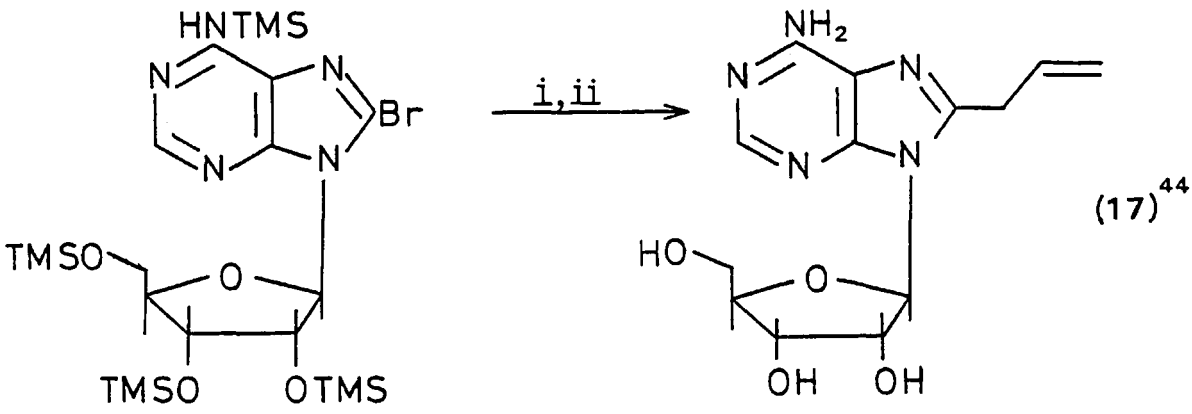
31 32 33

(16)[43]

i,n-BuLi; ii, $ZnCl_2$; iii, $PdCl_2(PPh_3)_2$; 5-iodo-3′, 5′-bis(trimethylsilyloxy)-2- deoxyuridine; 92%.

But, as will be seen later [1.A.(iv)] acetylenes can be smoothly coupled to aryl halides under mild conditions using a palladium copper catalyst system, (eqns.25-28), although in some circumstances the lithium and zinc acetylides may have the advantage of reacting at lower temperatures.

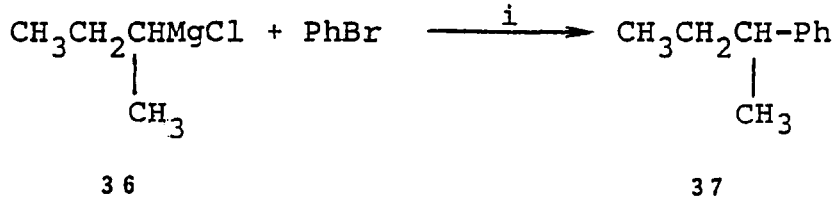
8-Bromopurine nucleosides and adenosine-3′, 5′-cyclicmonophosphates were coupled to Grignard reagents with catalytic palladium, providing a useful modification of position 8 (e.g. eqn.17).



34 35 (17)[44]

i, $PdCl_2(PPh_3)_2$; MgCl; THF; ii, H_2O.

None of the Grignard reagents presented so far are susceptible to β-elimination reactions, which are sometimes a problem in the coupling of alkyl Grignards to aryl halides. However, by the use of bidentate phosphine ligands which promote formation of the cis configuration required for fast reductive elimination, and lessen the availability of vacant co-ordination sites, by virtue of their chelating abilities,[23] the problems of β-elimination are minimised [39,45] (e.g. eqn.18)

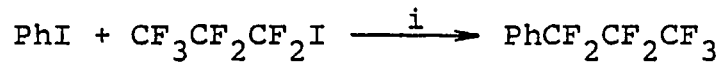


(18)[45]

i, $PdCl_2$(1,1′-bis(diphenylphosphino)ferrocene); Et_2O; -78° ⟶ RT; 1hr; 80%.

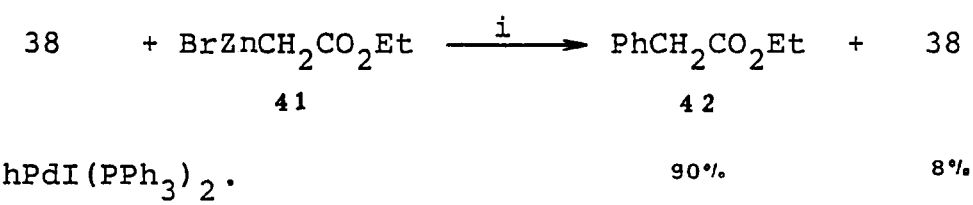
In the above reaction (eqn.18) use of $Pd(PPh_3)_4$ gave the product 37 in only 4% yield.[45]

Perfluoroalkyl zinc (eqn.19) and Reformatsky reagents (eqn.20) have also been arylated in the presence of palladium-(0) catalysts using aryl halides.



(19)[46]

i, $PdCl_2(PPh_3)_2$; THF; Zn; 30 mins; 78%.



(20)[47]

i, $PhPdI(PPh_3)_2$.

1.A. (iv) Acetylenes

The reaction of acetylenes with aryl halides in the presence of palladium and copper provides a general synthesis of both di- and mono-substituted aryl and heteroaryl acetylenes. Presumably, in these reactions (Scheme 3) the copper acetylide is formed (eqn.21) which reacts with the palladated aromatic giving the aryl alkynyl palladium (II) derivative (eqn.22) which then undergoes reductive elimination to product[48] (eqn.23). Although the mechanism proposed does not involve the acetylenic π system, the possibility of its actual involvement cannot be totally ruled out.

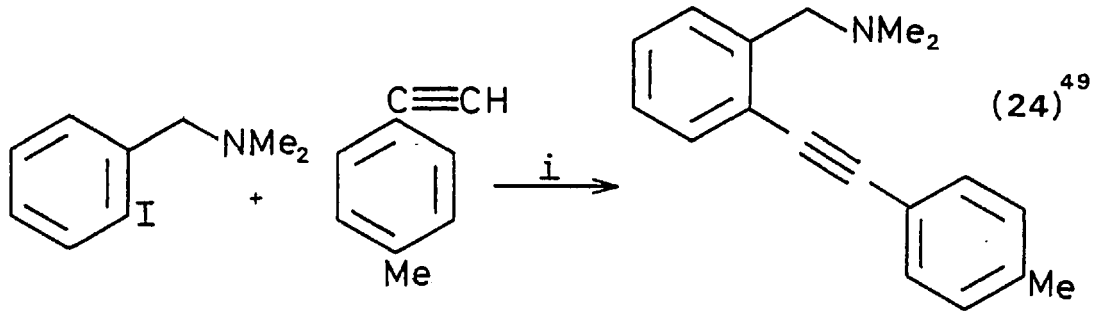
Scheme 3

$$RC{\equiv}CH + CuI + R_3N \longrightarrow RC{\equiv}CCu + R_3\overset{+}{N}H\bar{I} \quad (21)$$

$$RC{\equiv}CCu + ArPd^{II}X(L)_2 \longrightarrow (RC{\equiv}C)Pd^{II}Ar(L)_2 + CuX \quad (22)$$

$$(RC{\equiv}C)Pd^{II}Ar(L)_2 \longrightarrow RC{\equiv}CAr + Pd^{\circ}(L)_2 \quad (23)$$

Without using copper, unsymmetrical tolan derivatives were prepared (e.g. eqn.24), in this reaction the acetylenic anion is probably involved. This example is also of interest as the intermediate palladated aromatic is quite possibly a cyclometallated species (see Part 2).

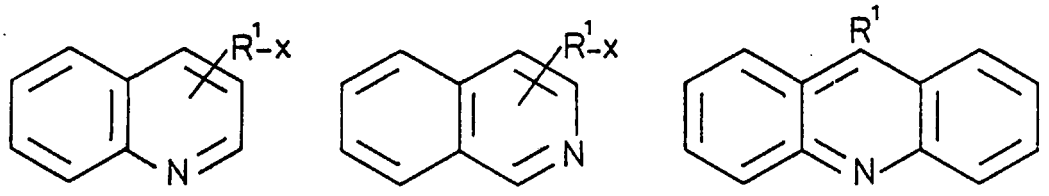


(24)[49]

43 44 45

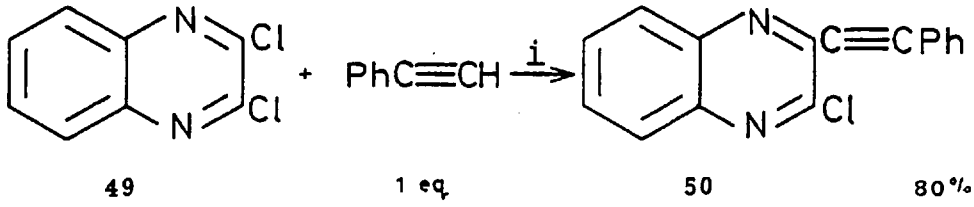
i, $Pd(PPh_3)_4$; NaOPh; DMF; 4hr; 100°;78%.

Monoaza - heteroaromatics such as haloquinolines (46, R^1=Br,I; X= 2-,3-,4-), haloisoquinolines (47, R^1=Br,I; X= 1-,3-,4-), and acridines (48, R^1=I,Br) were found to couple with monosubstituted acetylenes ($R^1C{\equiv}CH$, R^1=Ph, or n-Bu, or CH_2OH) in the presence of $PdCl_2(PPh_3)_2$, CuI, and Et_3N to yield products containing the acetylenic side chain on the pyridine moiety.[50]

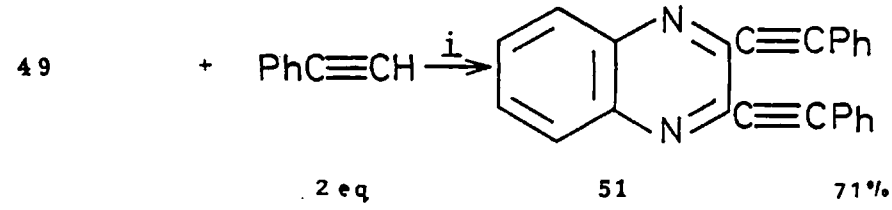


46 47 48

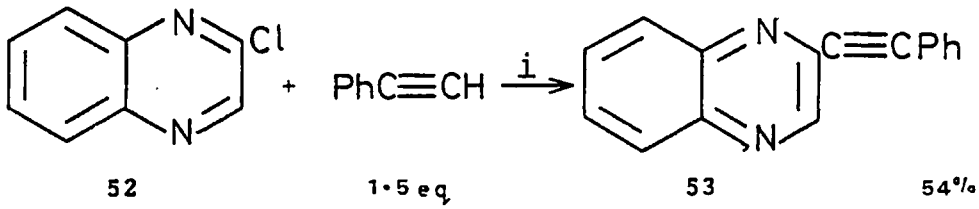
In the diaza-heteroaromatic series 3-halogenocinnolines,[36] monohalo and dihaloquinoxalines[51] reacted with terminal acetylenes in the presence of palladium and copper to give the corresponding arylated acetylenes (e.g. eqns. 25, 26, and 27).



49 1 eq 50 80% (25)[51]



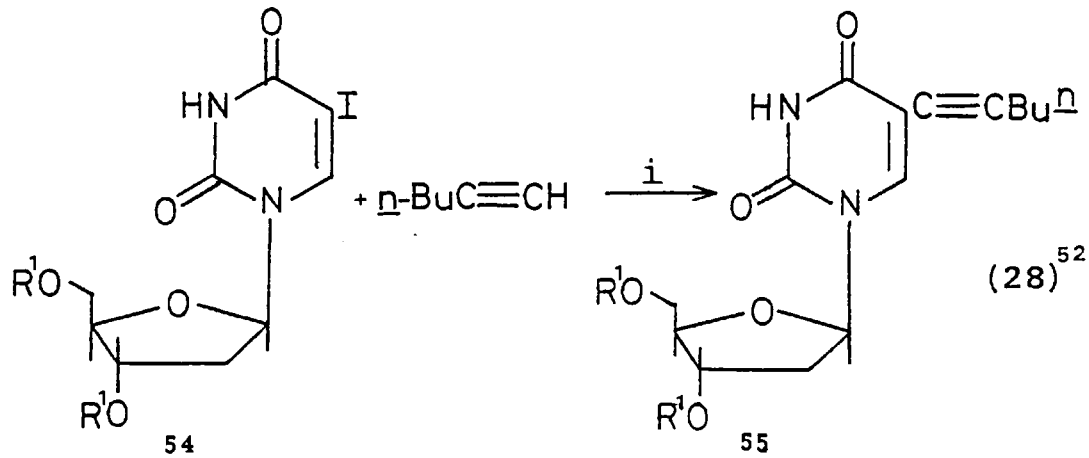
49 2 eq 51 71% (26)[51]



52 1·5 eq 53 54% (27)[51]

i, $PdCl_2(PPh_3)_2$; CuI; DMSO; Et_3N.

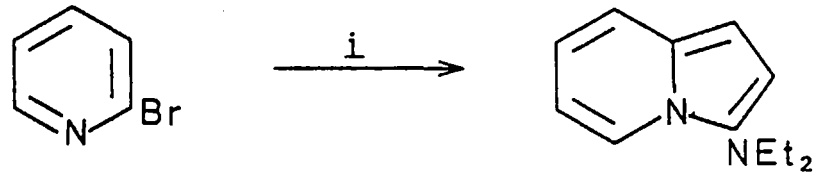
The compounds 50, 51 and 53 are useful as intermediates in the synthesis of polycyclic fused ring systems, to which the palladium/copper catalyst provides an efficient route. This catalyst system also allowed smooth alkynylation of 5-iodo-uracil nucleosides in excellent yields [52] (e.g. eqn.28).



54 55 (28)[52]

i, $PdCl_2(PPh_3)_2$; CuI; Et_3N; 150°; 89%. R^1= p-MeC_6H_4CO-

In the examples cited so far, the base present has generally been a tertiary amine, typically triethylamine. In the presence of a secondary amine the coupling of propargyl alcohol with α-halo:- pyridines, quinolines, isoquinolines, and pyridazines was found to result in a one step synthesis of a number of 3-(dialkylamino)-indolizines[53,54] (e.g. eqn.29).

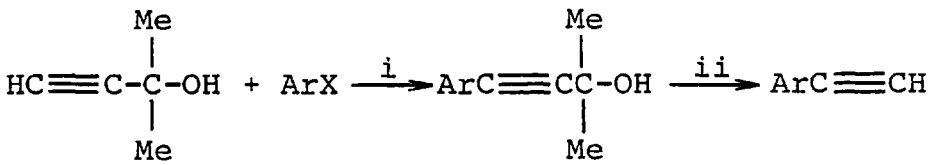


(29)

56 57

i, $PdCl_2(PPh_3)_2$; CuI; $HC{\equiv}CCH_2OH$; Et_2NH; 16hr; 80°; 36%.

To obtain, as a final product, a terminal aryl acetylene, in the initial coupling a protected acetylene has to be used. Acetylenes which have been found to meet this requirement are 2-methylbut-3-yn-2-ol 58 and ethynyltrimethylsilane 63, as shown in equations 30 and 31 respectively.



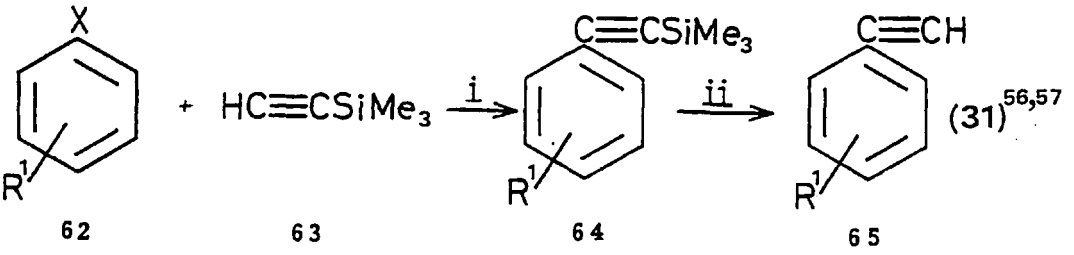
(30)[55]

58 59 60 61

ArX = Bromo:- pyridines, quinolines, isoquinolines, cinnolines and chloroquinoxalines.

i, $PdCl_2(PPh_3)_2$; CuI; Et_2NH; RT; 35-84%.

ii, NaOH; PhMe; reflux; 2hr; 49-90%.



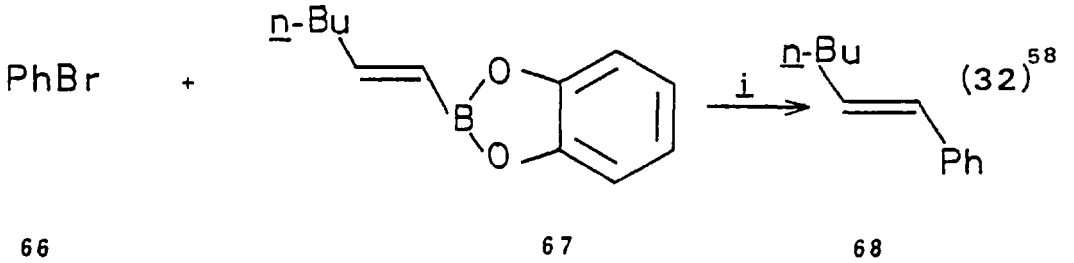
Typically X = Br, I; R^1 = p-NO_2, o-NO_2, p-NH_2, p-CN, p-MeCO, p-MeO_2C, or p-Ph.

i, $PdCl_2(PPh_3)_2$; CuI; Et_3N; RT; 70-92%.

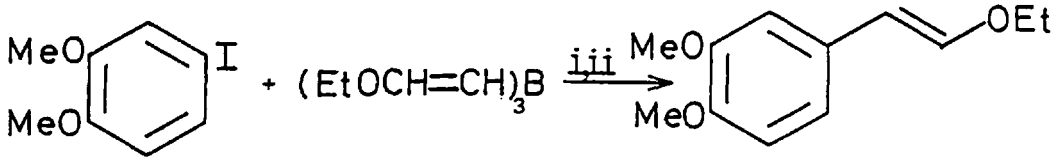
ii, KOH; MeOH; H_2O; RT; 79-94%.

1.A. (v) Organoboron Compounds

Vinyl boranes, like their zirconium analogues [1.A. (vi)] allow stereoselective production of (E)-olefins[58,59] (eqns.32 and 33); however, as will be seen later [1.A. (viii)], direct reaction of monosubstituted olefins with aryl halides in the presence of palladium catalysts normally results in the production of (E)-olefins. By the use of boron chemistry the (E)-enol ether 71 was formed in excellent yield, whereas direct reaction of aryl halides and enol ethers was found to give poor results [see 1.A. (viii)].



i, $Pd(PPh_3)_4$, 1%; C_6H_6; EtOH; EtONa, 2.2eq; Δ, 4hr; 98%.



69 70 71 (33)[59]

10 mmol 4 mmol 86 %

i, $Pd(PPh_3)_4$, 0.1 mmol; NaOH, 30 mmol; 4 hr; Δ.
ii, NaOH; H_2O_2.

Although no quantitative studies were carried out on the vinylation, from the experimental observations,[58,59] the oxidative addition of zerovalent palladium to the carbon halogen bond was proposed to be the rate determining step. Presumably, a stereospecific transfer of the vinyl moiety from the borane to the palladated aromatic followed (eqn.34) to produce an aryl alkenyl palladium intermediate which upon reductive elimination (eqn.35) gave the trans olefin product and the palladium (O) needed for the continuation of the catalytic cycle.

$$ArPd^{II}X(L)_2 + R^1_2BCH{=}{=}CHR^2 + R^3ONa \longrightarrow$$

$$\underline{\text{trans}} \qquad (34)$$

$$ArPd^{II}(CH{=}{=}CHR^2)(L)_2 + R^1_2BOR^3 + NaX$$

$$ArPd^{II}(CH{=}{=}CHR^2)(L)_2 \longrightarrow ArCH{=}{=}CHR^2 + Pd^{\circ}L_2 \qquad (35)$$

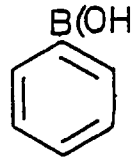
$$\underline{\text{trans}}$$

X = halogen

The presence of base in the reaction was also found to be essential.

In this proposed pathway, both the formation of the palladium to vinyl carbon σ bond and subsequent reductive elimination are invoked as processes in which the <u>trans</u> stereochemistry of the olefin is maintained. This provides a rationale for the observed retention of stereochemistry about the double bond, although involvement of the olefin π system is possible.

Phenyl boronic acid was found to undergo cross-coupling with halo-aromatics in the presence of bases and palladium to produce biaryls (eqn.36).



$$+\ R^1C_6H_4Br \xrightarrow{i} PhC_6H_4R^1 \qquad (36)^{60}$$

72 73 74

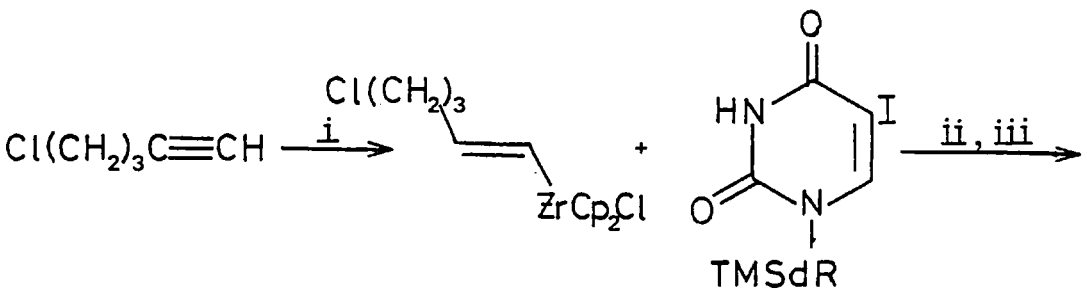
R^1=H, o-Me, p-MeO, p-Cl or p-MeO_2C.

i, $Pd(PPh_3)_4$; Na_2CO_3; C_6H_6; 40-94%.

The use of aryl boronic acids provides a mild alternative to the Grignard and organozinc reagents, which have already been mentioned [1.A. (iii)], for the preparation of unsymmetrical biaryls.

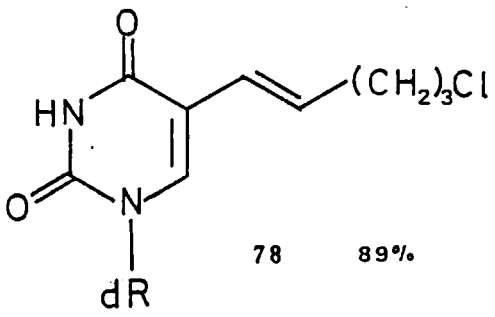
1.A. (vi) Vinyl Copper and Zirconium Reagents

The reaction of vinyl copper and zirconium reagents like the vinyl boranes [1.A. (v)], provides access to stereochemically pure (E) and (Z)-arylated olefins. Vinyl zirconium reagents, prepared by the hydrozirconation of terminal alkynes, produce (E)-arylated olefins, as shown by the reaction of 5-iodo-O-3′, 5′-bis(trimethylsilyl)C deoxyuridine 77, with the alkenyl zirconium compound 76 (eqn.37).



75 76 77

(37)[61]



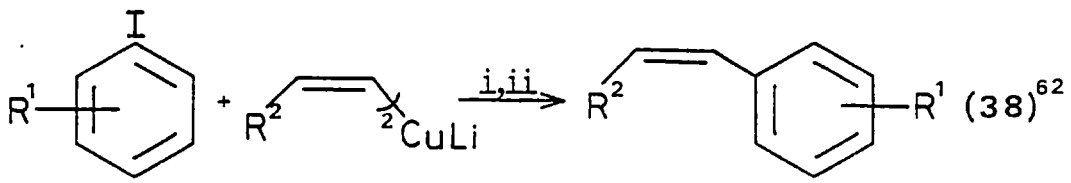
78 89%

Cp = cyclopentadienyl .

dR = desoxyribosyl .

i, $Cl(H)ZrCp_2$; C_6H_6; ii, $Pd(PhCN)_2Cl_2$, 2%; THF; iii, H_2O .

Complementing the vinyl boranes and zirconiums, vinyl copper reagents have been used to produce (Z)-arylated olefins in the presence of palladium and zinc bromide (eqn.38).



79 80 81

(38)[62]

R^1 = H, p-Br, p-MeO, p-NO_2, p-CO_2Me, or o-CO_2Me .

R^2 = Et or n-Pent .

i, $ZnBr_2$; THF; ii, $Pd(PPh_3)_4$, 5%; -10° → +20°; 2hr; 65-81%, (99%Z).

In the same manner, 2-iodo-thiophene was also successfully vinylated. The generality of the reaction, as seen by the toleration of the nitro and ester groups, is improved by use of the cuprate rather than vinyl-lithium or Grignard reagents.

1.A. (vii) Organotin and Silicon Reagents

The reaction of aryl halides with hexa-alkylditin reagents in the presence of palladium leads to the formation of trialkylaryltin compounds[63,64] (eqn.39).

$$\underset{82}{(Bu_3Sn)_2} + \underset{83}{R^1C_6H_4Br} \xrightarrow{i} \underset{84}{R^1C_6H_4SnBu_3} + \underset{85}{(R^1C_6H_4)_2} + \underset{86}{Bu_3SnBr} \qquad (39)^{63}$$

21 – 59% 0 – 18%

R^1 = o-, m-, p-NO_2; o-, m-, p-CN, or p-MeCO .

i, $Pd(PPh_3)_4$, 1 mol %; PhMe; 80°.

These reactions were believed to proceed by oxidative addition of palladium (0) to the aryl bromide producing the palladated aromatic, metathesis by the ditin reagent and finally reductive elimination producing the trialkylaryltin and zerovalent palladium.[63] If, as the reaction proceeds, the concentration of the ditin reagent becomes low the product aryltins 84 can take part in the metathesis reaction with the palladated aromatic to produce the biphenyls 85

as by-products.

The reaction (eqn.39) allows construction of aryltin compounds containing nitro, cyano and carbonyl substituents. Preparation of aryltins by other methods such as the reaction of either aryl-lithium or Grignard reagents with tin(IV) halides,[23] or the reaction of trialkylstannide anions with aryl halides,[65] does not generally tolerate such functionality on the aromatic substrate.

Hexamethyldisilane, like the ditin reagents, was also found to react with aryl halides under palladium catalysis to produce trimethylsilyl arenes.[66]

As indicated by the formation of the biphenyl by-product 85 in equation 39, tetrasubstituted tin reagents can also take part in the metathesis reaction to provide a useful coupling [20,67,68] (e.g. eqn.40).

$$\underset{87}{R^1X} + \underset{88}{R^2SnR^3_3} \xrightarrow{i} \underset{89}{R^1 - R^2} \qquad (40)^{67}$$

76%-95%

R^1X = p-$NO_2C_6H_4I$; 2,4-$(O_2N)_2C_6H_3Br$, or 2,4,6-$(O_2N)_3C_6H_2Cl$.

R^2 = Ph, m-MeC_6H_4, or PhC≡C; R^3 = Me.

i, $ArPdI(PPh_3)_2$, 2 mol %.

As shown in the above equation, aryl and alkynyl groups were transferred in preference to alkyl groups.

Similar preferences have been found for the unsymmetrical tin reagents 88 where R^3 = alkyl and R^2 = allyl,[1] vinyl[20] or benzyl.[20] Studies of the relative rates of reaction between tetramethyltin and a number of bromobenzenes[20] indicated the oxidative addition of palladium to the aryl halide was the rate determining step.

Trimethyltin cyanide reacted with iodobenzene in the presence of catalytic palladium (0) under carefully controlled conditions to produce benzonitrile.[69] Low concentrations of trimethyltin cyanide were needed in order to favour the oxidative addition of palladium (0) to iodobenzene, otherwise a competing reaction of the trimethyltin cyanide with the catalyst [tetrakis(triphenylphosphine) palladium (0)] occurred yielding a new complex 90. Although the complex 90 reacted with iodobenzene to produce benzonitrile it also deposited catalytically inactive palladium metal.

$$[Pd(PPh_3)\text{-}(Me_3SnCN)_2]_n$$

90

Trimethylsilyl groups were found to be displaced from aryls by palladium (II) salts (eqn.41).

$$\underset{91}{Me_3SiC_6H_4R^1} \xrightarrow{i} \underset{92}{Me_3SiOSiMe_3} + \underset{93}{C_6H_5R^1} \qquad (41)^{70}$$

R^1 = H, m-, p-Me; m-, p-Cl, or p-oMe .

i, Li_2PdCl_4; DMF; H_2O .

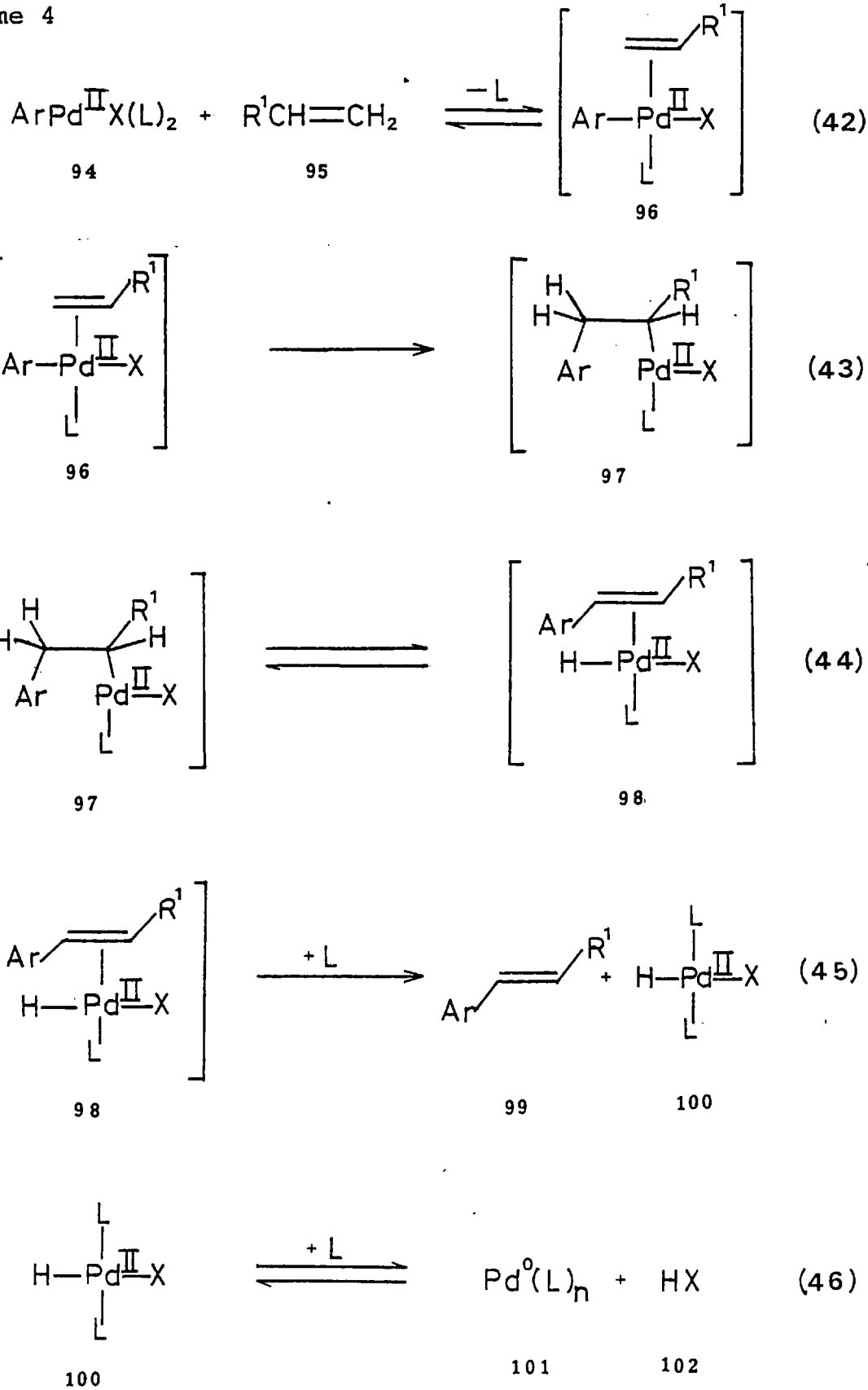
The reactive species was proposed to be Li_2PdCl_3OH which displaces silicon by an electrophilic attack. The proposal of an electrophilic substitution agreed with the experimentally observed rates. Of the substituents listed (eqn.41) only the para-methoxy group had a large effect on the rate.

1.A. (viii) Olefins

The reaction of aryl halides with olefins in the presence of catalytic palladium provides access to a wide variety of vinylated aromatics,[1,2,7] although there are some limitations as to the olefin and aromatic.

The exact mechanism of the vinylic substitution is not known in detail, but is believed to be close to the following[1,7,22,71] (Scheme 4).

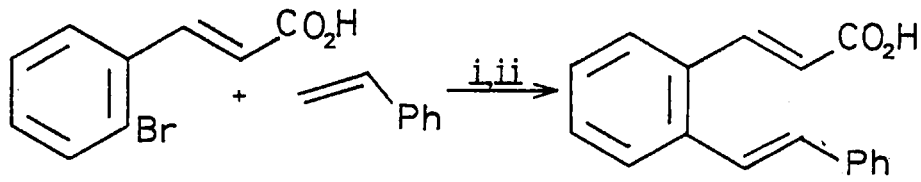
Scheme 4



X = halogen

The palladated aromatic 94 is formed by oxidative addition of palladium (O) to the aryl halide, a proposal supported by the observed order of reactivity, ArI>ArBr>ArCl (cf.1.A. page 7). Co-ordination of the olefin (eqn.42) is followed by the insertion (eqn.43). Here steric effects were found to dominate, the aryl group adding exclusively or predominantly to the least substituted carbon of the double bond. With 1,2-disubstituted olefins the reaction was found to be stereospecific. This is best explained by the insertion (eqn.43) and subsequent β-elimination (eqn.44) reactions being syn addition and syn elimination processes respectively. Loss of the olefin ligand and collapse of the hydrido-palladium species 98 (eqns. 45 and 46) produces the disubstituted olefin 99 and the palladium (O) required for the next catalytic cycle. The acid HX produced must be removed if a catalytic cycle is to be obtained. A base, typically triethylamine, is used for this. For steric reasons monosubstituted olefins react more rapidly than disubstituted olefins, as is demonstrated by the many syntheses of disubstituted olefins using this method.

Styrenes were found to react smoothly forming stilbene derivatives[25,36,72-74] (eqn.47).



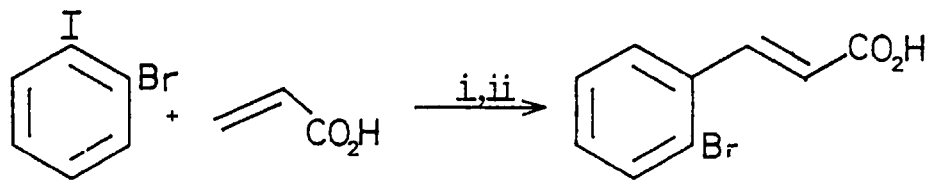
(47)[72]

103 104 105

i, $Pd(OAc)_2$, 1%; PPh_3, 2%; Et_3N, 2 eq; 44 hr; 100°C; ii, H_3O^+.

In the final product 105 the trans stereochemistry was obtained, presumably due to steric factors influencing the β-elimination process. The reaction tolerates a wide variety of substituents on the aryl halide[7,71] but, from other results, it is likely that very electron rich styrenes would not react efficiently.[75]

Acrylate esters[25,72-74,76,77] and acrylic acid itself[72,74] couple in good yields (eqns.48 and 49).

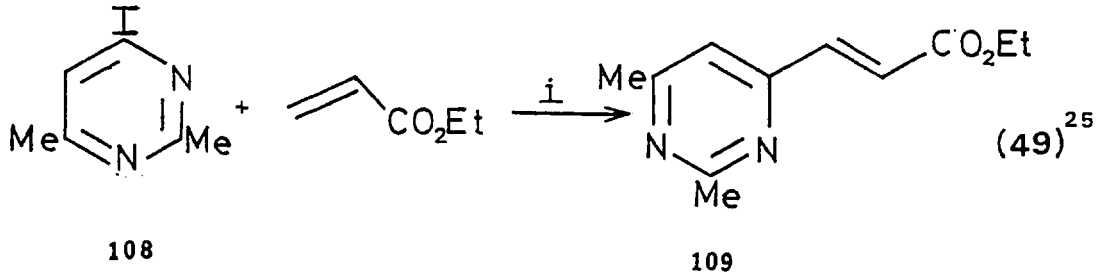


(48)[72]

106 107

82%

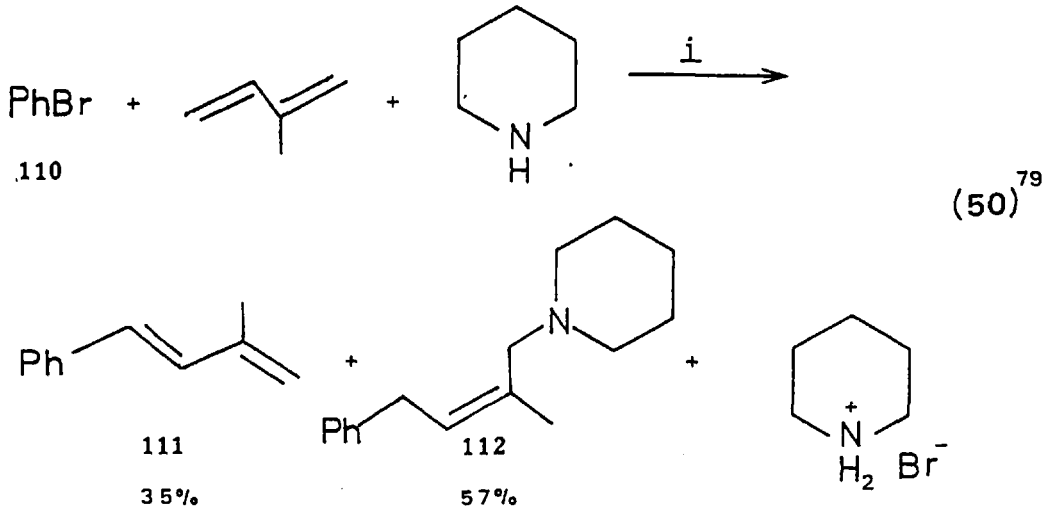
i, $Pd(OAc)_2$, 1%; Et_3N, 2 eq; 1 hr; 100°; ii, H_3O^+.



108 109 (49)[25]

i, Pd black, or Pd/C.

Due to the higher reactivity of iodides over bromides towards oxidative addition, as seen above (eqn.48), selective reactions are possible. In the reaction of the iodopyrimidine 108 with ethyl acrylate (eqn.49) use of other catalysts led to competing formation of the symmetrical biaryl [cf.eqn.3, 1.A. (i)]. Acrylonitrile, like the acrylates coupled with aryl iodides and bromides.[25,76,78] 1,4-Dienes were also arylated in the presence of catalytic palladium (eqn.50). The proposed intermediate in this reaction is the π allyl



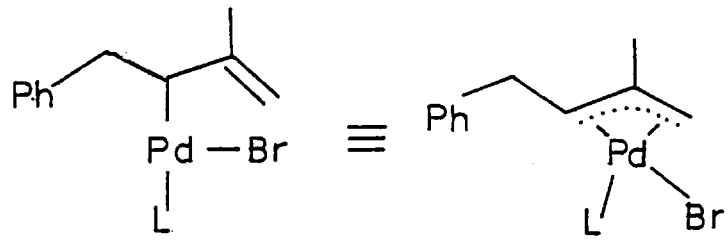
110 (50)[79]

111 35% 112 57%

i, $Pd(OAc)_2$, 1%; (o-MePh)$_3$P, 2%; 48hr; 100°C.

complex 113 formed by insertion of the vinyl group into the

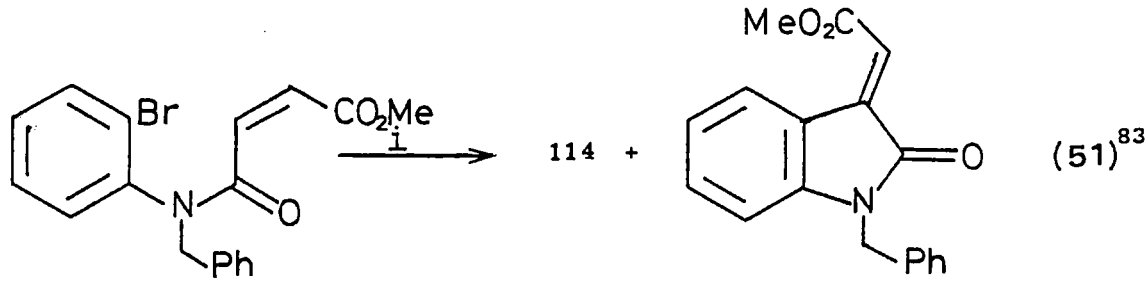
aryl palladium bond. Attack of the amine on



113

the π allyl complex 113 yields the trisubstitued olefin 112.

Aryl halides containing olefinic side chains can react in an intramolecular fashion to form benzo-fused rings, such as indoles,[80,81] oxindoles,[82,83] and quinolones[82] (e.g. eqn. 51).



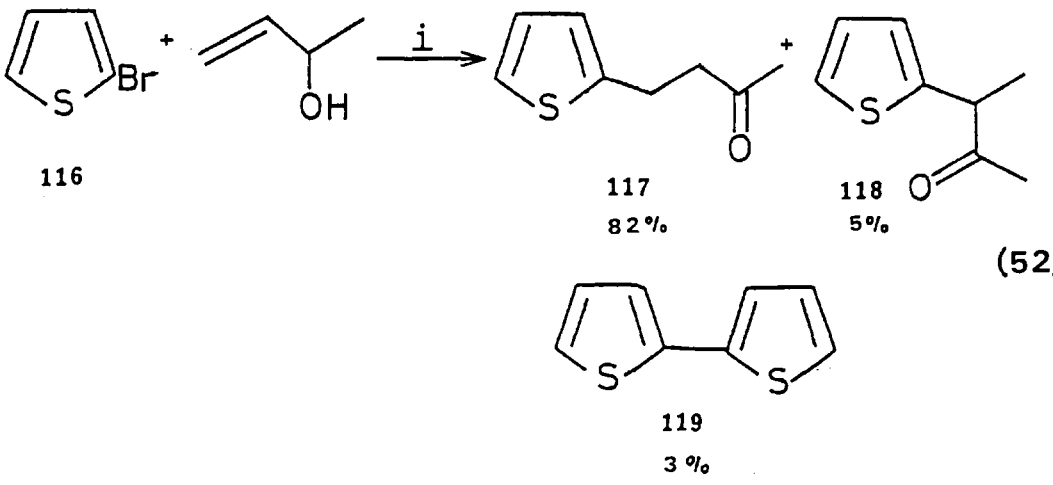
114 + 115 (51)[83]

114 23·8 %

115 47·7 %

i, $Pd(OAc)_2$; PPh_3; n-Bu_3N; CH_3CN; 6hr; 70°.

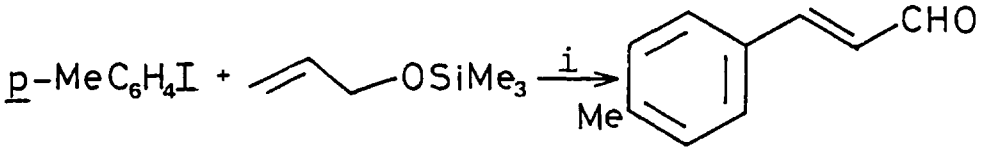
Primary and secondary allyl alcohols on reaction with aryl halides produced aromatics with carbonyl containing side chains[84,85] (e.g. eqn.52) whereas allyltrimethylsilyl ethers gave arylated α,β-unsaturated carbonyl compounds[86] (eqn. 53).



116 117 82% 118 5% 119 3%

(52)[84]

i, $Pd(OAc)_2$, 1%; PPh_3, 3%; NaI, 3.5%; $NaHCO_3$, 1.2eq; HMPT; 3hr; 120°.



120 121 122

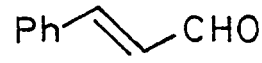
(53)[86]

i, $Pd(OAc)_2$; LiCl; DMF; 7hr; 100°; 40%.

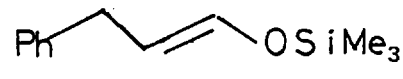
Compound 117 (eqn.52) presumably arises from β-elimination to give the enol ether and not the allyl alcohol. In support of this,[86] it was found that compound 123 was not converted to cinnamaldehyde 124 upon treatment with palladium acetate and lithium chloride in dimethylformamide, whereas iodobenzene reacted smoothly with trimethylsilyl-allyl ether 121 to form cinnamaldehyde 124, presumably via the trimethylsilyl enol ether 125, under identical reaction conditions.



123

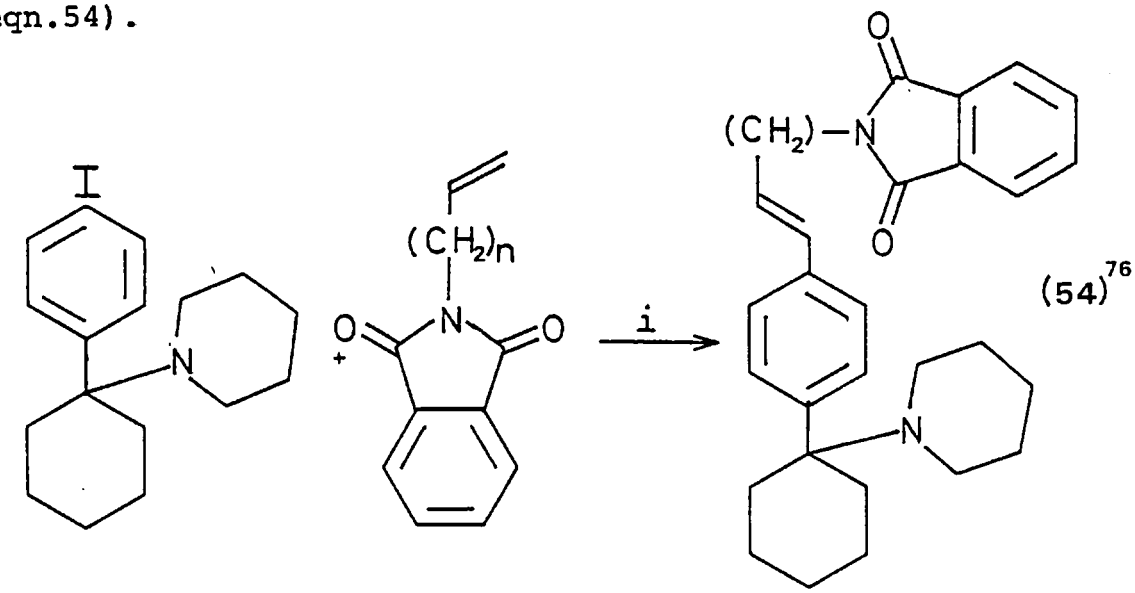


124



125

N-allyl- and N-4-butenyl- phthalimides gave the products 128 (n = 1 or 2) with the olefin in conjugation with the aromatic ring on reaction with the aryl iodide 126 (eqn.54).



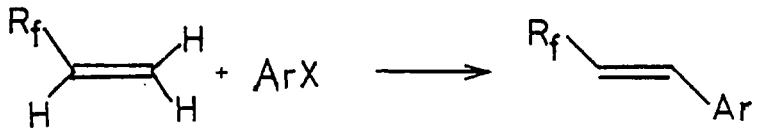
(54)[76]

126 127 128

n = 1 or 2, 83%

i, $Pd(OAc)_2$, 1%; (o-MePh)$_3$P, 2%; Et_3N; CH_3CN; 100°.

The fluorine containing olefins, 3,3,3-trifluoropropene and pentafluorostyrene reacted with aryl halides to produce the trifluoromethyl styrene and 2,3,4,5,6-pentafluorostilbene compounds respectively[87] (eqn.55).

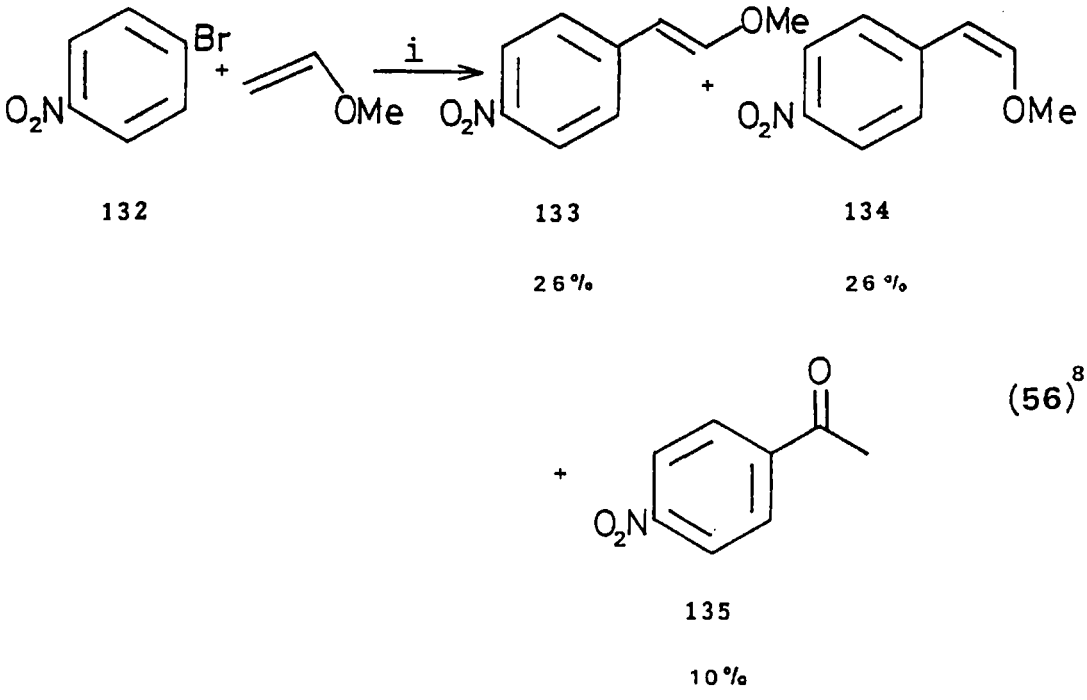


129 130 131

(55)[87]

R_F = CF_3 or C_6F_5; X = I, or Br.

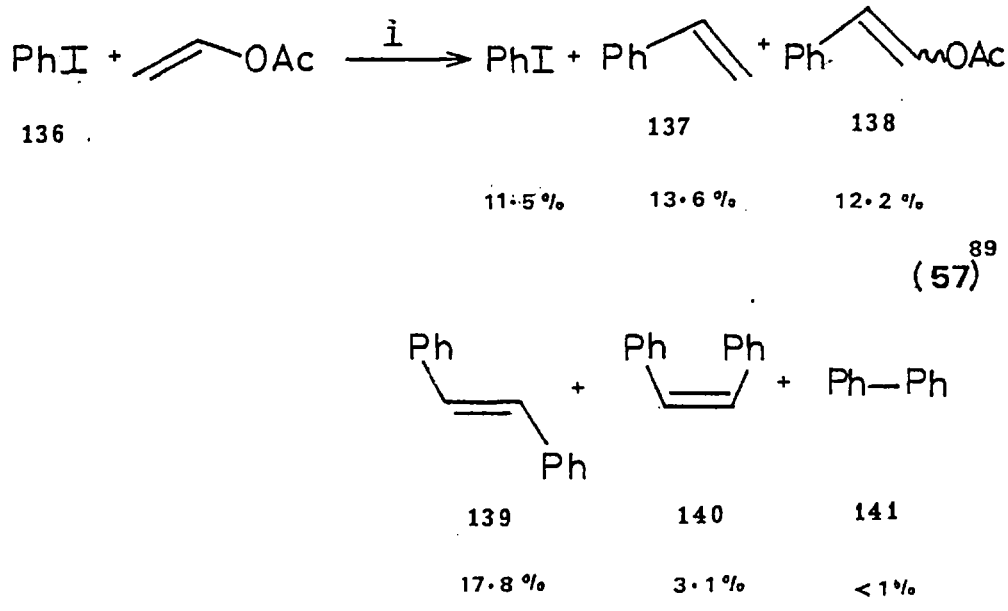
The olefins discussed so far have been bonded to other functionality via a carbon-carbon bond; however, enol ethers and vinyl acetates, which are useful C_2 units, did not appear to react smoothly or selectively (eqns. 56 and 57 resp.).



132 133 (26%) 134 (26%) 135 (10%)

(56)[88]

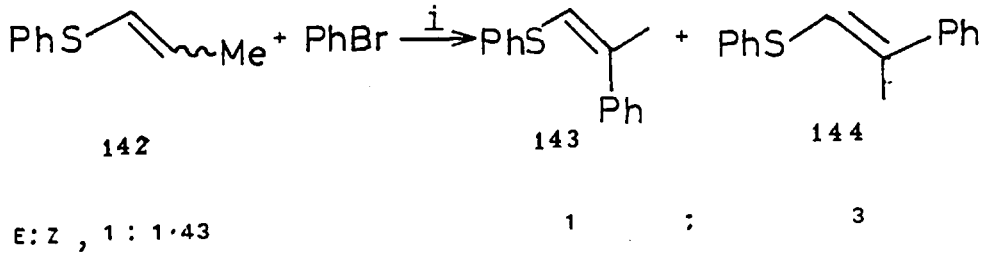
i, $Pd(OAc)_2$, 1%; Et_3N; CH_3CN; 6 hr; 120°.



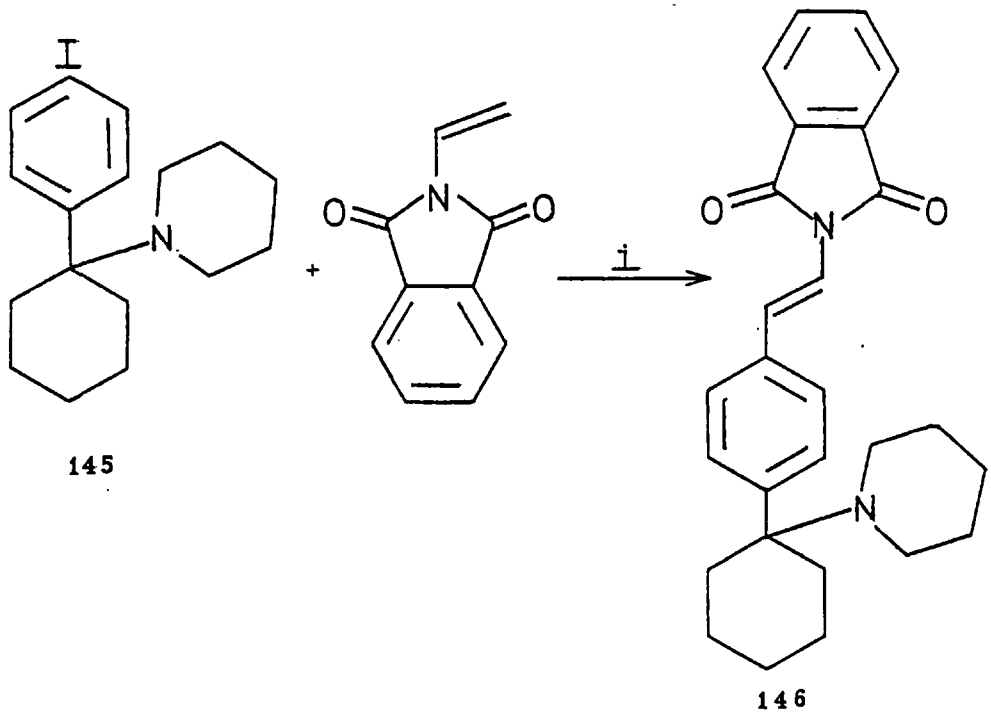
i, $Pd(OAc)_2(PPh_3)_2$, 1%; Et_3N; 3 hr; 130°.

Aryl acetaldehyde enol ethers (e.g. compound 133) can, however, be prepared in good yields by the reaction of vinyl boranes with aryl halides in the presence of palladium catalysts [see 1.A. (v),eqn. 33].

Enol thioethers[90] and N-vinylphthalimide[76] gave better results (eqns. 58 and 59 resp.) than the vinyl acetates and enol ethers, possibly because the olefin moiety in the enol thioether and N-vinylphthalimide is less electron rich.



i, $Pd(OAc)_2$, 2-10%; PPh_3; TMEDA; CH_3CN; trace H_2NNH_2; reflux; 49-65%.



145 146

(59)[76]

i, $Pd(OAc)_2$, 1%; (o-MePh)$_3$P, 2%; Et_3N; CH_3CN; 100° 46%.

1. A. (ix) Carbonylation

Carbonylation is formally an insertion of carbon monoxide into the palladium carbon σ bond of the palladated aromatic to form an aroyl palladium species[22,23] (Scheme 5). The reaction can be divided into two steps; co-ordination of carbon monoxide to the metal (eqn.60) followed by migration of the aryl group to the carbon monoxide ligand[91] (eqn.61). Carbonylation is a facile process. The aroyl palladium species can be isolated (e.g. eqn.63), but more usually it is generated in situ.

Scheme 5

$$\underset{147}{ArPdX(L)_2} \underset{-CO,+L}{\overset{-L,+CO}{\rightleftharpoons}} \underset{148}{ArPdX(CO)(L)} \qquad (60)$$

$$\underset{149}{ArPdX(CO)(L)} \underset{-L}{\overset{+L}{\rightleftharpoons}} \underset{150}{ArCOPdX(L)_2} \qquad (61)$$

It is of course possible that in some catalytic reactions the zerovalent palladium has a carbonyl ligand co-ordinated prior to oxidative addition to the aryl halide. If the carbonyl ligand is not lost during the oxidative addition, the first step (eqn.60) in Scheme 5 is avoided and the likelihood of the carbonylation reaction occurring is increased.

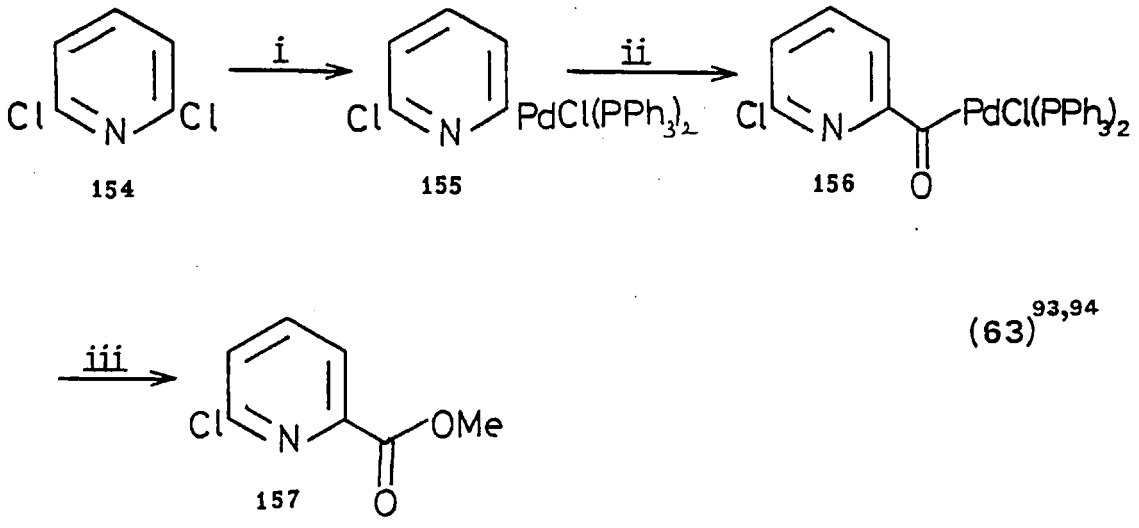
Cyanocarbonylation was found to yield the aroyl cyanide with only a trace of the direct cyanation product, benzonitrile 153, being obtained (eqn.62).

$$PhI + KCN \xrightarrow{i} \underset{152}{PhCOCN} + \underset{153}{PhCN} \qquad (62)^{92}$$

$$48\% \qquad 1{\cdot}7\%$$

i, $PhPdI(PPh_3)_2$, 0.025 mmol; PhI, 3.75 mmol; THF; CO, 20 atm; 15hr; 100°.

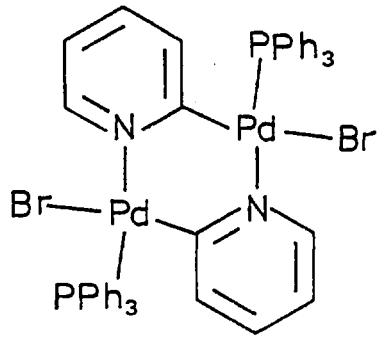
Carbonylation of 2-, 3- and 4- halopyridines also worked well[93,94](eqn.63). In this study it was noted that dinuclear complexes such as 158 did not react with carbon monoxide, whereas mononuclear complexes such as 155 reacted smoothly. This is probably due to the stability of the metallated ring in the dinuclear complex 158.



154 155 156 157

(63)[93,94]

i, $Pd(PPh_3)_4$; PhMe; 95%: ii, CO, 73%: iii, MeOH, 60%.



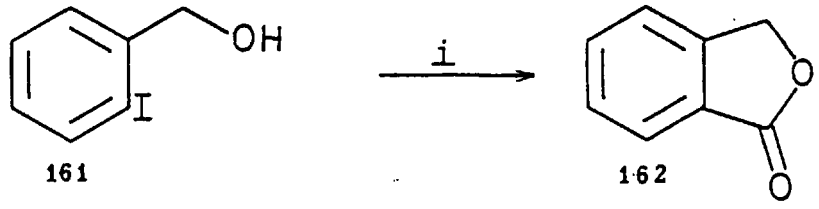
158

A catalytic turnover of 4100 cycles was obtained for the carbonylation of iodobenzene in methanol using bis(triphenylphosphine) [bis(diphenylphosphino)ethane] palladium (0), $[Pd(diphos)(PPh_3)_2]$, (eqn.64).

$$\underset{159}{PhI} + MeOH + CO \xrightarrow{i} \underset{160}{PhCO_2CH_3} \qquad (64)^{95}$$

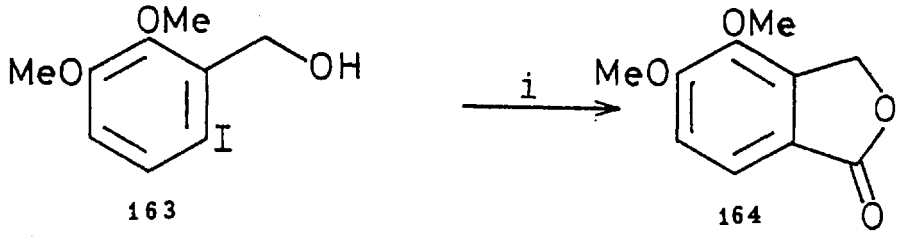
i, $Pd(diphos)(PPh_3)_2$, 0.02 mol%; CO, 3 atm; 14.5hr; 55°; 82%.

With an internal hydroxyl nucleophile, intramolecular cyclisation occurred to form benzolactones[95,96] (eqns.65,66 and 67).



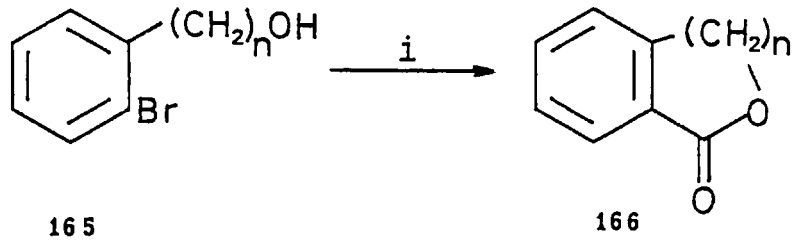
161 162 (65)[95]

i, $PdCl_2(PPh_3)_2$, 0.82 mol%; DMF; K_2CO_3; trace H_2NNH_2; CO, 1 atm; 72hr; 60°; 100%.



163 164 (66)[95]

i, $PdCl_2(PPh_3)_2$, 2 mol%; DMF; K_2CO_3; trace H_2NNH_2; CO, 4 atm; 60hr; 50°; 78%.

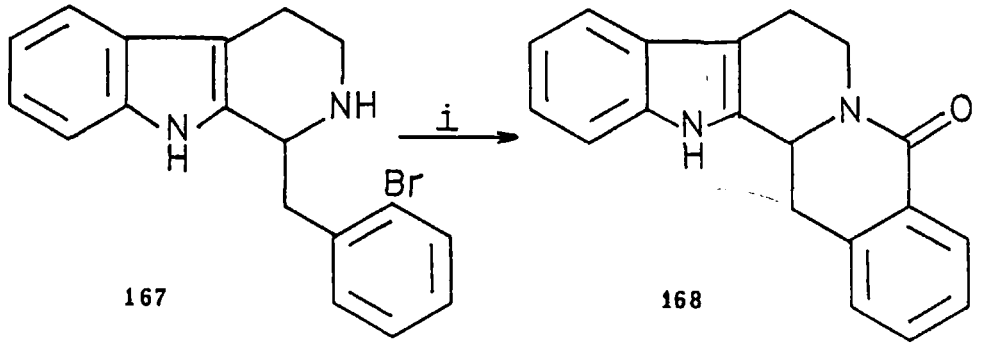


165 166 (67)[96]

i, $Pd(OAc)_2$, 2.2 mol%; PPh_3, 60 mol%; n-Bu_3N, 1 eq; n = 1, 81.9; 2, 69.8; and 3, 41.6%*.

From the examples shown (eqns. 65,66 and 67), it appears that five membered rings can be formed more readily than six or seven membered rings. Also, aromatic iodides give better results than the corresponding bromides, possibly because of the ease of oxidative addition to iodides.

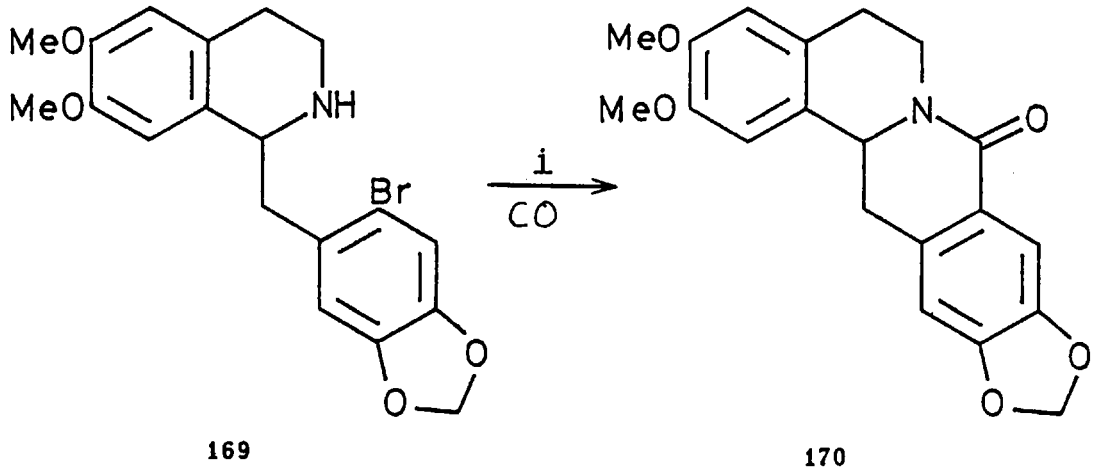
The use of nitrogen instead of oxygen as the internal nucleophile allowed new routes to the yohimbane and berbine alkaloid skeletons[97,98] (eqns. 68 and 69 resp.).



167 168 (68)

i, $Pd(OAc)_2$; PPh_3; n-Bu_3N; CO; 76hr; 100°.

* Conditions quoted were for compound 165 ⟶ 166, where n = 1; however, it was claimed similar conditions were used for the compounds where n = 2 and 3

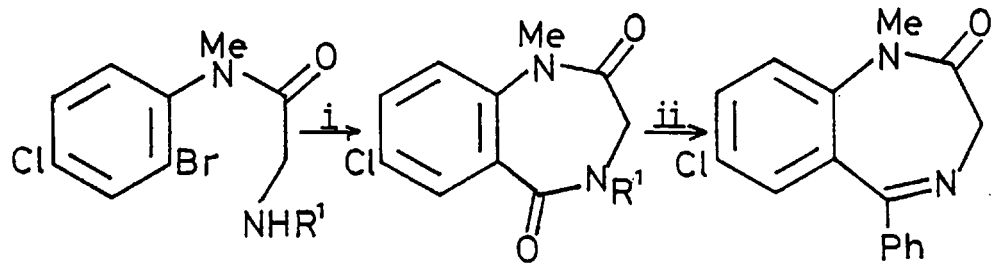


(69)

169 170

i, $Pd(OAc)_2$, 4 mol%; PPh_3, 6 mol%; n-Bu_3N; 30 hr; 100°;50%.

The carbonyl compounds 168 and 170 were readily converted to the corresponding methylene compounds by reduction with lithium aluminium hydride.[97,98] Commercially important benzodiazepine compounds have also been synthesised in this manner[99,100] (eqn.70). However, there are limitations on the type of nitrogen nucleophile that can be used.



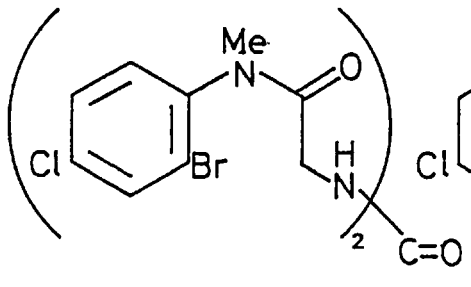
(70)

171 172 173

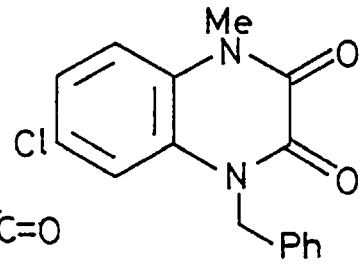
i, R^1 = Ac; $Pd(OAc)_2$, 10 mol%; PPh_3, 1 eq; CO, 5 atm; 40hr; 100°; 48%.

ii, R^1 = Ac; a, PhMgCl; b, NH_2OH; c, $NaHSO_3$.

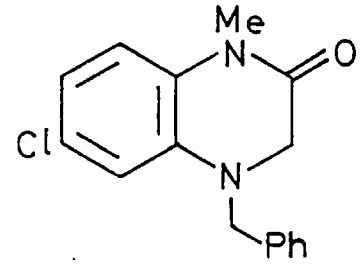
If the amine 171 (R^1 = H) is used, the carbonylation reaction does not give the expected seven membered ring product 172 (R^1 = H). Instead, the urea derivative, 174, was the only isolated product (22.9% yield). The benzyl protecting group, 171 (R^1 = CH_2Ph), was also found to be unsuitable, giving a mixture of products from which the desired product 172 (R^1 = CH_2Ph) was isolated in only 9.3% yield, together with the compound 175 (36% yield), which was thought to have arisen by direct attack of the amine onto the palladated aromatic yielding 176 which oxidised to 175 on workup.



174



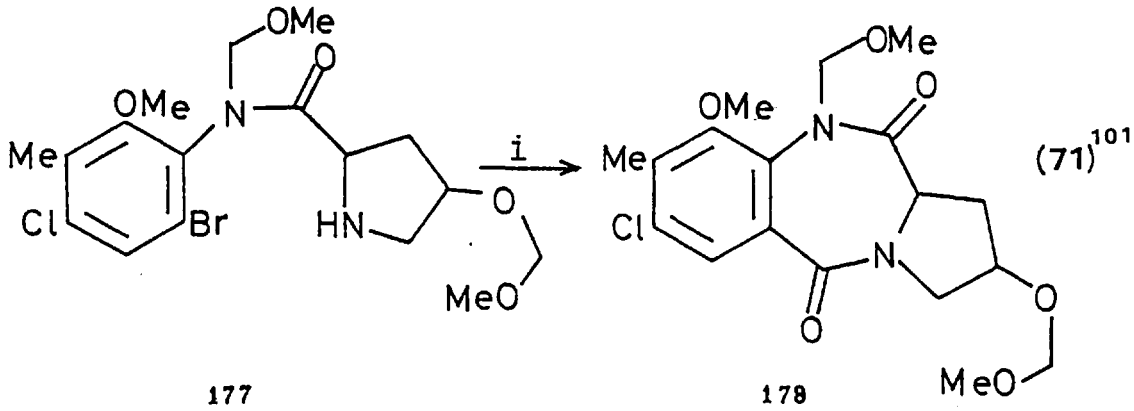
175



176

The acetyl group (R^1 = Ac) was found to give the best results (eqn.70), presumably because it lowers the nucleophilicity of the nitrogen atom by both providing steric hinderance and removing electron density.

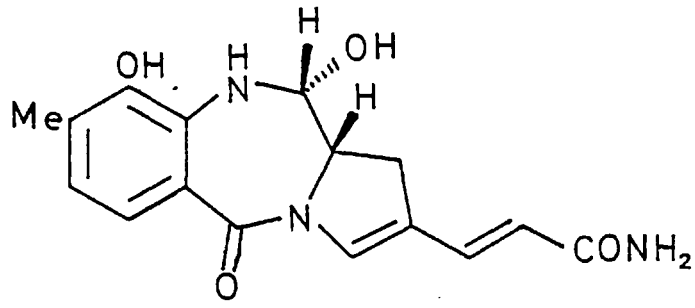
This palladium catalyzed diazepine ring synthesis has recently been applied to a formal synthesis of anthramycin, 179. The synthesis is, however, multistep and the key ring closure (177 ⟶ 178) only proceeded in moderate yield (eqn.71).



(71)[101]

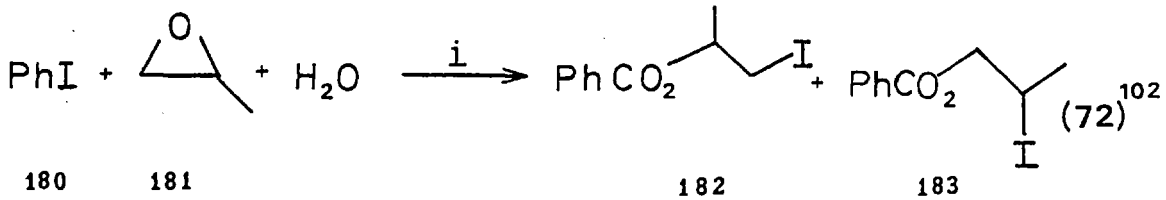
177 178

i, $Pd(OAc)_2$; PPh_3, 1 eq; $\underline{n}$-Bu_3N, 1.5 eq; PhMe; CO, 5 atm; 48hr; 110°; 27%.



179

Carbonylation of aryl halides in the presence of cyclic ethers yielded halohydrin esters (eqn.72).



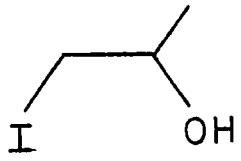
(72)[102]

180 181 182 183

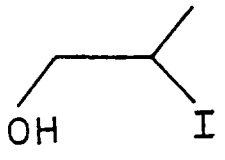
79 : 21

i, $PhPdI(PPh_3)_2$, 1 mol%; CO, 2 atm; 120°; 69.3%.

Since no bases were present any hydrogen iodide produced by reactions of the palladated aromatic and aroyl palladium intermediates will be scavenged by the epoxide 181 to form a mixture of the iodohydrins 184 and 185.



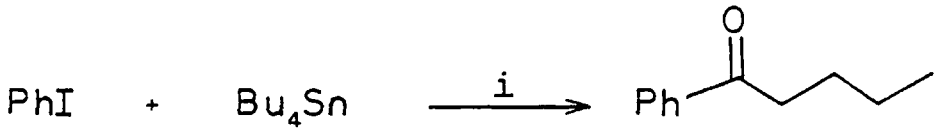
184



185

It is well known[1] that carbonylation reactions in the presence of alcohols produce esters. The reaction of the alcohols 184 and 185 with the aroyl palladium intermediate could conceivably lead to the formation of the esters 182 and 183 with the liberation of zerovalent palladium and hydrogen iodide for continuation of the process. Alternatively, if the aroyl palladium intermediate were to react with water, benzoic acid would be the initial product. A subsequent esterification with the alcohols 184 and 185 would yield the esters 182 and 183 respectively.

Carbonylation of aryl halides in the presence of tetra-alkyltins[103](eqn.73) or terminal acetylenes[104] (eqn.74) gave ketones.



(73)[103]

186

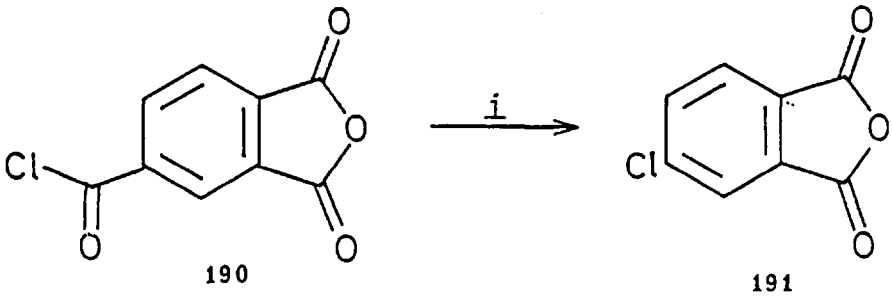
i, $PhPdI(PPh_3)_2$; HMPT; CO, 30 atm; 120°; 73%.

$$\underset{187}{\text{p-}O_2NC_6H_4I} + \underset{188}{HC{\equiv}CPh} \xrightarrow{i} \underset{189}{\text{p-}O_2NC_6H_4COC{\equiv}CPh} \qquad (74)^{104}$$

i, $PdCl_2$(dppf); CO, 20 atm; 1.5hr; 100°.

For the preparation of acetylenic ketones (eqn.74) the best catalyst was found to be dichloro[1,1′-bis(diphenylphosphino)ferrocene] palladium (II) [$PdCl_2$(dppf)]. For instance, use of $PdCl_2(PPh_3)_2$ in the carbonylation of iodobenzene with phenylacetylene resulted in the formation of diphenylacetylene. The reaction (eqn.74) was found to tolerate a variety of ring substituents (p-MeO, p-EtO_2C, p-Cl) as well as being applicable to heteroaromatic halides such as 2-bromothiophene.

Carbonylation is a reversible process as exemplified by the decarbonylation of aroyl chlorides,[105] although forcing conditions are required (eqn.75).



190 191 (75)

i, 5% Pd/C; 310°, melt; 2hr; 100% .

1. B. Reactions of Aryldiazonium Salts in the Presence of Palladium

These reactions are believed to proceed via aryl-palladium (II) intermediates.

$$\underset{192}{ArN_2^+X^-} + Pd^\circ \longrightarrow \underset{193}{ArPd^{II}X} + N_2 \qquad (76)$$

Oxidative addition of palladium to aryldiazonium salts (eqn.76) does not necessarily proceed by the electron transfer process shown in Scheme 6 since it has been reported that aryldiazonium tetrafluoroborates react with tetrakis(triphenylphosphine) palladium (O) (eqn.79) to produce a mixture of the palladated aromatic 195 and aryldiazenato-palladium (II) species 196. The related

Scheme 6

$$ArN_2^+ + Pd^\circ(L)_4 \longrightarrow Pd^I(L)_4^+ + ArN_2^\cdot \xrightarrow{-N_2} Ar^\cdot \qquad (77)$$

$$Ar^\cdot + Pd^I(L)_4^+ \longrightarrow ArPd^{II}(L)_3^+ + L \qquad (78)$$

platinum (O) complex $Pt(PPh_3)_3$ also reacts with aryldiazonium salts to produce aryldiazenatoplatinum (II) salts 197, from which the extrusion of nitrogen is a facile process (eqn.80).[107]

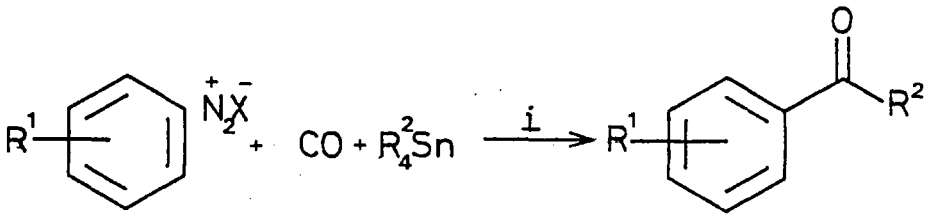
$$\underset{194}{ArN_2^+BF_4^-} + Pd^{\circ}(PPh_3)_4 \longrightarrow \underset{195}{ArPd^{II}(PPh_3)_3^+BF_4^-} + \underset{196}{ArN_2Pd^{II}(PPh_3)_3^+BF_4^-} \qquad (79)^{106}$$

$$\underset{197}{ArN_2Pt^{II}(PPh_3)_3^+BF_4^-} \longrightarrow \underset{198}{ArPt^{II}(PPh_3)_3BF_4^-} + N_2 \qquad (80)^{107}$$

Addition of bis(dibenzylideneacetone)palladium (0) to solutions of aryldiazonium salts resulted in the immediate evolution of nitrogen even at cardice/methanol temperatures. The rate of nitrogen evolution was slowed by the presence of co-ordinating ligands[106] such as triphenylphosphine, 1,2-bis(diphenylphosphino)ethane and tetramethylethylene⊂ diamine.

Arylpalladium (II) complexes formed by oxidative addition of zerovalent palladium to aryl halides (see section 1.A.) necessarily contain a halide ligand, this could be removed with silver tetrafluoroborate to provide a more reactive arylpalladium species. However, this is not practical in catalytic reactions, whereas the reactions of aryldiazonium tetrafluoroborate salts in the presence of catalytic palladium presumably proceed <u>via</u> the more reactive cationic arylpalladium (II) complexes (as 195).

Using catalytic palladium, aryldiazonium salts have been converted directly to aryl ketones[108] (eqn.81), carboxylic acids[109] (eqn.82), mixed anhydrides[110] (eqn.83) and vinylated aromatics[106,111-113] (eqns.84 and 85).



(81)[108]

199 200 201

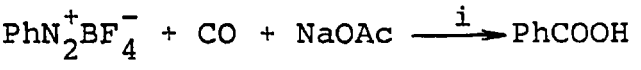
55-90%

R^1 = o-, p-Cl; p-Br, p-I, m-, p-NO_2, or H.

R^2 = Me, Et or Ph. X^- = BF_4^- or PF_6^- .

i, $Pd(OAc)_2$, 2 mol%, CH_3CN.

In this reaction (eqn.81) the iodo and bromo substituents have not entered into the reaction due to the higher reactivity of the diazonium group. Carbonylation and subsequent alkylation of the aroylpalladium species with tetraalkyltin compounds to produce aryl ketones has already been mentioned for palladated aromatics derived from aryl halides [1.A. (ix)].



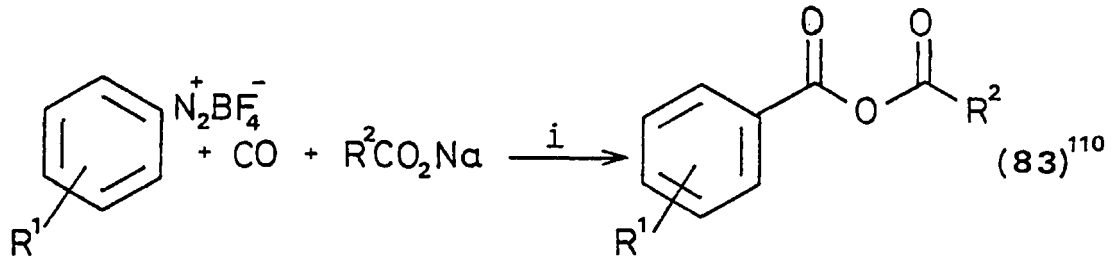
(82)[109]

202 203

i, $Pd(OAc)_2$, 4 mol %; CH_3CN; ½ hr; 85%.

In the above reaction (eqn.82) it is likely the initial product is the mixed anhydride, which hydrolyses on workup to produce benzoic acid 203. Indeed mixed anhydrides can be isolated from this reaction as demonstrated below (eqn.

83) and again iodo and bromo substituents remain unaffected.



204 205 206

28 - 86%

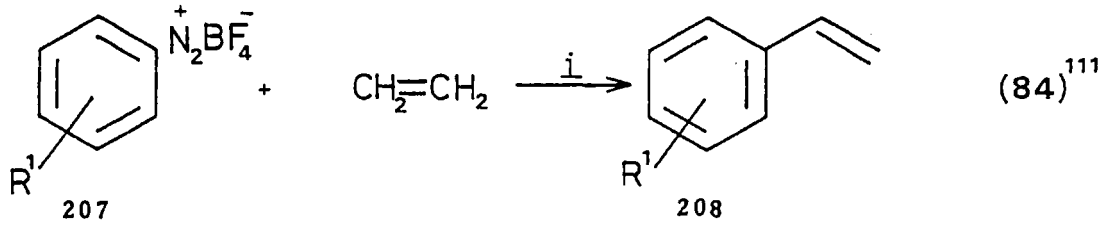
(83)[110]

R^1 = m-, p-Me; o-MeO, H, p-Br, p-I, m-, or p-NO_2.

R^2 = H, Me, Et, t-Bu, or Ph.

i, $Pd(OAc)_2$, 1-2%; MeCN; 25°

In the vinylation reaction (eqn.84) the best results were obtained where R^1 was more or less electronically neutral (e.g. R^1 = Me).



207 208

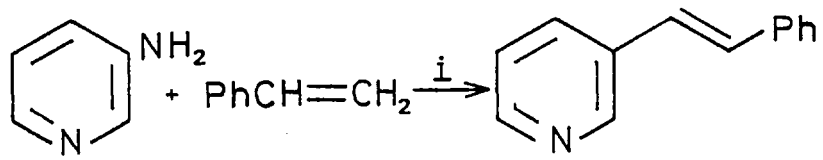
3 - 78%

(84)[111]

R^1 = o-, m-, p-Me; o-, m-, p-Cl; 2,4,6-$(Me)_3$, p-OMe, p-CO_2Me, p-Br, o-, or p-NO_2.

i, Bis(dibenzylideneacetone)palladium (0); $(CH_3)_2CO$, CH_2Cl_2; NaOAc; -78° ⟶ RT.

One of the problems in using diazonium salts as precursors to palladated aromatics is their instability; in some cases this is more evident than others. However, the combination of an arylamine and alkyl nitrite, used in the Doyle modification of the Meerwein[114] and Sandermeyer[115] reactions, was found to reduce the problems caused by the instability of certain diazonium salts, resulting in significant improvements. Application of this methodology to the palladium catalysed reaction (eqn.85) allowed the vinylation of aromatic amines such as 3-aminopyridine to proceed in reasonable yield.[112,113]



(85)[112]

209 210

i, Bis(dibenzylideneacetone) palladium (0), 5%; t-BuONO; AcOH, $ClCH_2COOH$; 50°; ½ hr; 69%

Previously, it was demonstrated [1.A. (viii)] that the reaction of allyl alcohol with aryl halides in the presence of palladium yielded the arylated propanals. Likewise, the reaction of phenyldiazonium chloride with allyl alcohol in the presence of palladium gave a 41% yield of a mixture of 3-phenylpropanal and 2-phenylpropanal in the ratio of 9 : 1 respectively[106] suggesting that after the

initial formation of the arylpalladium (II) species similar reaction paths were followed.

An interesting reaction that is related to the diazonium work is the catalytic carbonylation of 1,3-diaryltriazenes to produce arylamides (eqn.86).

$$R^1NHN{=}{=}NR^1 \quad (211) \quad + \; CO \xrightarrow{i} R^1NHCOR^1 \quad (212) \qquad (86)^{116}$$

R^1 = Ph, p-MeC_6H_4, p-FC_6H_4 or p-ClC_6H_4.

i, $PdCl_2(PPh_3)_2$, 5%; C_6H_6.

One of the mechanistic paths suggested for this reaction involved initial co-ordination of the palladium to the primary nitrogen of the triazene 211, insertion of palladium into the nitrogen-nitrogen single bond, extrusion of nitrogen (eqn.87), carbonyl insertion (eqn.88) and finally reductive elimination (eqn.89) to give the amide 212.

$$ArNHPdN{=}{=}NAr(L)_2 \xrightarrow{-N_2} ArNHPdAr(L)_2 \qquad (87)$$

$$ArNHPdAr(L)_2 \xrightarrow{CO} ArNHPdCOAr(L)_2 \qquad (88)$$

$$ArNHPdCOAr(L)_2 \xrightarrow{+2L} ArNHCOAr + Pd(L)_4 \qquad (89)$$

Many variations on the above pathway are of course possible, but the scheme outlined was a tentative suggestion. However, further evidence will have to be obtained if the true mechanism is to be discerned.

1. C. Reactions Based on the Transmetallation of Aryl Mercury and Related Compounds by Palladium (II)

Cleavage of a metal carbon bond by a metal electrophile (EM), represented schematically as:

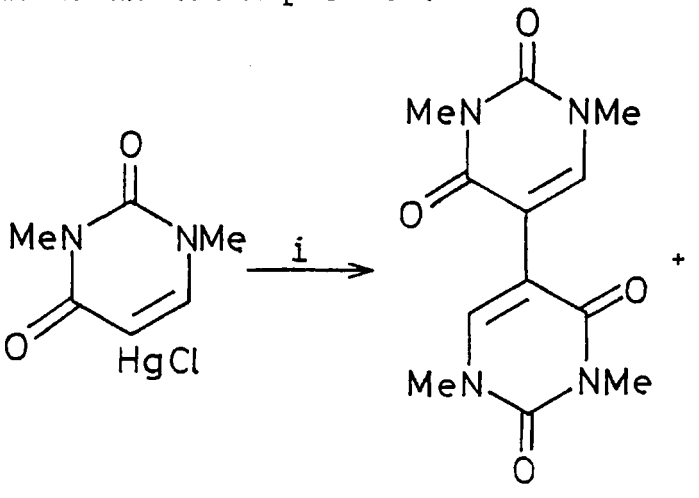
$$ArM^{II} + EM^{2+} \longrightarrow ArEM + M^{2+} \qquad (90)$$

is commonly designated as transmetallation.

Transmetallation of aryl mercury, tellurium, tin and thallium compounds with palladium (II) salts provides access to palladated aromatics.[1,22,117,118] However, the reactions discussed earlier (Sections 1.A. and 1.B.) are for the most part truly catalytic i.e. the zerovalent palladium produced at the end of each catalytic cycle is at the correct oxidation state to begin the next. The transmetallation reaction requires palladium (II), therefore an oxidant is required to convert the palladium (0) produced into palladium (II) if the catalytic cycle is to be continued. However, this is not always possible.

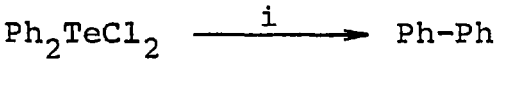
1. C. (i) Homo and Hetero Coupling

The oxidative coupling of aromatics via metallation, followed by transmetallation with palladium giving biaryls is a well known process.[118,119] The selective synthesis of symmetrical biaryls from the corresponding aryl mercury[120] tellurium[121] and thallium[122] compounds (eqns. 91, 92 and 93 resp.) depends largely upon the regiospecificity of the initial metallation process.



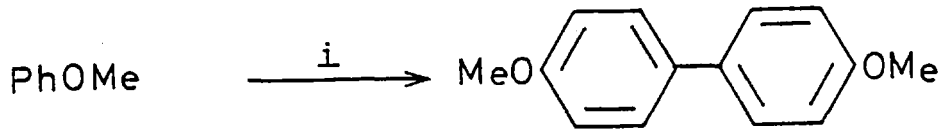
213 214 (72 %) + 215 (12 %) (91)[120]

i, $PdCl_2$, 1 eq; LiCl, 2 eq; CH_3CN; RT.



216 217 (92)[121]

i, $PdCl_2$, 1 eq; NaOAc; AcOH; reflux; 35%.



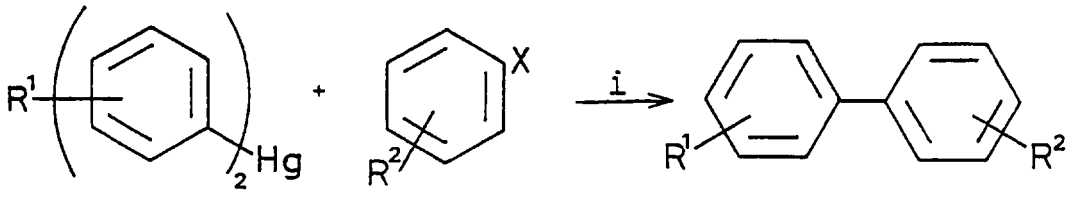
(93)[122]

218 219

i, $Tl(TFA)_3$, 1 eq; $Pd(OAc)_2$, 10% w.r.t. $Tl(TFA)_3$; 46hr; 50°; 79% w.r.t. $Tl(TFA)_3$.

The last example (eqn.93) is catalytic in palladium as the thallium (III) produced by the transmetallation process is able to oxidise palladium from the zero to the plus two oxidation state. It must be noted, however, that electron rich aromatic rings can be symmetrically coupled to form biaryls under the influence of thallium (III) salts alone.[123]

Coupling to produce unsymmetrical biaryls has been achieved by the reaction of aryl mercury compounds with aryl halides in the presence of palladium[124,125] (eqn.94).



(94)[125]

220 221 222

R^1 = p-MeO, p-Me, H, or p-Cl.

R^2 = p-O_2N; 2,4-$(O_2N)_2$; 2,4,6-$(O_2N)_3$. X = Br, or I.

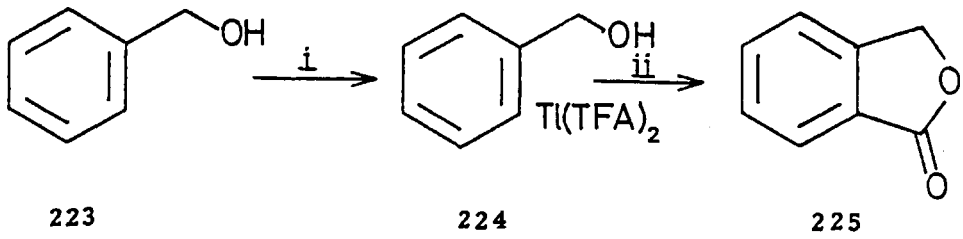
i, $PhPdI(PPh_3)_2$, catalytic; HMPT; $Bu_4N^+I^-$.

The above reaction (eqn.94) is catalytic in palladium. This can be rationalised by assuming the first step to be oxidative addition of zerovalent palladium to the aryl halide and the last step to be reductive elimination yielding palladium (0) for the continuation of the catalytic process, as was seen in the reactions of aryl halides (1.A.). As an intermediate step in the catalytic cycle, transmetallation of an aryl mercury compound by the palladated aromatic to produce a bis(aryl)palladium (II) species, is possible. It was noted that without the tetrabutylammonium iodide, significant amounts of the symmetrical biaryls $(R^1C_6H_4)_2$ were formed as by-products from the homocoupling of the aryl mercury compounds.

1. C. (ii) Carbonylation and Vinylation

Aryl palladium (II) species produced by transmetallation were found to react with olefins and carbon monoxide in a similar manner to that described for the aryl halides [1.A. (vii) and (ix) resp.].

Thallation of benzyl alcohol and similar aromatic compounds was directed by the hydroxyl group[117,126] producing ortho-thallated aromatics. For example, benzyl alcohol was converted to the benzolactone 225 by carbonylation of the thallated compound 224 in the presence of a palladium catalyst (eqn.95).

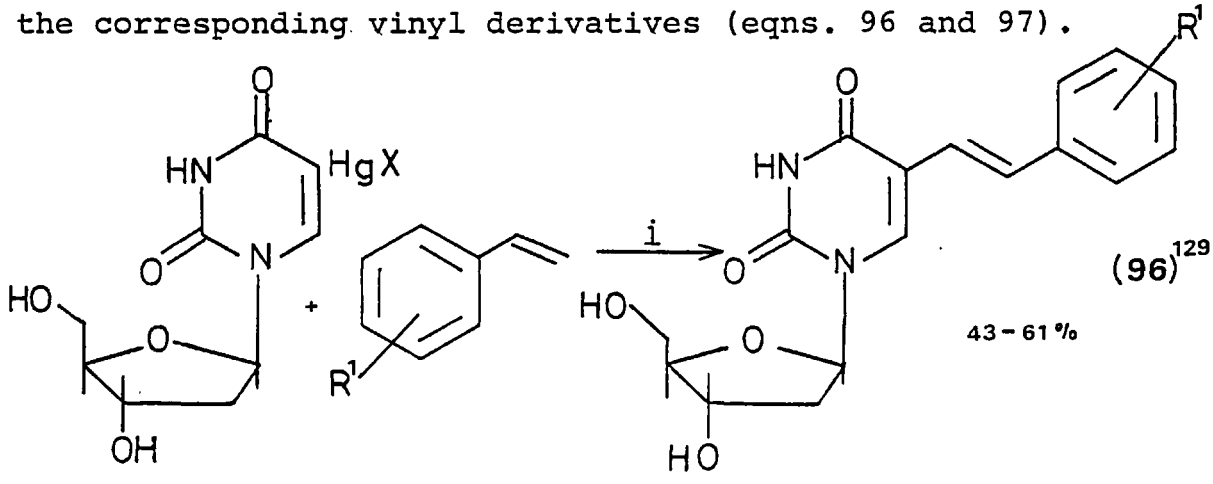


223 224 225 33% (95)[126]

i, $Tl(TFA)_3$; CF_3COOH; ii, Li_2PdCl_4, 10%; CO; THF.

Only a catalytic amount of palladium was required, as thallium (III) is a good enough oxidant to convert palladium from the zerovalent to the plus two oxidation state (c.f. eqn.93).

Styrenes[127-129] and acrylates[127,130] were smoothly coupled to mercurated aromatics with palladium to produce the corresponding vinyl derivatives (eqns. 96 and 97).



226 227 228 43-61% (96)[129]

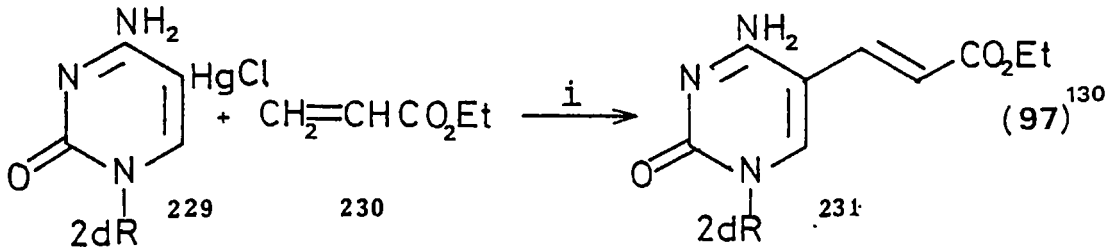
R^1 = H, m-NO_2. X = Cl, OAc, or O_2CCF_3.

i, Li_2PdCl_4, 1 eq*; MeOH.

In the above example (eqn.96) the electron deficient p-nitrostyrene coupled in only 8% yield,[129] and it was also

* On addition of excess $CuCl_2$ only 10% of Li_2PdCl_4 was required.

found that the electron rich 3,4-dimethoxystyrene coupled to phenyl mercuric acetate in poor yield (3%).[127] These examples indicate that the method may not be suitable for highly polarised styrenes.

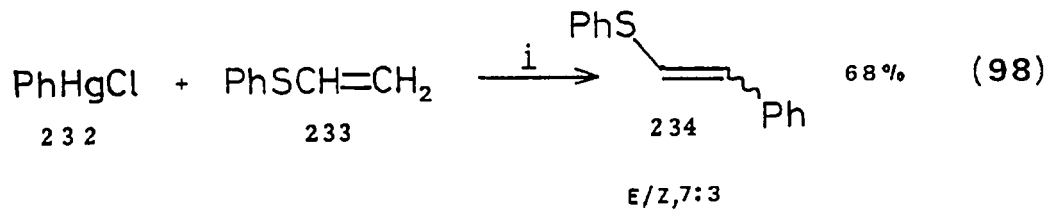


(97)[130]

i, Li_2PdCl_4. 2dR = deoxyribosyl

Aryl tellurium compounds can also be vinylated by styrenes or acrylates in the presence of stoichiometric amounts of palladium,[121] to produce the corresponding stilbenes and styrenes.

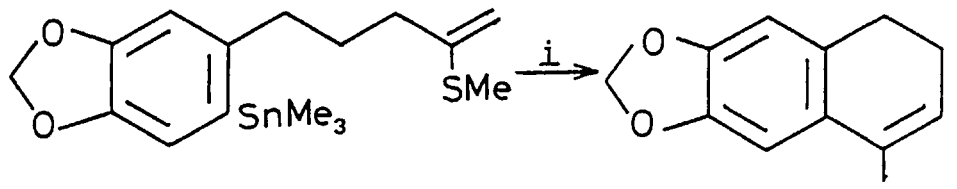
Vinyl sulphides were arylated with phenylmercuric chloride, with a palladium copper catalyst system (eqn.98).



(98)

i, Li_2PdCl_4, 6 mol %; $CuCl_2$, 1 eq; THF; RT.

Intramolecular arylation of vinyl sulphides with aryltins provided a synthesis of benzofused rings[90] (eqn. 99).

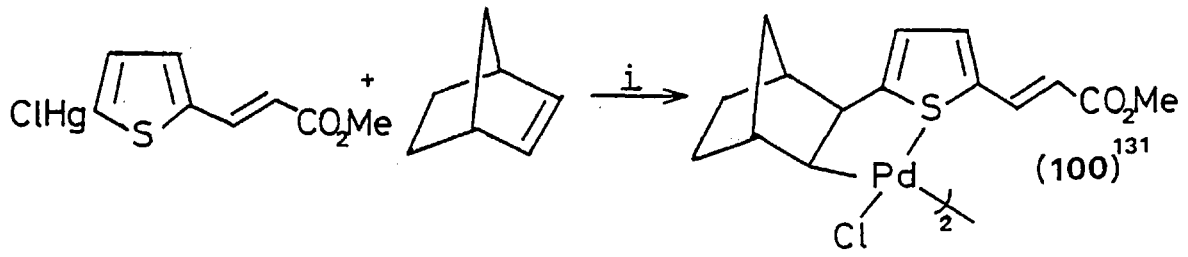


(99)[90]

235 236

i, $PdCl_2$, 1 eq; CH_3CN; 74%.

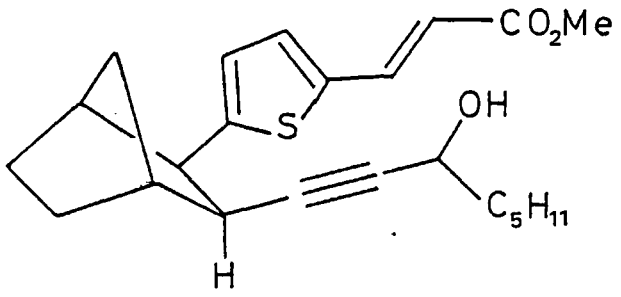
Reaction of the mercurated thiophene 237 with norbornene 238, and a stoichiometric amount of palladium produced the cyclometallated complex 239. This complex was further elaborated to produce some thiophene containing prostaglandin endoperoxide analogues e.g. 240.



(100)[131]

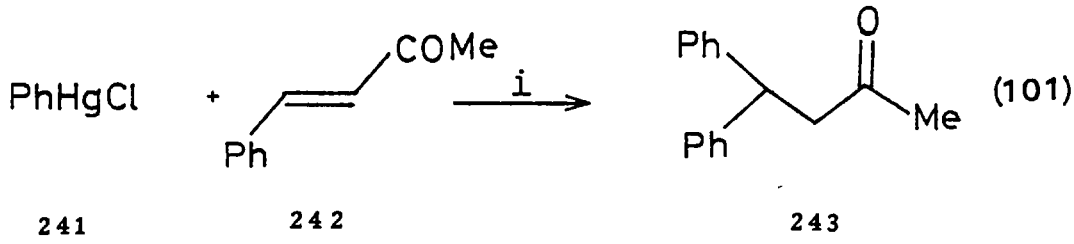
237 238 239

i, $PdCl_2$; 1 eq; LiCl, 2 eq; CH_3CN; 0° ⟶ RT.



240

Using an acidic two phase system, with tetrabutylammonium chloride as the phase transfer catalyst, α, β —unsaturated ketones were found to give conjugate addition products upon reaction with aryltin and aryl mercury compounds in the presence of palladium chloride[132,133] (eqn.101).



(101)

241 242 243

i, $PdCl_2$, 5 mol%; n-$Bu_4N^+Cl^-$, 10 mol%; 3N HCl, CH_2Cl_2, H_2O; RT; 5 hr; 85%.

This conjugate addition was found to accommodate a wide variety of aryl functional groups, both electron withdrawing and donating. The main limitations arose from steric hindrance caused by the substituents on the starting enone.

1. D. Reactions Based on the Electrophilic Substitution of Aromatics by Palladium (II)

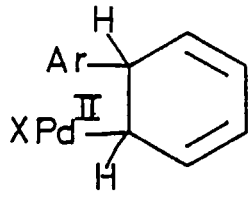
The reactions of palladium (II) salts with aromatic compounds are believed to proceed by an initial electrophilic substitution of the aromatic ring by palladium (II) to form the arylpalladium species.[22] As is evident from this statement, the products formed by the reactions of the arylpalladium species will reflect the regiospecificity of the initial electrophilic substitution, therefore mixtures of isomeric products are often obtained.

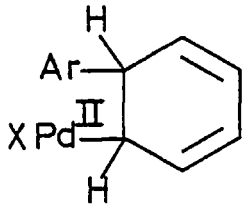
The arylpalladium intermediate can react further with another molecule of the aromatic substrate to produce biaryls or, as will be dealt with at the end of this section, ring substitution by the anionic ligand on palladium can occur if a suitable oxidising agent is present. A suggested mechanism[22] for the coupling of aromatics (Scheme 8) involves electrophilic attack by palladium (eqn.102) to form the arylpalladium intermediate followed by several steps which, in total, resemble the mechanism given for the vinylation of aryl halides [1.A. (viii)]. Alternatively, the arylpalladium (II) intermediate could electrophilically substitute a second aromatic to produce a diarylpalladium (II) species, which on reductive elimination would give the biaryl and palladium (0).

Scheme 8

$$ArH + Pd^{II}X_2 \rightleftharpoons ArPd^{II}X + HX \quad (102)$$

$$ArPd^{II}X + PhH \longrightarrow \quad (103)$$

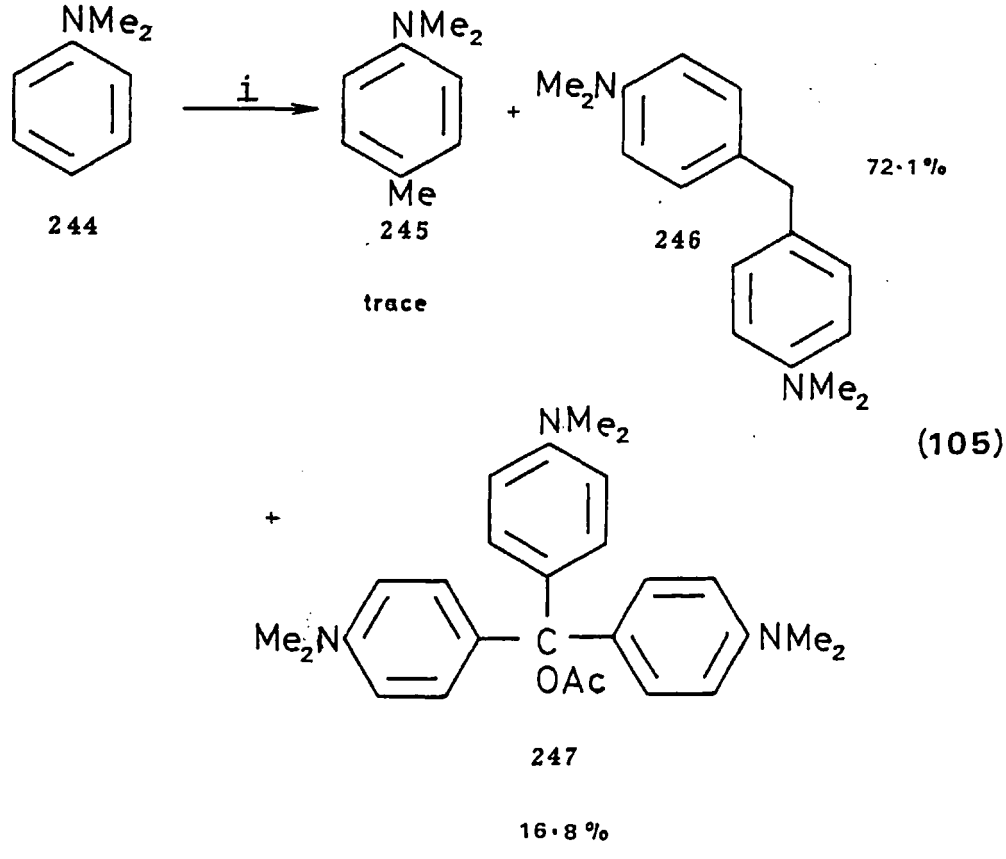




$$\longrightarrow ArPh + HPd^{II}X \quad (104)$$

In the reaction of palladium acetate and toluene in the presence of oxygen at 150° for 16 hours bitolyls were obtained in 20,600% yield, based on palladium.[134] Here the reaction was believed to proceed *via* free aryl radicals. The reactions of palladium (II) compounds with arenes are far from simple and further mechanistic work will be required before any of the pathways are fully elucidated.

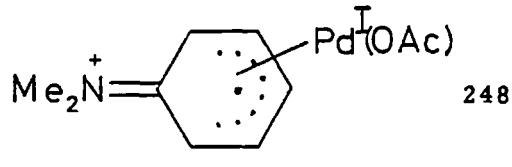
An unusual coupling was observed on the treatment of *N*, *N*-dimethylaniline with palladium acetate in acetic acid (eqn.105). Instead of the expected biaryl product (*N*, *N*, *N*′, *N*′- tetramethyl-4, 4′-diaminobiphenyl) the diphenylmethane 246 was obtained, as the major product in 72% yield[135,136] based on *N*, *N*-dimethylaniline.



(105)

i, $Pd(OAc)_2$, 0.5 eq; AcOH; 80°.

The origin of the $-CH_2-$ group was suggested to be the methyl group of palladium acetate and the formation of a radical cation palladium (I) complex 248 was tentatively suggested as a key step in the mechanism.[136] However, further work is required before any firm conclusions can be reached.

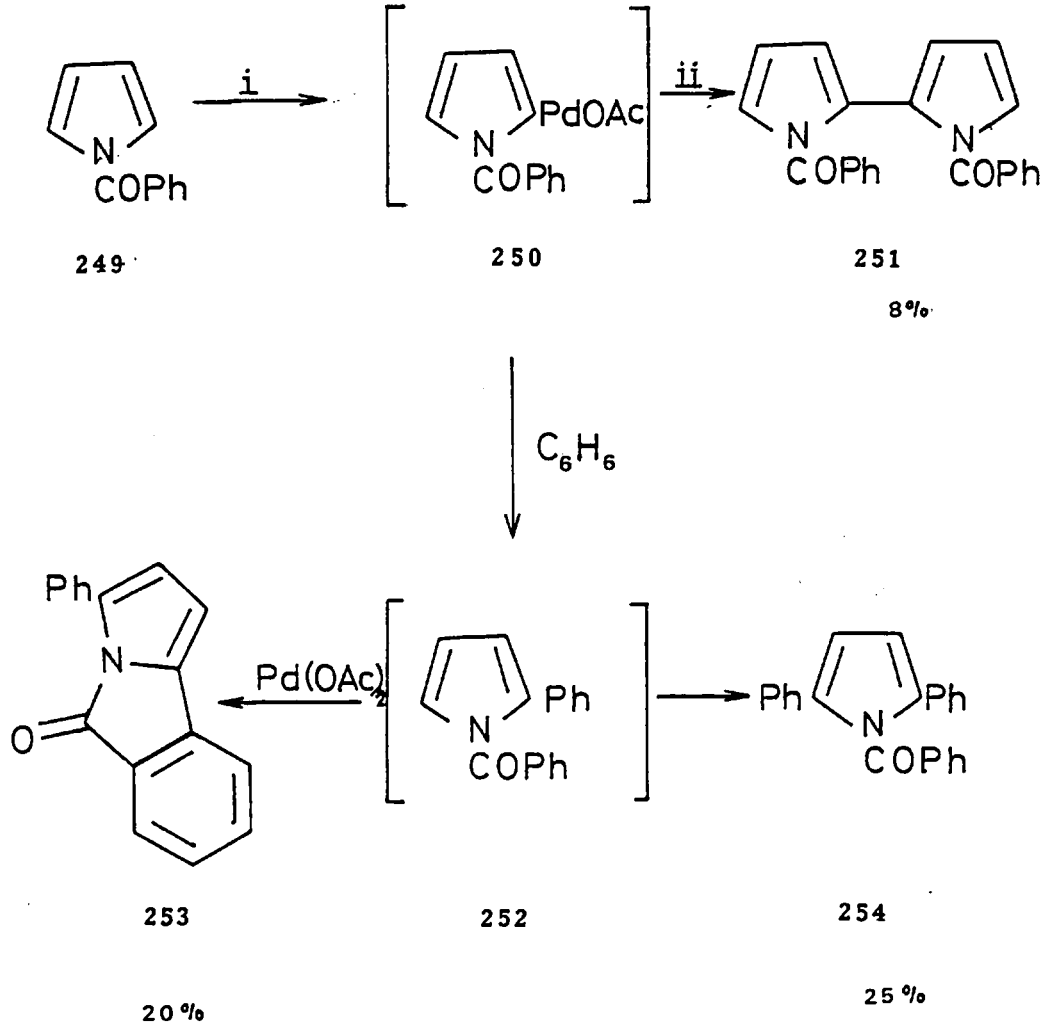


248

Treatment of N-benzoylpyrrole with palladium acetate in acetic acid containing benzene gave a mixture of products,[137] the formation of which is shown in scheme 9. The product 253 was formed by reaction between the pyrrole and benzene

rings.

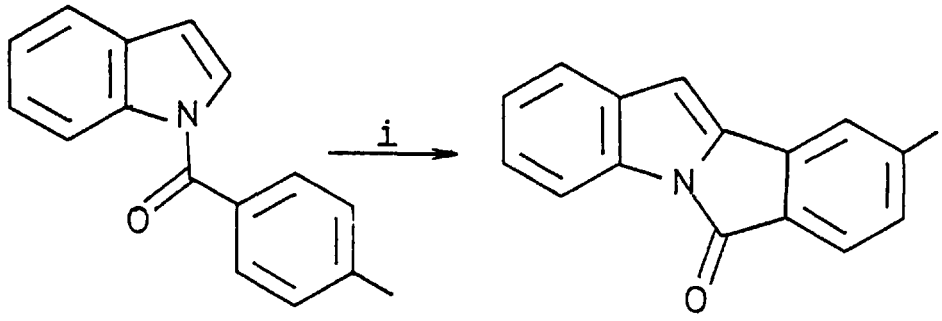
Scheme 9



i, $Pd(OAc)_2$, 1 eq; AcOH, C_6H_6; 14hr.

ii, 249 .

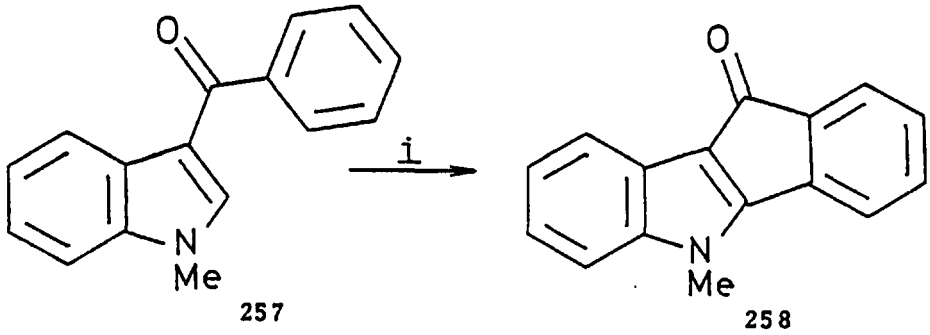
Analogously, with N-(p-methylbenzoyl) indole 255 and N-methyl-3-benzoylindole 257 the products of intramolecular reaction between the benzene and indole rings were obtained on treatment with palladium acetate in acetic acid (eqn.106 and 107 resp.).



(106)[138]

255 256

i, $Pd(OAc)_2$, 0.5 eq; AcOH; 110°; 15 hr; 42%

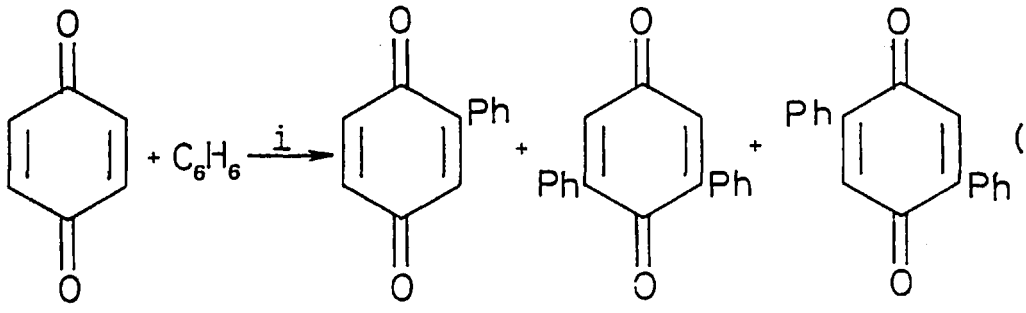


(107)[139]

257 258

i, $Pd(OAc)_2$, 0.5 eq; AcOH; 110°; 15 hr; 60%.

para-Quinone was arylated in the presence of palladium acetate and acetic acid (eqn.108) to produce a mixture of products.[140]

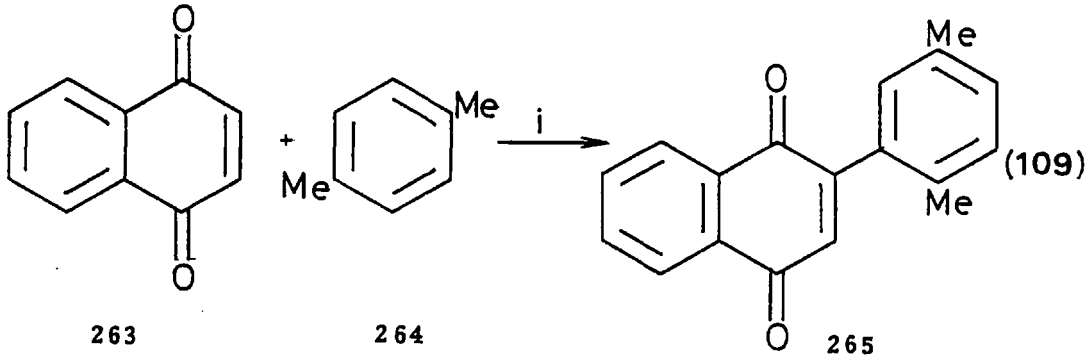


(108)

259 260 41% 261 12% 262 3%

i, $Pd(OAc)_2$, 1 eq; AcOH; reflux; 14 hr.

Arylation of 1,4-naphthaquinone 263 gave the 2-aryl-1, 4-naphthaquinones in good yields.[140,141] (eqn.109).



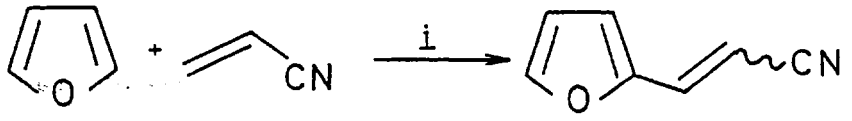
263 264 265

i, $Pd(OAc)_2$, 1 eq; AcOH; reflux; 14 hr; 78%.

The above reactions (eqns.108 and 109) are stoichiometric in palladium; however, addition of an oxidant such as copper (II) acetate may allow a catalytic process to take place.

The arylation of olefins by palladated aromatics is a well known reaction [1.A. (viii), 1.B.eqns. 84 and 85, 1.C. eqns.96-100]. As a working hypothesis quinones can be classed as a subdivision of the olefins; on this basis reaction of <u>para</u>-quinone with aryl halides to produce arylated quinones should be possible using catalytic palladium, in the presence of a suitable base.

In the presence of copper (II) salts, arenes have been successfully vinylated by olefins such as acrylonitrile,[142,143] ethylene,[144] styrene[143] and acrylates,[142,143] using catalytic amounts of palladium (e.g. eqn.110).

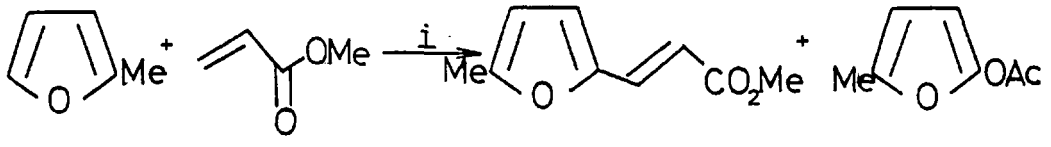


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266 267 (110)[142]

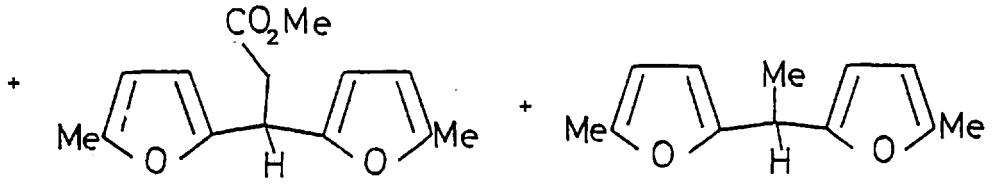
i, $Pd(OAc)_2$, 0.04 mmol; $Cu(OAc)_2$, 4.0 mmol, dioxan ; 8 hr; 100°; 1952% based on $Pd(OAc)_2$.

The vinylation of 2-methylfuran with methyl acrylate in the presence of a stoichiometric amount of palladium acetate resulted in the formation of a mixture of products[145] (eqn. 111). The products 271 and 272 were thought to have arisen by reaction of the palladated furan with the acrylate derivative 269.



268 269 270

(111)[145]



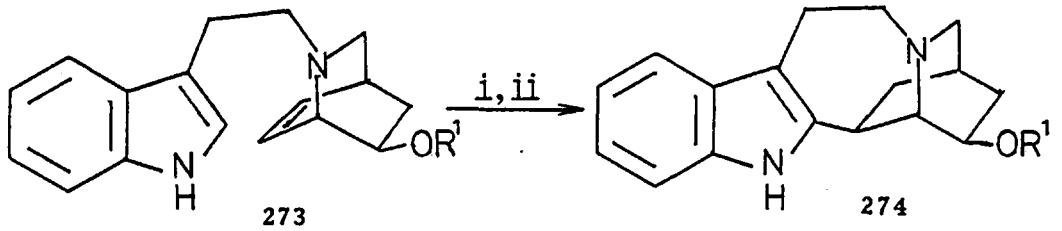
271 272

i, $Pd(OAc)_2$, 1 eq; dioxan ; reflux; 8 hrs.

Intramolecular reaction of the indole nucleus with olefins provided an elegant synthesis of 6 and 7 membered rings fused to the indole moiety.[146] This methodology was used as the key step in the syntheses of a number of iboga

alkaloids[146-149] (e.g. eqn.112).

(112)[148]



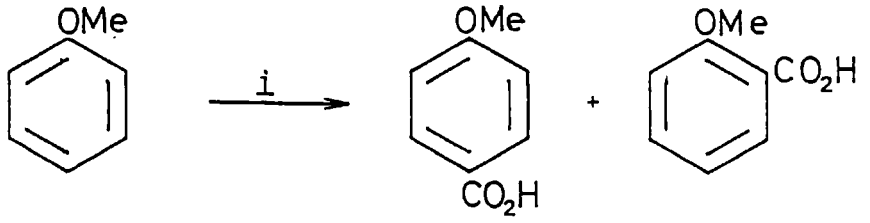
273 274 22%

$R^1 = COBu^t$

i, $PdCl_2(CH_3CN)_2$; $AgBF_4$; Et_3N; CH_3CN; 25 → 67°.

ii, $NaBH_4$; MeOH; 0°.

Direct carboxylation of aromatic compounds with carbon monoxide was found to be possible[150] and arenes such as benzene, toluene, anisole, chlorobenzene, furan and thiophene were carboxylated in the presence of palladium in low to moderate yields (e.g. eqn.113). The product distribution and the order of reactivity found for substituted benzenes indicated that electrophilic attack by palladium (II) was involved.



(113)

275 276 43% 277 5%

i, $Pd(OAc)_2$; CO, 15 atm; 20 hr; 100°.

The reaction mechanism suggested (Scheme 10) involved electrophilic attack of palladium (II) to form the aryl-palladium species (eqn.114), carbonyl insertion to form the aroylpalladium intermediate (eqn.115) then reductive elimination to form the mixed anhydride and palladium (0) (eqn.116).

Scheme 10

$$PhH + Pd(OAc)_2 \longrightarrow PhPdOAc + AcOH \quad (114)$$

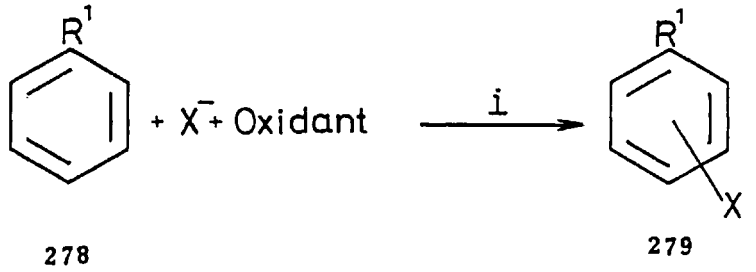
$$PhPdOAc + CO \longrightarrow PhCOPdOAc \quad (115)$$

$$PhCOPdOAc \longrightarrow PhCOOAc + Pd^{\circ} \quad (116)$$

$$PhCOOAc + AcOH \longrightarrow PhCO_2H + Ac_2O \quad (117)$$

It was later reported[151] that by carrying out the above reaction under slightly different conditions anhydrides could be isolated. Carbonylation of benzene in the presence of palladium (II) chloride and copper (II) chloride at 180-190° produced initially benzophenone which on further carbonylation produced anthraquinone.[152]

The reaction between aromatics and palladium acetate, as mentioned earlier, generally leads to biaryls; however in the presence of an added oxidant, biaryl formation is suppressed and ring acetoxylation becomes the major reaction.[1,10] It was found that not only acetate, but also other nucleophiles could be introduced into the aromatic ring with palladium acetate in the presence of strong oxidants[1,10,153] (eqn.118).



278 279 (118)

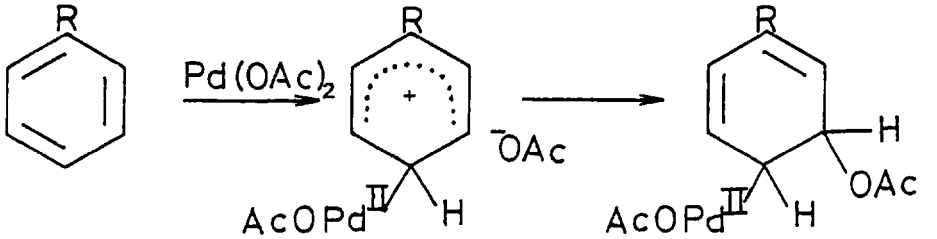
Oxidant = $K_2Cr_2O_7$; $KMnO_4$; $Pb(OAc)_4$; $NaClO_4$; $NaNO_3$; or CrO_3.

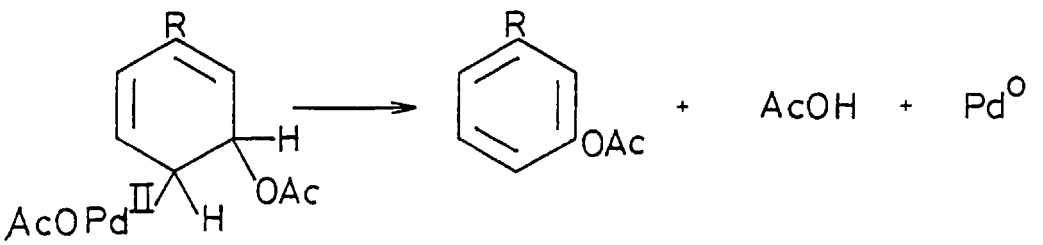
X^- = Cl^-, NO_2^-, N_3^-, SCN^-, AcO^-.

i, $Pd(OAc)_2$.

When the substituent on the aromatic nucleus 278 R^1 was an ortho, para directing group, the isomer distributions obtained were rich in the meta isomer. The isolation of high amounts of the meta isomers is explained by the mechanism proposed below[10,22,154,155] (Scheme 11).

Scheme 11





Kinetic studies were carried out on the reaction of benzene and palladium acetate in acetic acid (eqn.119) in the presence of sodium dichromate.[153]

$$C_6H_6 \xrightarrow{i} \underset{40\,3\%}{C_6H_5OAc} + \underset{<1\%}{Ph\text{-}Ph} \qquad (119)$$

i, $Pd(OAc)_2$, 1 eq; $Na_2Cr_2O_7$, 15 eq; AcOH; 90°; 16 hr; yields based on palladium.

It was noted that use of lower concentrations of oxidant resulted in more of the biphenyl by-product being formed. Kinetic data suggested that for both biphenyl formation and ring acetoxylation phenylpalladium (II) acetate is a common intermediate. This intermediate could react with benzene in a second electrophilic substitution reaction to yield diphenylpalladium (II) which on reductive elimination would give biphenyl and palladium (0). In the presence of dichromate it was suggested that phenylpalladium (II) acetate was intercepted and oxidised to an unstable phenylpalladium (IV) compound, decomposition of which provides phenyl acetate and regenerates the electrophilic catalyst as shown in eqns. 120 and 121.

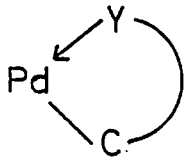
$$C_6H_5Pd^{II}OAc \xrightarrow{OX} C_6H_5Pd^{IV}(OAc)_3 \qquad (120)$$

$$C_6H_5Pd^{IV}(OAc)_3 \longrightarrow C_6H_5OAc + Pd^{II}(OAc)_2 \qquad (121)$$

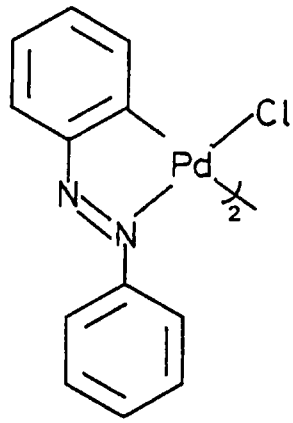
OX = Oxidant

PART 2 REACTIONS OF CYCLOPALLADATED AROMATICS

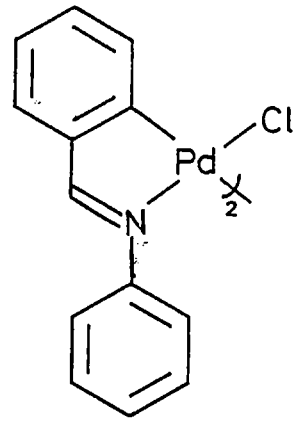
Organopalladium compounds which fall into the class of cyclopalladated are those which contain the ring system shown below.



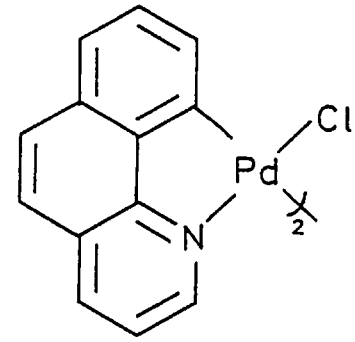
The palladium is covalently bound to carbon and coordinated by a Group V (N, P, As) or Group VI (O, S) donor atom "Y". The chemistry of these compounds has been the subject of several review articles.[156-158] The cyclopalladated complexes dealt with in this review are those in which the palladium is bonded to an aromatic system with the donor atom "Y" being N, O, or S. Numerous examples of these complexes are known,[159] a few of which are listed below.



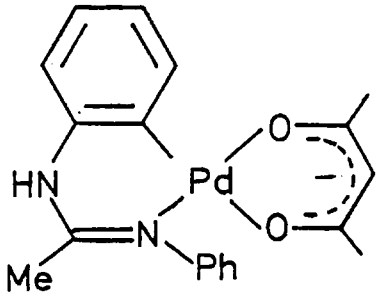
280 (ref.160)



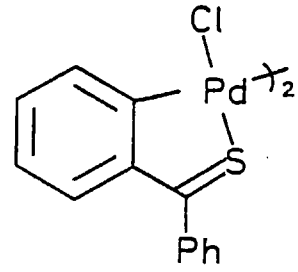
281 (ref.161)



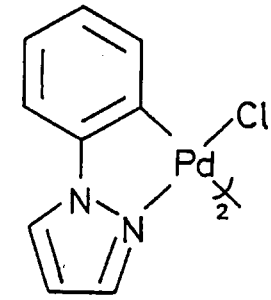
282 (ref.162)



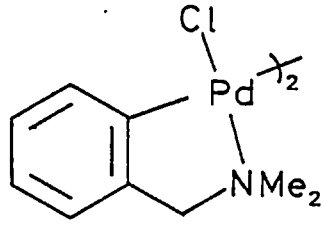
283 (ref.163)



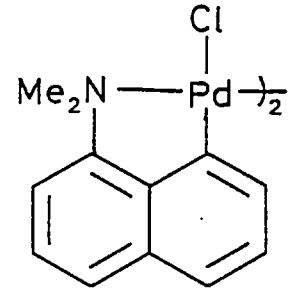
284 (ref.164)



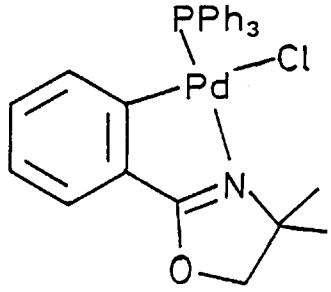
285 (ref.165)



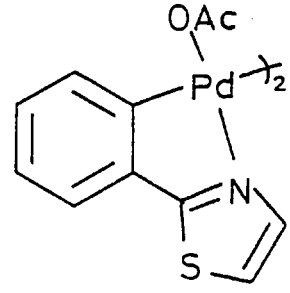
286 (ref.166)



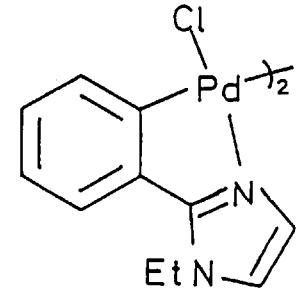
287 (ref.167)



288 (ref.168)



289 (ref.169)



290 (ref.170)

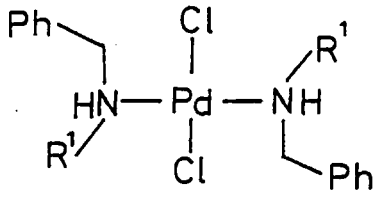
Of the vast number of these complexes known, relatively few have been used in organic synthesis and it is the recent work on the organic reactions of these complexes that this review will cover.

In Part 1 of this review the reactions of palladated aromatics were surveyed; many of the reactions described have been applied to cyclopalladated aromatics. With this in mind, this part of the review has been divided in a similar manner, the reactions of the complexes with a particular class of substrate will be grouped together under a heading denoting the substrate concerned.

Unlike the palladated aromatic species dealt with in Part 1, the cyclopalladated aromatics are, in general, stable and easily isolated, thus enabling a full characterisation to be carried out.

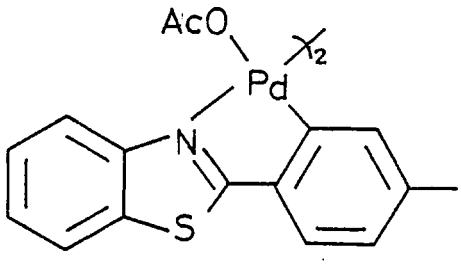
From experimental observations, certain criteria for the formation of cyclopalladated aromatics containing a nitrogen donor atom have been deduced.[156,157,171-177] Initial co-ordination of the palladium (II) by the nitrogen donor ligand is followed by an electrophilic attack onto the carbon ortho to the substituent containing the nitrogen donor ligand. As would be expected for an electrophilic process, electron releasing substituents on the aromatic ring enhance the reaction and electron withdrawing substituents retard it. The cyclopalladation reaction

is favoured if a five membered ring containing palladium is formed by the electrophilic attack. The substitution of the nitrogen atom is important. Primary and secondary benzylamines were found to give only ML_2X_2 type complexes[166] where L is only co-ordinated *via* nitrogen to the metal and X is an anionic ligand as shown below. For steric reasons

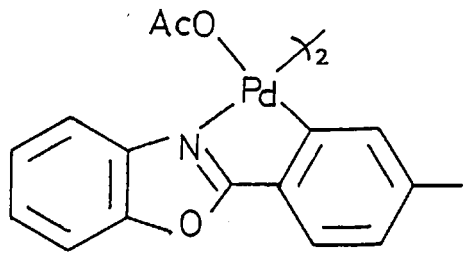


primary and secondary amines should co-ordinate more strongly to the metal than tertiary amines, the stronger co-ordination was suggested[158] to decrease the electrophilic character of the metal sufficiently so that in some cases electrophilic attack upon the aromatic does not occur.

Cyclopalladated aromatics containing a sulphur donor ligand are less easily formed than the corresponding nitrogen analogues.[178,179] Nitrogen donation is found to be preferred over both sulphur and oxygen[180] *cf.* compounds 288, 289, 291 and 292.

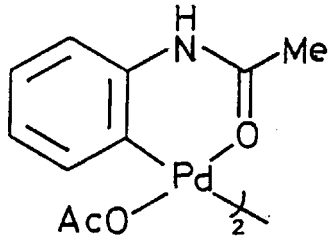


291 (ref. 180)



292 (ref. 180)

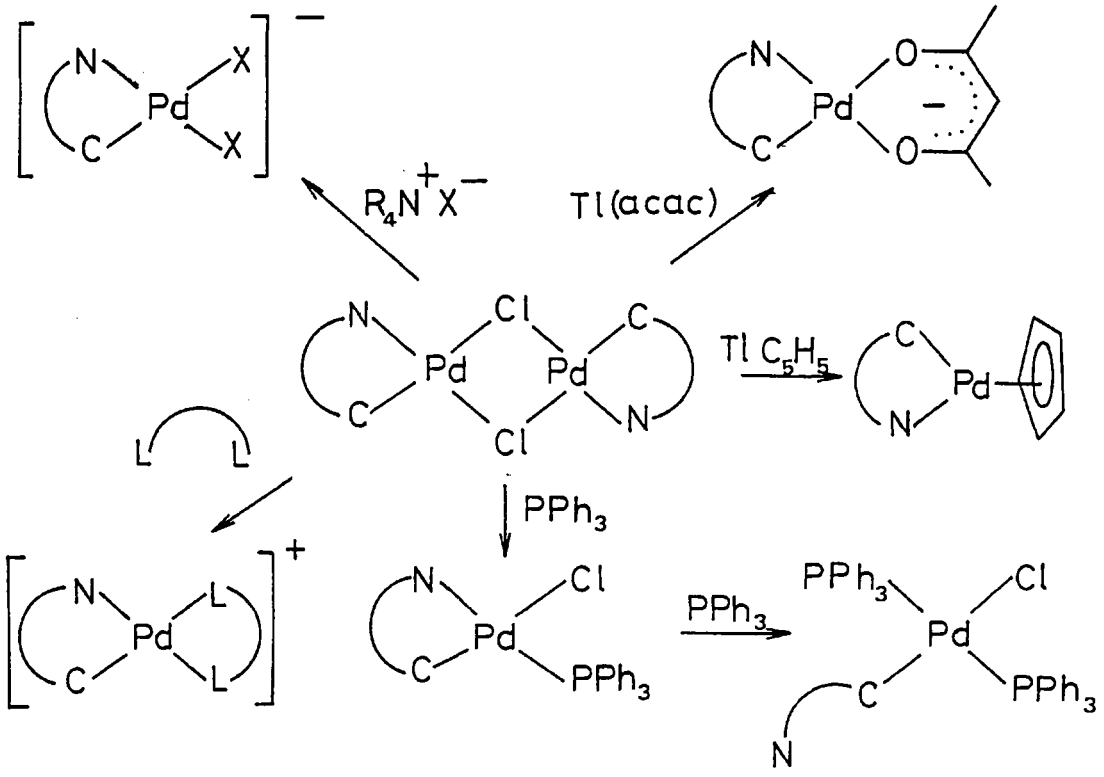
Few cyclopalladated complexes with oxygen donor ligands are known,[156,163,180,181] one example being the acetanilide complex 293.



293 (refs.181,182)

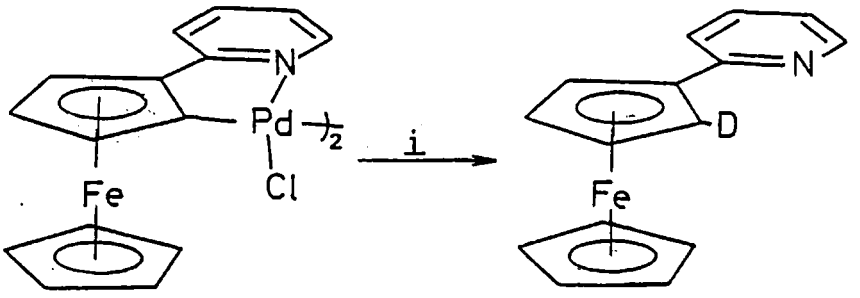
The metal carbon σ bond in cyclopalladated complexes is fairly robust, a variety of reactions can be carried out which leave it intact.[156,157] A selection of these are shown below (Scheme 12).

Scheme 12



2. (i) Reduction

The reduction of ortho-palladated complexes with lithium aluminium hydride was first reported by Cope;[160] reduction with lithium aluminium deuteride leads to the direct replacement of palladium with deuterium, providing a method for structural elucidation[160,183-185] (eqn.122).



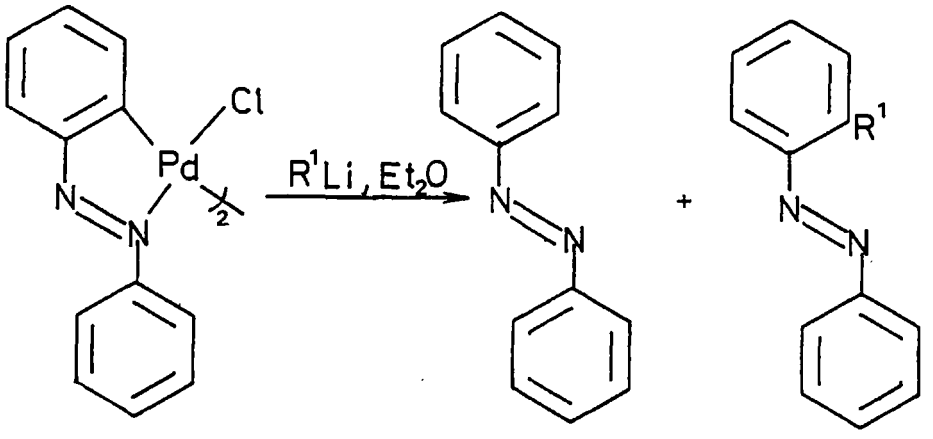
(122)[183]

294 295

i, $LiAlD_4$; Et_2O.

2. (ii) Nucleophiles

The reaction of ortho-palladated complexes with organolithium or Grignard reagents results in regiospecific carbon-carbon bond formation.[183,186,187] The reaction of the azobenzene complex 296 with organolithium reagents resulted in the formation of the reductive products 297 as well as the desired ortho-substituted products 298 (eqn.123).



(123)[187]

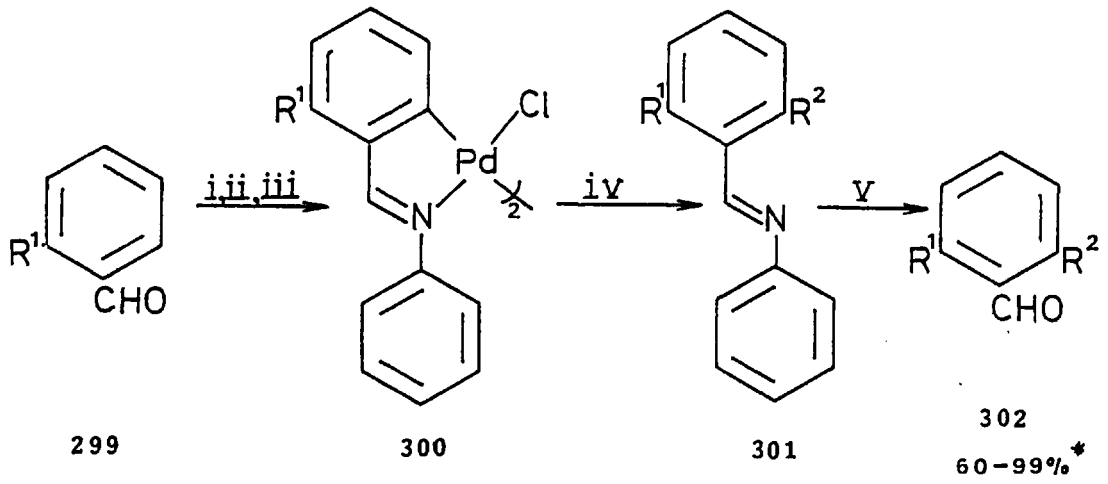
296 297 298

R^1 = Ph	58 %	42 %
R^1 = Me	44 %	55 %

Addition of four equivalents of triphenylphosphine to the reaction (eqn.123,R^1 = Me) resulted in a 91% yield of the ortho-substituted product 298 being obtained with none of the reductive product 297. The triphenylphosphine can co-ordinate the dimeric palladium complexes initially splitting them into monomers, as shown in scheme 12, thus solubilizing the complexes and also stabilizing them throughout the reaction.

The reaction of Schiff base complexes with organo-lithium or Grignard reagents provides a route to ortho-substituted benzaldehydes (Scheme 13).[186,187]

Scheme 13



299 300 301 302

60-99%*

R^1 = H, Me, OMe, Cl; R^2 = Me, n-Bu, Ph, n-Pr.

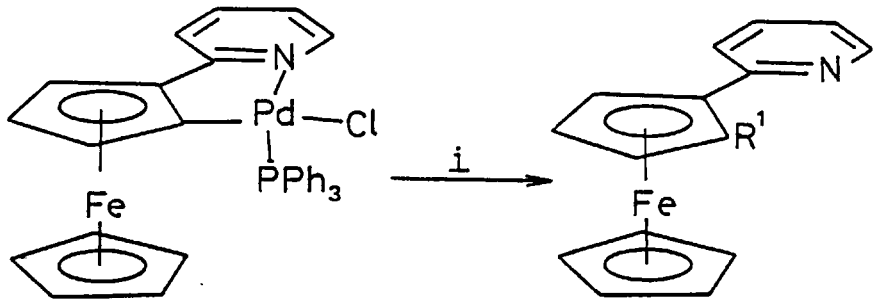
i, $PhNH_2$; ii, $Pd(OAc)_2$, AcOH; iii, NaCl; $(CH_3)_2CO$, H_2O

iv, R^2Li; Et_2O; v, H_3O^+.

A variation on the above reaction (Scheme 13), using 6 - 8 molar equivalents of triphenylphosphine, has been patented[188] for the preparation of various 2-formylbiphenyls.

The ortho-palladated 2-pyridylferrocene complex 303 was treated with n-butyl-lithium and phenyl-lithium to give 2-butyl-1-(2-pyridyl)ferrocene and 2-phenyl-1-(2-pyridyl)ferrocene in 34% and 27% yields respectively (eqn.124).

* Based on the palladium complex 300.



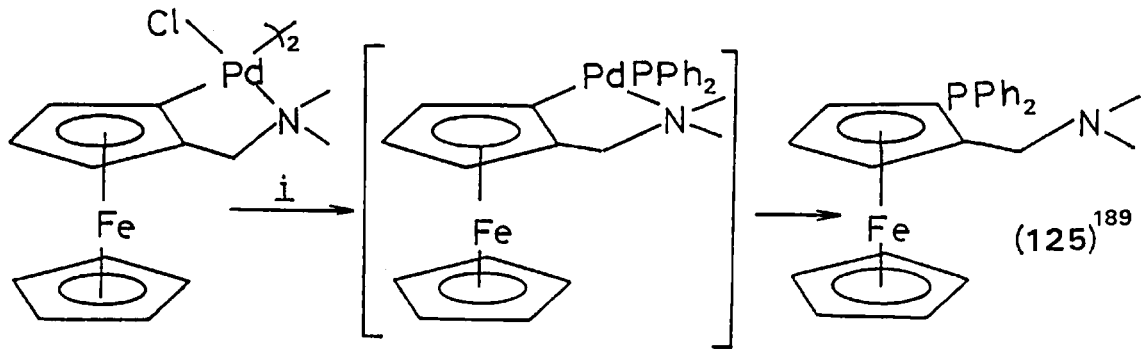
(124)[183]

303 304

R^1 = Ph or n-Bu.

i, R^1Li; Et_2O, PhH; 50°; 8hr.

The reaction of the N,N-dimethylaminomethylferrocene complex 305 with lithium diphenylphosphide in tetrahydrofuran at 10° (eqn.125) yielded 1-diphenylphosphino-2-dimethylaminomethylferrocene 307, presumably via the intermediate 306. By starting with optically active 305, preparation of the aminophosphine 307 in high enantiomeric purity was possible. Optically active aminoalkylferrocenylphosphine ligands have been claimed to be effective in asymmetric hydrogenation hydrosilylation and coupling reactions.[189]



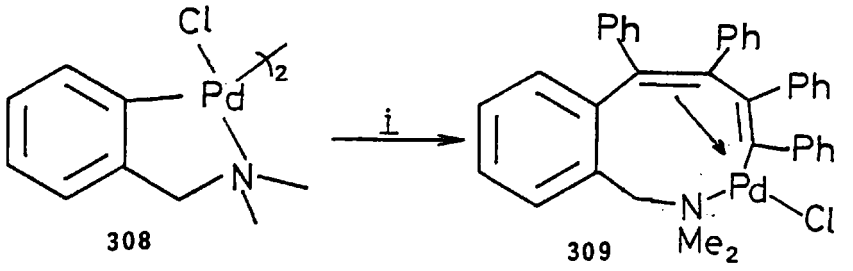
(125)[189]

305 306 307

i, $LiPPh_2$; THF; 10°.

2. (iii) Acetylenes

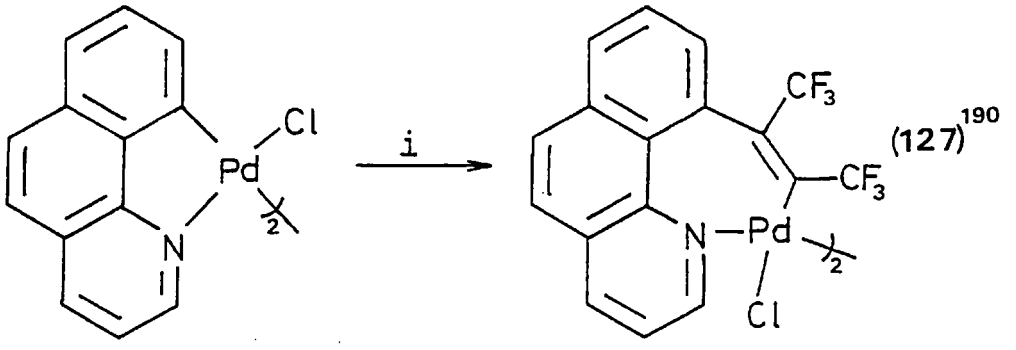
The reaction of disubstituted acetylenes with ortho-palladated complexes has been reported to give isolable insertion adducts[190] (eqn.126).



308 309 (126)[190]

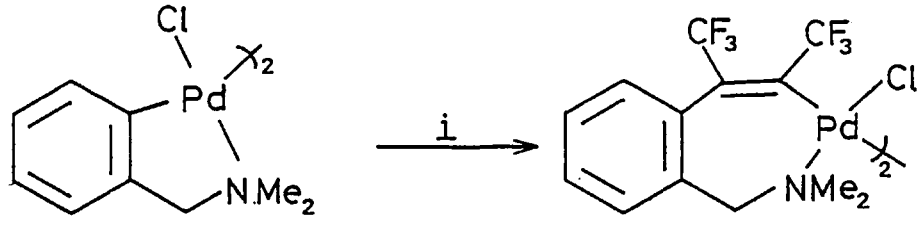
i, PhC≡CPh; CH_2Cl_2; 24 hr; reflux.

No reaction took place between the cyclopalladated complexes formed from benzo[h]quinoline, azobenzene or N, N-dimethyl-1-naphthylamine (cf. complexes 282, 280, and 287 resp.) and diphenylacetylene.[190] However, the benzo[h] quinoline complex 282 reacted with hexafluoroprop-2-yne to give the mono-insertion adduct (eqn.127) as did the N, N-dimethylbenzylamine complex (eqn.128).



282 310 (127)[190]

i, CF_3≡CF_3; CH_2Cl_2; 60°.

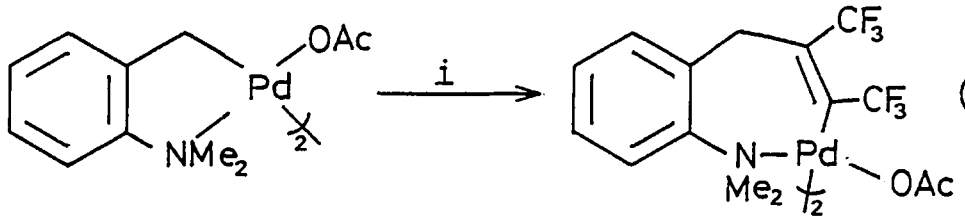


(128)[190]

311 312

i, $CF_3{\equiv}CF_3$; CH_2Cl_2; reflux; 20-24 hr.

Similar reactions were observed when the related complex 313 was treated with hexafluoroprop-2-yne.[191,192] (eqn.129)



(129)

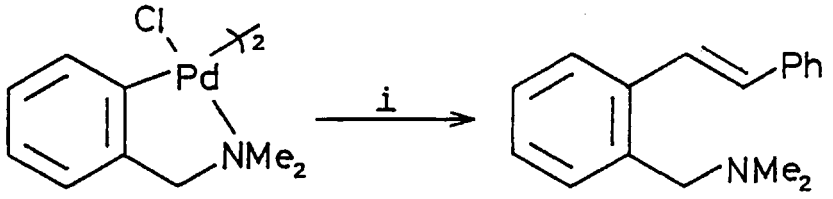
313 314

i, $CF_3{\equiv}CF_3$.

As a first step, π co-ordination of the acetylene to the palladium splitting the dimeric complex into monomers would seem reasonable. Insertion of acetylenes into the palladium carbon σ bond in a cis fashion is well known.[22] Repetition of this process, as is known for the cyclo-oligomerization of acetylenes,[22] would yield the "doubly inserted" products 309.

2. (iv) Olefins

The first report of the reaction of a cyclopalladated aromatic complex with an olefin was made by Tsuji[193] (eqn. 130), however few details were given. Since that time, a wide variety of olefins have been found to react with

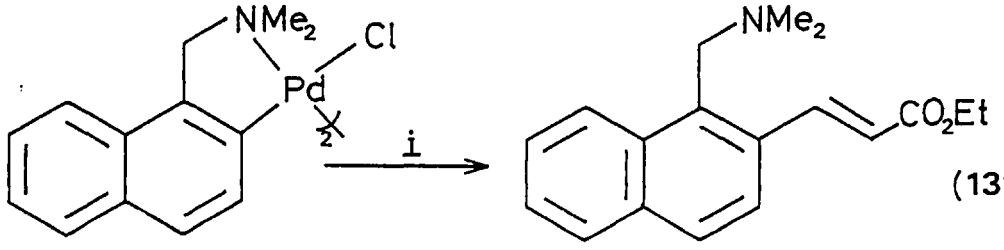


(130)[193]

315 316

i, $PhCH{=}{=}CH_2$, AcOH.

N, N-dimethylaminomethylarene complexes (cf. cpds. 316,317). Ethyl acrylate was found to smoothly react with the N, N-dimethylaminomethylnaphthalene complex 317 to produce the

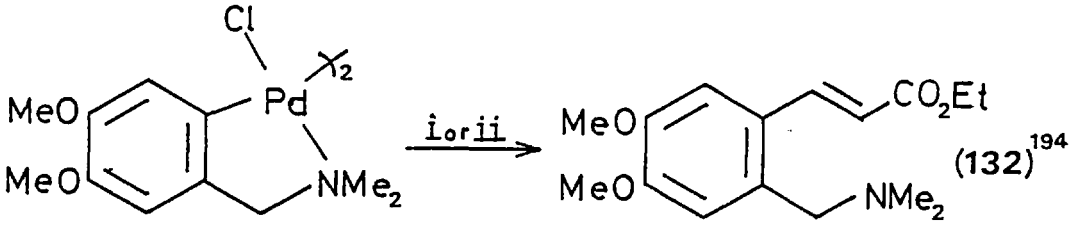


(131)[184]

317 318

i, $CH_2{=}{=}CHCO_2Et$; AcOH; 100°; 70%.

ortho-substituted product 318. Similar results were found for the reaction of the 3,4-dimethoxy-N,N-dimethylbenzylamine complex 319 with acrylate[194] (eqn.132).



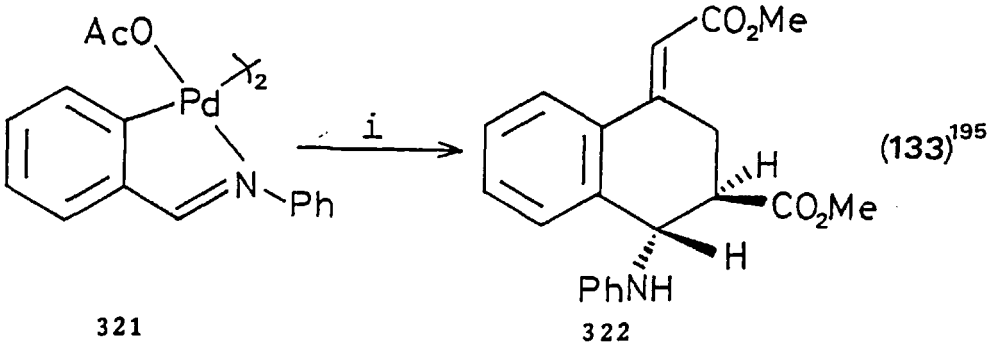
(132)[194]

319 320

i, $CH_2{=}CHCO_2Et$; PhH; Et_3N; reflux; 2 hr, 85%.

ii, $CH_2{=}CHCO_2Et$; AcOH, CH_2Cl_2, 3:1; Et_3N; 0° → RT; 48 hr, 93%.

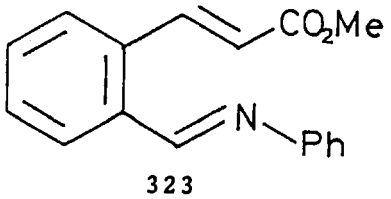
Reaction of the Schiff base complex 321 with methyl acrylate at 100 - 150° in acetonitrile was reported to yield the tetralin derivative 322 (eqn.133), the formation of which was rationalised by the addition of a second acrylate molecule to the initial insertion product 323.



(133)[195]

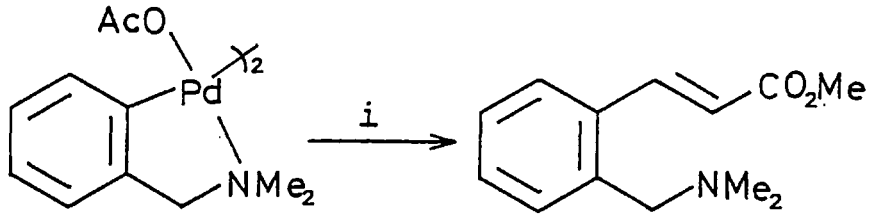
321 322

i, $CH_2{=}CHCO_2Me$; CH_3CN; 100-150°; 10%.



323

Treatment of the acetate bridged N,N-dimethylamine complex 324 with methyl acrylate in acetonitrile at 150° gave the expected insertion product 325 but only in low yield (eqn.134).

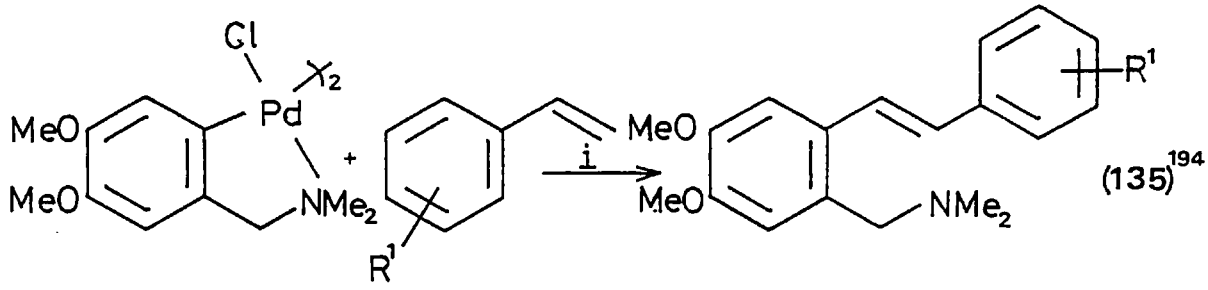


(134)[195]

324 325

i, $CH_2{=}{=}CHCO_2Me$; CH_3CN; 150°; 51hr; 17.5% isolated; 39% by gas chromatography.

It was claimed that at lower temperatures no reaction occurred. It is possible that the solvent, acetonitrile, co-ordinated to palladium lowering the extent of co-ordination by the methyl acrylate. It has also been reported[194,196] that styrene did not react with the related chloro bridged N,N-dimethylamine complex 326 in refluxing toluene or benzene in the presence of triethylamine. However, by carrying out the reaction in acetic acid/dichloromethane mixtures, high yields of the expected trans-stilbene derivatives were obtained (eqn.135) and best yields were obtained with R^1 = H or p-Cl.



(135)[194]

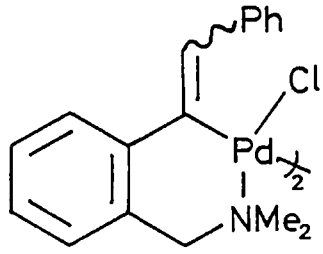
326 327 328

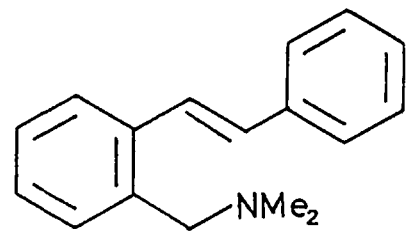
32 - 94%

R^1= H; p-OMe; o-, m-, p-Cl; o-, m-, p-NO_2.

i, AcOH, CH_2Cl_2, 3:1; Et_3N; 0° ⟶ RT; 48 hr.

In contrast to the above results (eqn.135), other workers reported[196] that reaction of the complex 326 with styrene in benzene/acetic acid mixtures gave a new complex, whose structure was tentatively assigned as 329. After

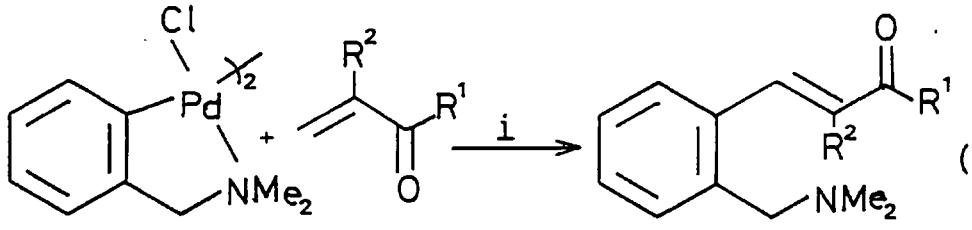




329 330

further work[197] on this reaction it was claimed that carrying out the reaction under an oxygen atmosphere resulted in the formation of the complex 329, whereas under an argon atmosphere the normal product 330 was obtained.

Treatment of N,N-dimethylbenzylamine complex with α, β-unsaturated enones in refluxing toluene or benzene containing an excess of triethylamine gave rise to the corresponding β-aryl enones (eqns. 136 and 137).



(136)[198]

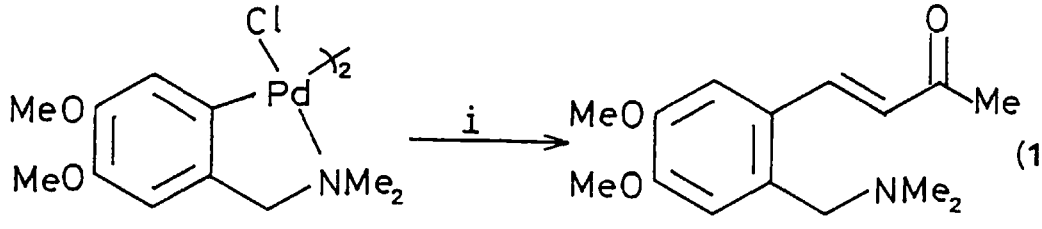
331 332

80 - 96%

R^1 = Me, Cyclo-C_6H_{11}, or Ph, R^2 = H; R^1 = Me, R^2 = Ph.

i, PhMe, Et_3N, reflux.

In the above reaction, α-substituents on the enone were tolerated but with more hindered enones containing a β-substituent, i.e. 3-pentene-2-one and cyclopentenone, no reaction occurred.

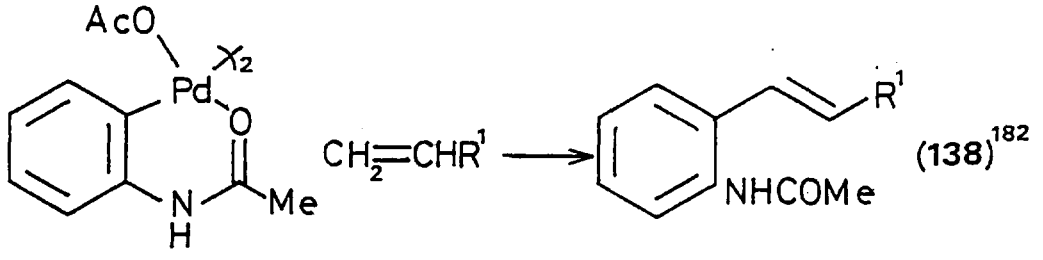


(137)[194]

333 334

i, CH_2=CHCOMe; PhH; Et_3N; reflux; 2 hr; 98%.

The acetanilide complex 335 was found to react with a wide variety of olefins in refluxing toluene in the presence of triethylamine[181,182](eqn.138).



335 336 (138)[182]

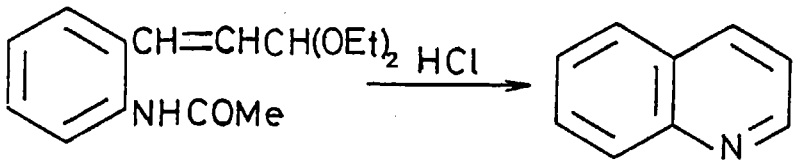
40 - 83%

R^1 = Ph, 3,4-$OCH_2OC_6H_3$, 3-AcO-4-$MeOC_6H_3$, CN, $CH(OEt)_2$, CO_2Me, COMe, OAc, or H*.

The electron rich olefins 3,4-methylenedioxystyrene and vinyl acetate gave only moderate yields, 43% and 44% respectively, of the desired product 336 [cf. 1.A.(viii)], while 3-acetoxy-4-methoxystyrene, in which the olefin would be expected to be slightly less electron rich than the 3,4-methylenedioxystyrene, gave the ortho-substituted product 336 in good yield, 80%. A number of ring substituted acetanilide complexes, containing methyl,methoxy,chloro,acetyl and ethoxycarbonyl groups, were synthesised and were also found to react smoothly with methyl vinyl ketone or ethylene. The ortho-vinylated acetanilides produced by this methodology were shown to be useful precursors to quinolines, quinaldines

* The reactions of ethylene were carried out at 3 atmospheres pressure, 50°.

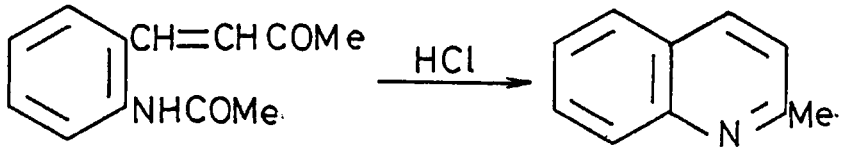
and carbostyrils as shown by the examples (eqns.139, 140 and 141 resp.) below.



337 338

80%

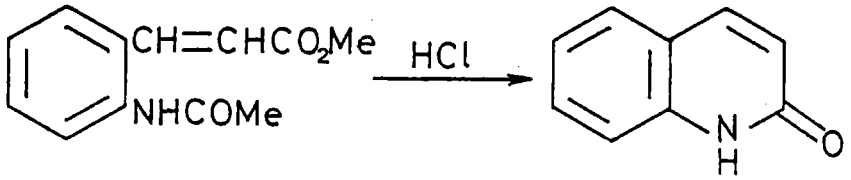
(139)[182]



339 340

70%

(140)[182]

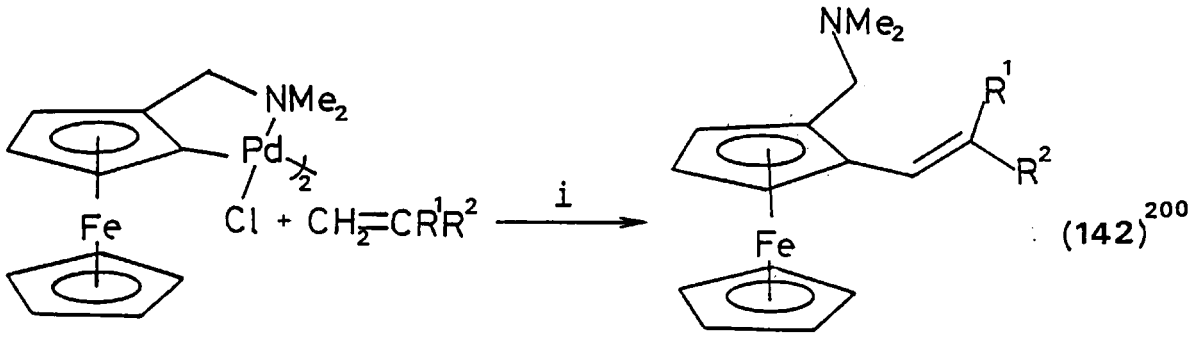


341 342

54%

(141)[182]

ortho-Palladated ferrocene and ruthenocene complexes have been vinylated by a number of olefins[185,199-202] (e.g. eqns. 142,143 and 144).

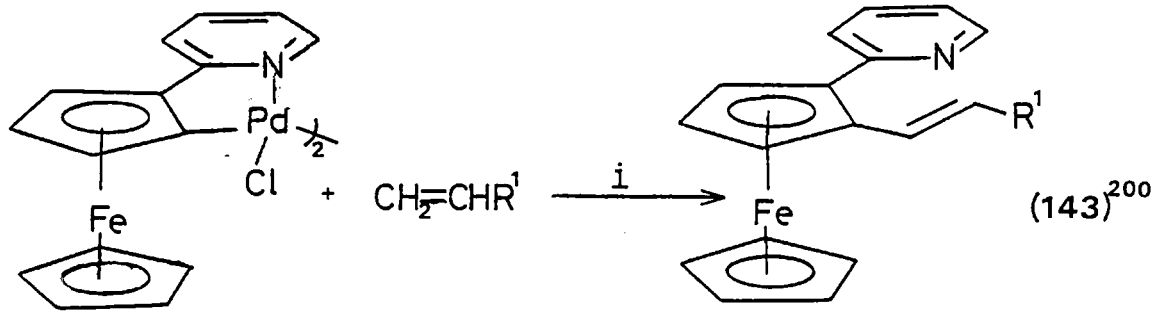


343 344 (142)[200]

27 - 59%

R^1 = H, R^2 = Ph, CO_2Et, CN, COMe, or COPh.

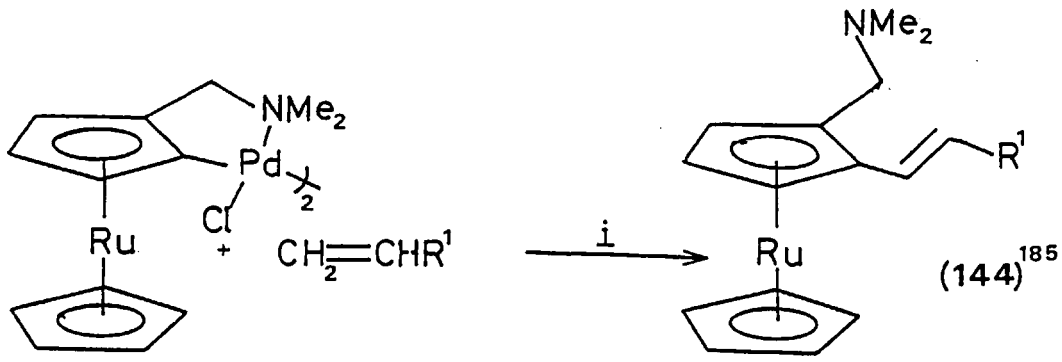
R^1 = Me, R^2 = CO_2Me.



345 346 (143)[200]

R^1 = COMe, COPh; 8% and 20% resp.

i, Et_3N; PhMe; 100°.



347 348

89 - 94%

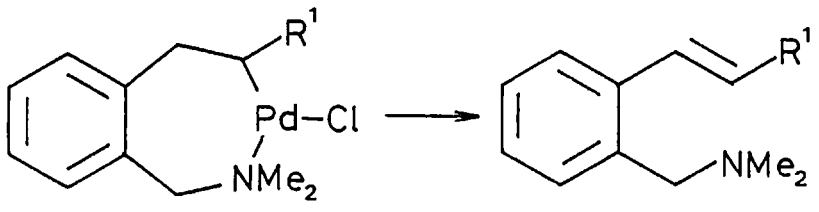
(144)[185]

R^1 = COMe, COPh, or Ph.

i, Et_3N; PhMe; 80°; 5 hr.

Reactions in which optically active N, N-dimethyl-aminoalkylferrocene cyclopalladated complexes have been used, yield the optically active ortho-vinylated product.[199,201,202]

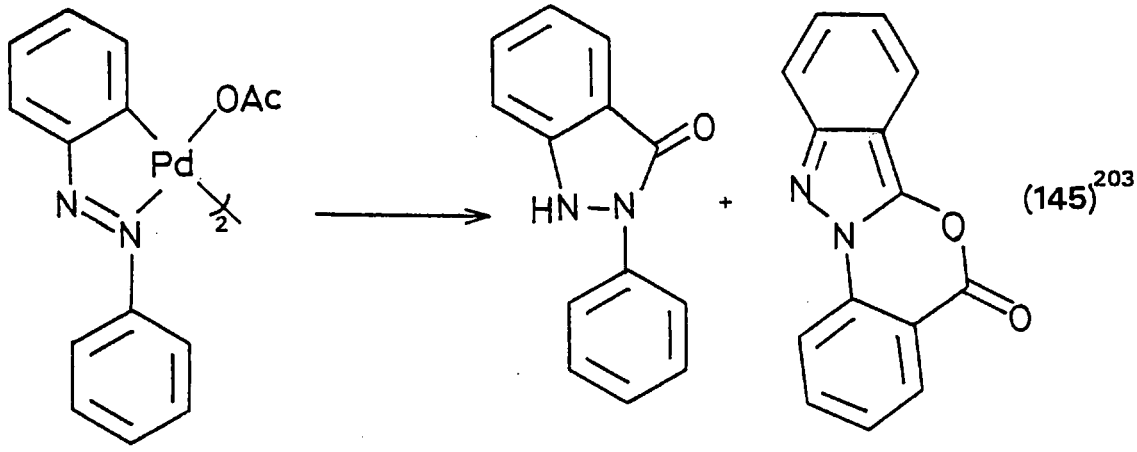
The mechanism of olefin insertion is believed to be basically the same as that mentioned earlier[194,195] [1.A. (viii)]: co-ordination of the olefin to palladium, insertion to produce the large ring chelate structure 349 and finally β-elimination to product. The trans stereochemistry obtained is due to steric considerations in the β-elimination process.



349 350

2. (v) Carbonylation

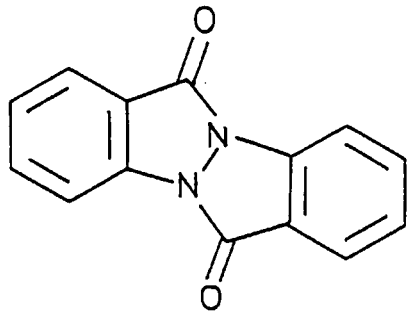
Earlier work on the carbonylation of cyclopalladated complexes has been covered in the reviews quoted.[156-158] However, one reaction, the carbonylation of the azobenzene complex 351 in chlorobenzene at 100°, was reported[203] to give 2-phenyl-1H-indazolone 352 and the lactone by-product 353 (eqn.145).



(145)[203]

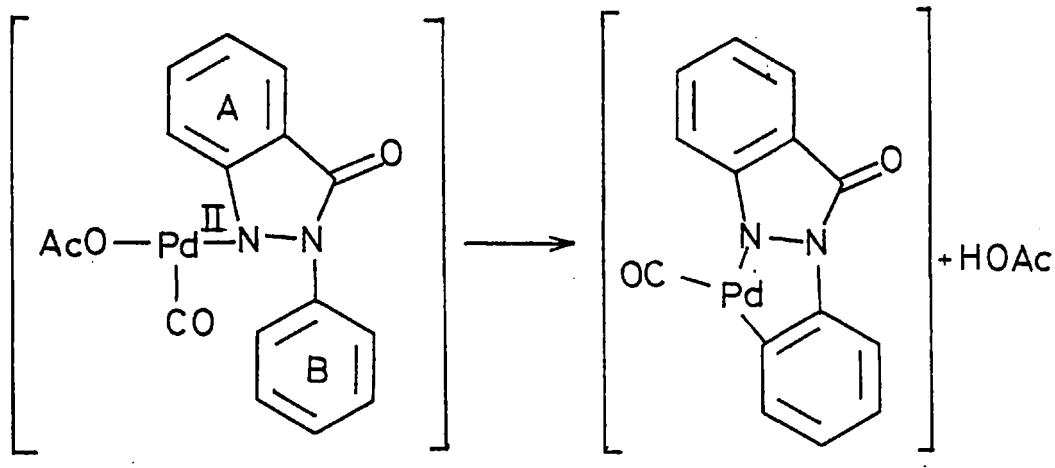
351 352 353

In a recent review[204,205] on the synthesis of heterocycles using transition metals, it was claimed that the structure of the by-product 353 has been incorrectly assigned, its true structure being the condensed indazolone derivative 354.



354

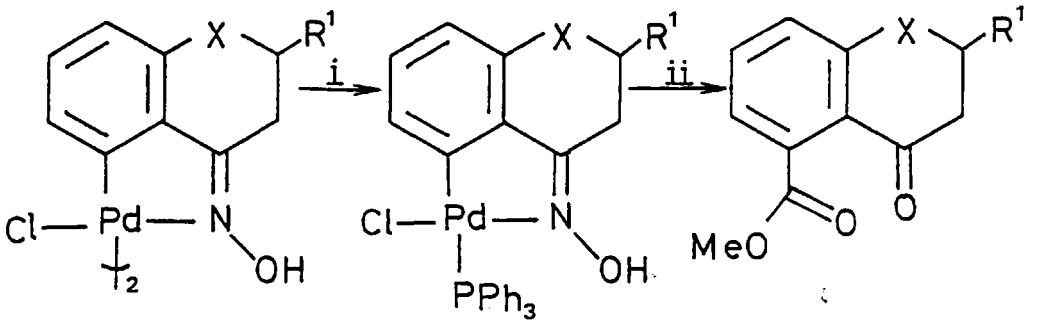
One of the intermediates proposed by Heck[203] for the carbonylation of azobenzene complex 351 is that shown below 355. Electrophilic attack by palladium on



355 356

ring B could give a new cyclometallated complex 356, carbonyl insertion into the palladium-carbon or possibly the palladium-nitrogen bond, followed by reductive elimination would yield 354.

In more recent examples, the reaction of carbon monoxide with cyclopalladated complexes has been used for the introduction of ortho-carboxylate substituents. Carbonylation of dimeric 4-chromanone oxime complexes 357 (eqn.146) was found to be unsuccessful. However, the momomeric complexes 358 were readily carbonylated in the presence of methanol to give the esters 359.



(146)[206]

357 358 359

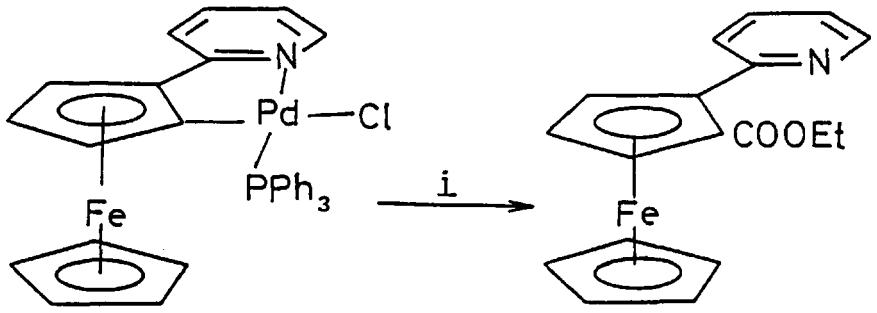
65 - 75 % 28 - 45 %

R^1 = H, X = O; R^1 = Ph, X = O; R^1 = Me, X = S.

i, PPh_3; PhH .

ii, MeOH; CO, 60 atm; 100°.

Similarly, carbonylation of chloro-[2-[(dimethylamino)⊃ alkyl] ferrocenyl]-(triphenylphosphine)palladium (II) complexes,[199,201] chloro-[2-[(dimethylamino)methyl] ⊃ ruthenocenyl]-(triphenylphosphine)palladium (II),[185] and chloro-[2-(2-pyridyl)ferrocenyl]-(triphenylphosphine) palladium (II)[183] in alcoholic solvents led to the introduction of an ortho-carboxylate substituent (e.g. eqn.147). If optically active ortho-palladated ferrocene complexes are used, optically active ferrocence carboxylates are isolated.[199,201,202]

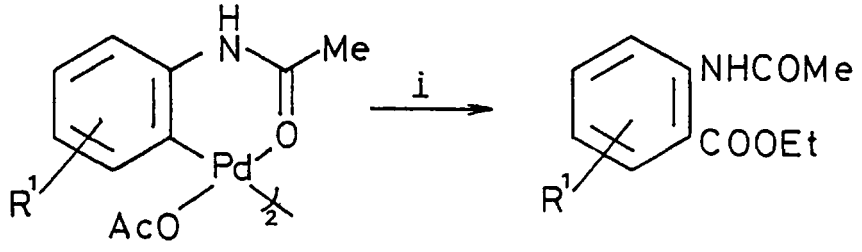


(147)[183]

360 361

i, EtOH; CO, 80 atm; 100°; 10 hr; 37%.

Carbonylation of the acetanilide complexes 362 in ethanol gave the corresponding N-acetylanthranilic esters[181,182] (eqn. 148) in moderate to good yields. Methyl, methoxy, chloro, ethoxycarbonyl and acetyl substituents were tolerated, the best yields being obtained where R^1 = H or p-Cl (79 and 99% resp.).

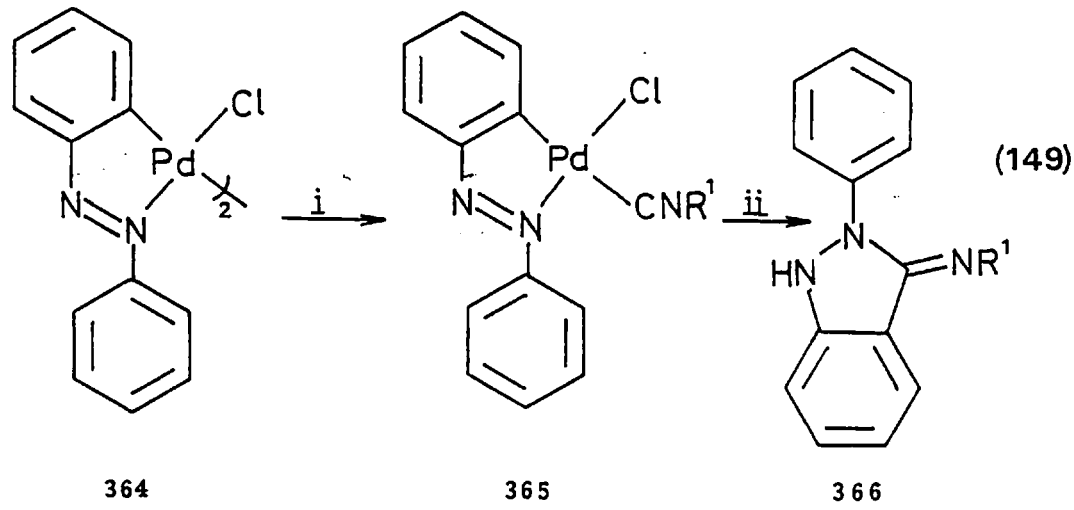


(148)[182]

362 363

i, EtOH; CO, 2 atm; 60 min; RT.

Closely related to the carbonyl insertion reactions, outlined above, is the insertion of isocyanides into palladium-carbon sigma bonds. The first case involving an ortho-palladated complex is shown below (eqn.149), the intermediate complex 365 is stable and can be easily characterised.[207,208]



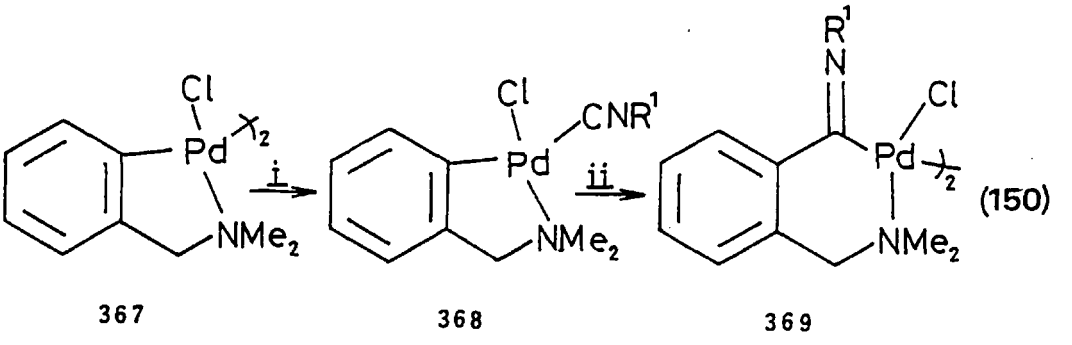
(149)

364 365 366

R^1 = o-MeC_6H_4.

i, $R^1NC;CH_2Cl_2$,PhH; RT. ii, PhMe; Δ ; 89%.

Later work[209] on the reaction using N, N-dimethylbenzylamine complexes allowed isolation of the insertion adduct 369 (eqn.150).



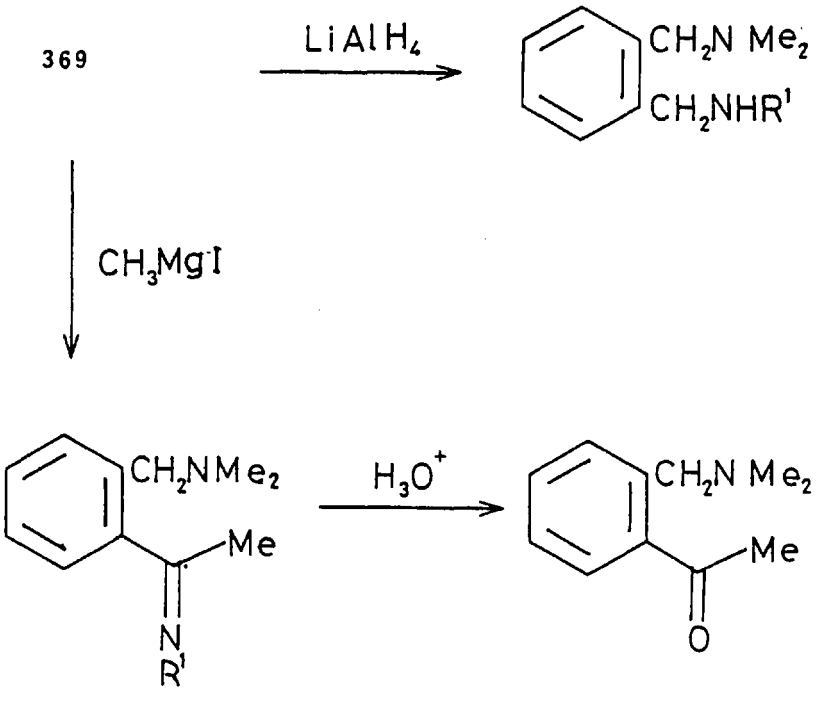
367 368 369

R^1 = o-MeC_6H_4 .

i, R^1NC; CH_2Cl_2; RT; 85%. ii, THF; Δ; 75%.

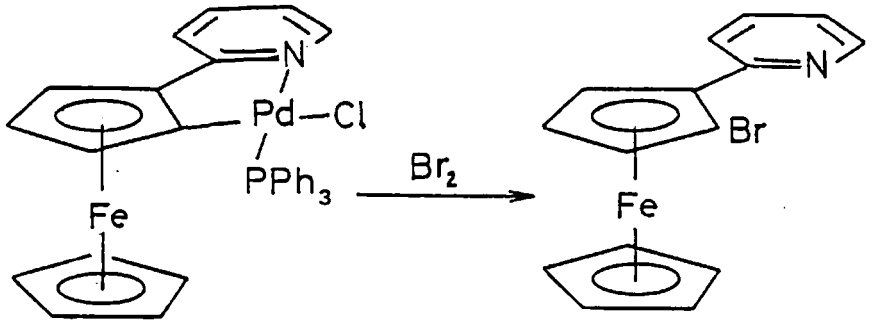
Several reactions were carried out upon the insertion adduct 369, e.g. scheme 14, indicating its possible use as a precursor to a large variety of ortho-substituted aromatics.

Scheme 14



2. (vii)

Treatment of cyclopalladated complexes with halogen results in the introduction of an ortho-halogen substituent. The first reported reaction, by Fahey,[210,211] was the chlorination of the cyclopalladated azobenzene complex 280, this reaction has been dealt with in previous reviews.[1,156-158] Treatment of the cyclopalladated (2-pyridyl)ferrocene complex 370 with bromine in chloroform resulted in a 35% yield of 2-bromo-1-(2-pyridyl)ferrocene (eqn.151).

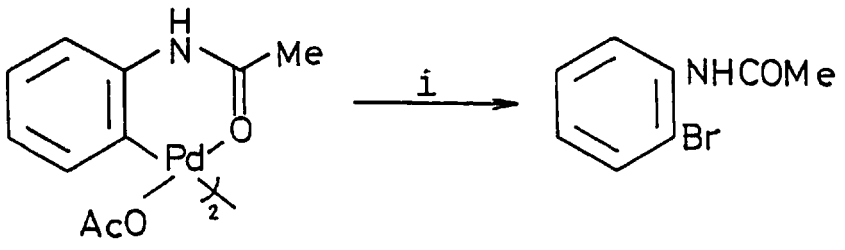


(151)[183]

370 371

It has been claimed that reaction of the related N,N-dimethylaminomethylferrocene cyclopalladated complex 343 with iodine would yield the ortho-iodo-N,N-dimethylaminomethylferrocene derivative.[201]

Bromination of the acetanilide complex 372, resulted in selective ortho-bromination[182] (eqn.152), uncomplexed acetanilide on treatment with bromine gives the p-bromoacetanilide.

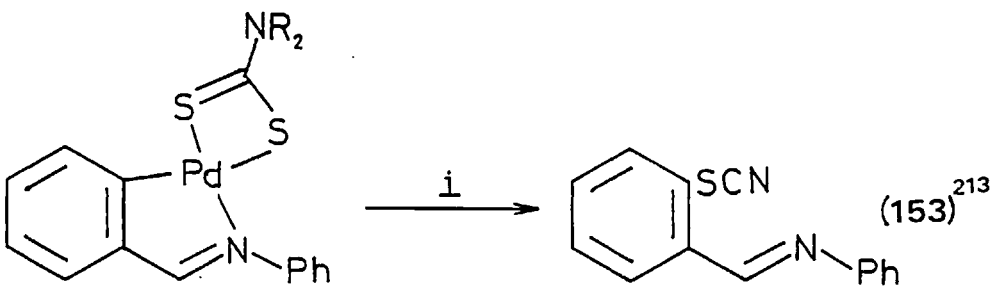


(152)

372 373

i, Br_2; NaOAc; CH_2Cl_2, CCl_4; 30 mins; RT; 70%.

It is well known that aromatic compounds undergo electrophilic substitution reactions with halogens, the halogenation of cyclopalladated complexes could be viewed as an electrophilic displacement of palladium (II) by the halogen electrophile. Alternatively, oxidative addition of the halogen to palladium (II) to give an unstable palladium (IV) complex, which would reductively eliminate to produce the aryl halide and palladium (II) could occur. It is known that platinum (II) complexes can react with halogens to afford isolable hexa-co-ordinate platinum (IV) complexes, whereas the equivalent palladium (IV) complexes are too unstable to allow isolation.[212] Thiocyanogen, which is also an electrophilic reagent, reacted with various cyclopalladated complexes to give the corresponding thiocyanato compounds[213] (e.g. eqn.153)

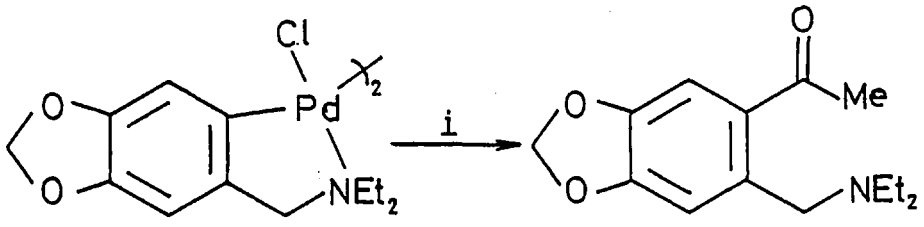


(153)[213]

374 375

i, $(SCN)_2$; $CHCl_3$.

N, N-Dialkylbenzylamine complexes were found to react with acid chlorides under mild conditions to give aryl ketones[214] (eqn.154). Complexes in which the aryl ring contained electron donating substituents gave the best results; with chloro substituents the reaction did not proceed at all, this is in agreement with an electrophilic type mechanism. It was suggested[214] that oxidative addition of the acid chloride to the cyclopalladated complex might give rise to a complex 378 possessing a hexa- or penta-co-ordinate

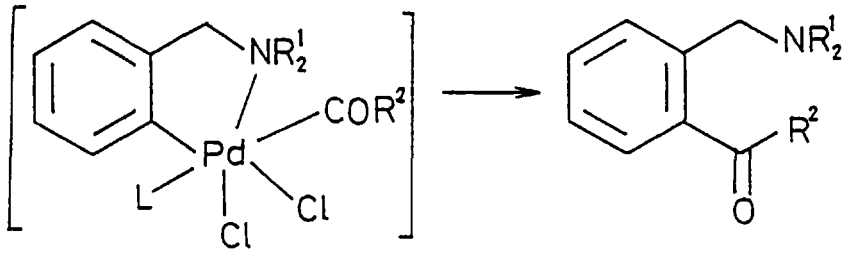


(154)

376 377

i, CH_3COCl; CH_2Cl_2;reflux; 12 hr; 81%.

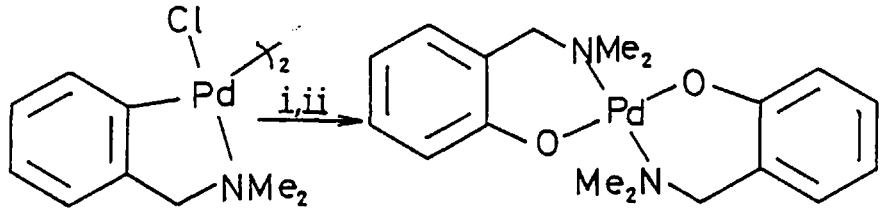
Pd(IV) aryl, as a transient intermediate, and collapse of the complex 378 to the observed products via reductive elimination would proceed rapidly (eqn.155).



(155)

378 379

Oxygenation of the N, N-dimethylbenzyamine cyclopalladated complex 380 was found to be possible using m-chloroperbenzoic acid (eqn.156).



(156)[215]

380 381

i, MCPBA; CH_2Cl_2; 0°; 30 mins; ii, MeOH; $NaBH_4$.

In this section all the reactions quoted (eqns. 151 - 156) can be classed as reactions of electrophiles with cyclopalladated aromatic complexes. The reactions of many more electrophiles with these complexes will have to be carried out before the mechanism can be discerned. The intermediacy of palladium (IV) complexes has been mentioned; another possibility involves direct displacement of the metal by an electrophilic attack on the aromatic ring at the site of the metal. However, this presumably would require fairly powerful electrophiles.

CONCLUSION

In the first part of this review four methods for the generation of palladated aromatics were presented, namely:-

Part 1.A. Oxidative addition of palladium (O) to carbon-halogen bonds of aryl halides.

Part 1.B. Reaction of palladium (O) with aryldiazonium salts.

Part 1.C. Transmetallation of metallated aromatics by palladium (II).

Part 1.D. Electrophilic substituion of arenes by palladium (II).

The reactions quoted in Parts 1.A. and 1.B. of the review are generally catalytic with respect to palladium, making the generation of palladated aromatics from aryl halides or aryldiazonium salts attractive methods for economic synthesis.

Aryldiazonium salts are more reactive towards palladium (O) than aryl halides as shown by the reactions of aryldiazonium salts carried out in the presence of iodide substituents (Review Pt. 1.B. eqns. 81 and 83). One drawback, the instability of some diazonium salts, can be overcome, in part, by the generation of the diazonium salt from the aryl amine in situ (Review Pt. 1.B. eqn. 85). Palladated aromatic species prepared from aryldiazonium tetrafluoroborate salts have the weakly co-ordinating

tetrafluoroborate ion as the anionic ligand, which enhances their reactivity over the corresponding arylpalladium species containing a halide ligand. However, the availability and stability of aryl halides as well as the simplicity of the reactions involving them often outweigh any advantage that may be gained by using aryldiazonium salts.

The reactions quoted in Parts 1.C. and 1.D. of the reivew require palladium (II) to form the palladated aromatic intermediate and as such generally need an added oxidant to make the reactions catalytic. Formation of the arylpalladium intermediates by transmetallation of metallated aromatics by palladium (II) is a process that can be carried out under mild conditions. However, an oxidant is required to reoxidise the palladium to the divalent state in order to complete a catalytic cycle. The same is true for the reactions quoted in Part 1.D. where the palladated aromatic was generated by electrophilic substitution of an arene. This has the advantage that an unsubstituted aromatic can be used as the starting material, although the regiochemistry is now determined by the rules of electrophilic substitution, so in many cases mixtures of products are obtained. The last section of the review (Part 2) deals with cyclopalladated complexes; these are generated by an ortho directed electrophilic substitution providing a method for the regioselective functionalization

of the aromatic nucleus.

By the use of palladated aromatics carbonyl, alkyl, vinyl, acetylenic and aryl substituents can be introduced onto the aromatic nucleus. The introduction of carbonyl and alkyl substituents is possible using more conventional chemistry i.e. Grignard and Friedel-Crafts reactions, however the reaction conditions are more vigorous. The intermediacy of palladated aromatics allows the direct preparation of vinylated aromatics aryl acetylenes in high yield. Alternative synthesis of these compounds often require more vigorous and lengthy procedures. The introduction of an aryl substituent constitutes a synthesis of biaryls. Using palladium chemistry the selective synthesis of unsymmetrical biaryls is possible. Of particular interest is the coupling of aryl halides with aryl boronic acids (eqn. 36); here the very mild conditions make this an attractive route to biaryls when compared to some of the classical biaryl synthesis, although classical methods such as the Ullmann reaction often have their own merits.

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RESULTS AND DISCUSSION

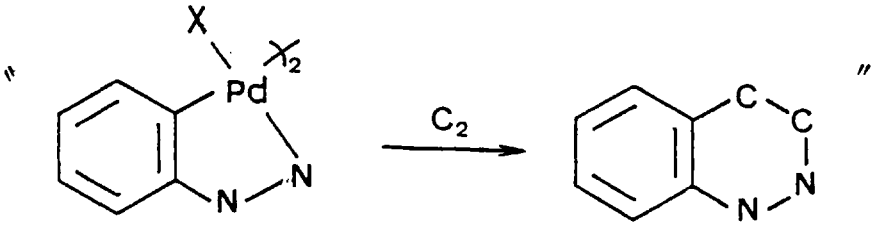
INTRODUCTION

The regiospecific substitution of functionalised aromatics *via* cyclometallated intermediates is a powerful synthetic method[1-3] as is amply demonstrated by the large amount of work using *ortho*-lithiated aromatics.[2,3] Transition metal cyclometallated complexes are well known,[1,4,5] though their potential applications to organic synthesis, for the most part, remain unrealised. The chemistry of palladated aromatics has been fairly well investigated (Review Pt. 1), a wide variety of transformations being possible, often under mild conditions. Palladium is also well known for its ability to form cyclopalladated complexes[1,4,5] making these attractive intermediates for organic synthesis.

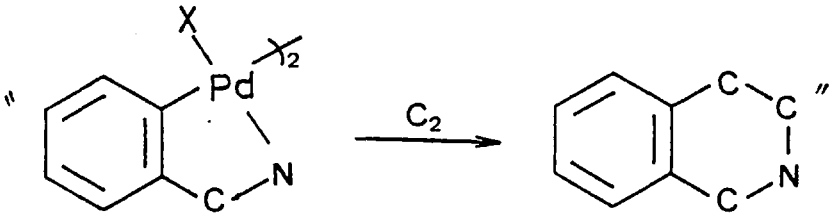
Functionalisation of the position *ortho* to the chelating group on an aromatic system can be applied to the preparation of benzofused heterocyclic systems.[6,7] It had already been demonstrated[8,9,10] that the carbonylation of *ortho*-palladated *N*,*N*-dialkylbenzylamines, Schiff bases and azobenzenes, led to various phthalimidine and indazolone derivatives. Analogously,[11,12] the reaction of isocyanides with *ortho*-palladated azobenzene complexes had also been shown to yield indazolone derivatives.

Both carbon monoxide and isocyanides are C_1 units, which in the above reactions led to benzofused 5 membered heterocyclic compounds. Many naturally occurring heterocyclic

compounds, particularly the alkaloids, contain benzofused, six membered nitrogen heterocycles. From the reaction of an ortho-palladated complex containing a nitrogen donor atom with a suitable C_2 unit a synthesis of benzofused six membered heterocyclic compounds seemed possible as is schematically illustrated below (eqns. 1 and 2).



(1)

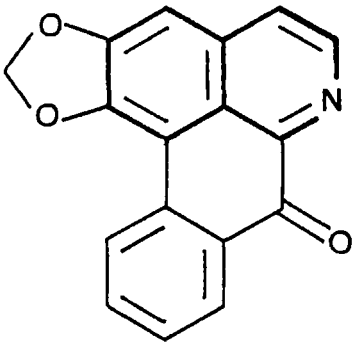


(2)

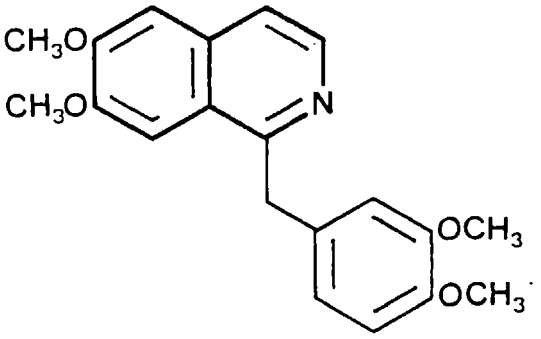
X = Anionic Ligand.

Whilst this work was in progress, it was shown (Review Pt. 2 eqns. 139-141) that reaction of olefins that constituted C_3 units with ortho-palladated acetanilide complexes provided a route to various quinolines.[13]

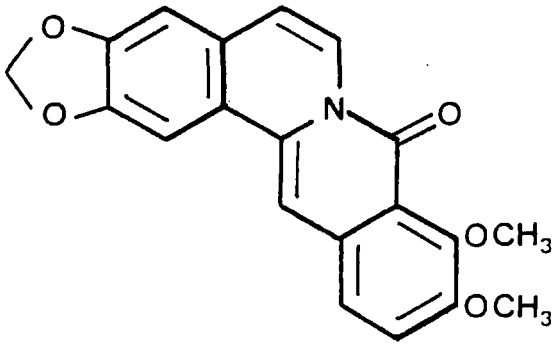
The isoquinoline unit is present in many naturally occurring alkaloids, a few representitive examples of which are shown below.



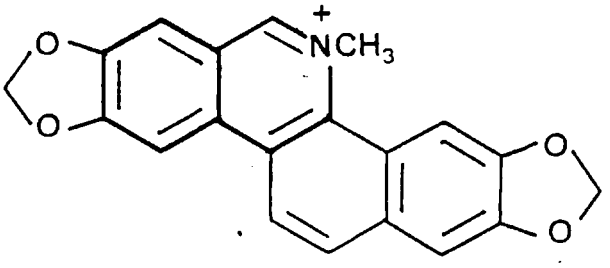
LIRIODENINE



PAPAVERINE



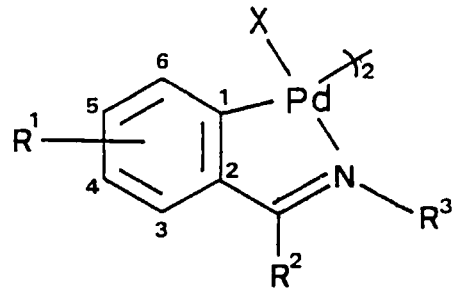
OXYBERBERINE



AVICINE

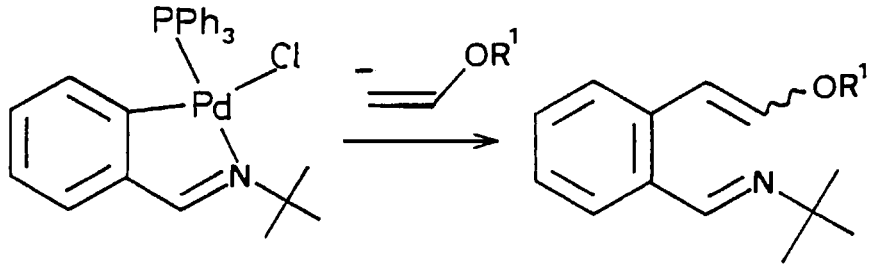
The complexes chosen for this work were the ortho-palladated Schiff bases. Although ortho-palladated N, N-dialkylbenzylamine complexes have the nitrogen in the correct position with regard to the isoquinoline skeleton, the imine function is synthetically more versatile.[14,15] As a starting

point, complexes of the general type shown below were considered.

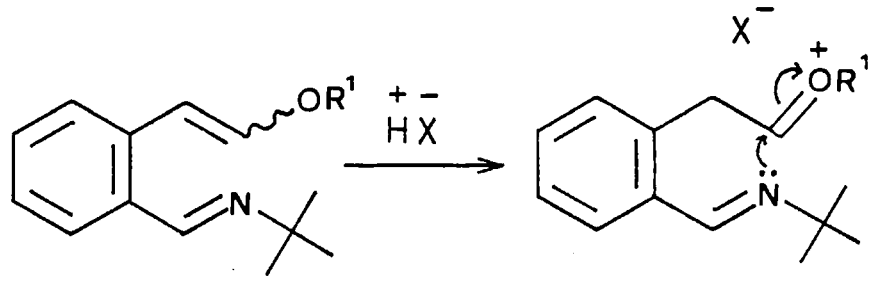


X = anionic ligand.

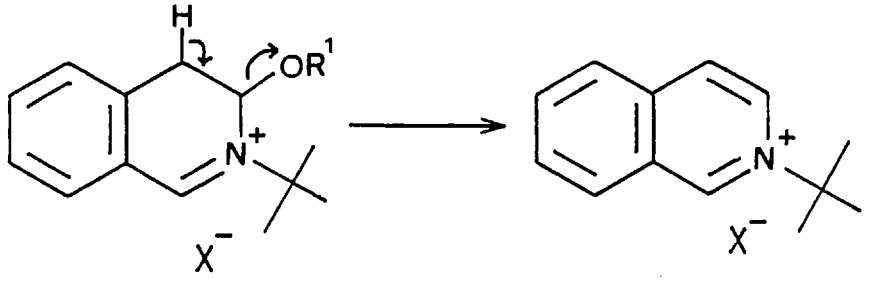
The reaction of this type of complex with carbon monoxide has already been mentioned and the one report[16] of their reaction with olefins was somewhat unsuccessful with regard to an isoquinoline synthesis (Review Pt. 2 eqn. 133). However, it had been demonstrated[17,18] that these complexes reacted with carbanions to produce, on hydrolytic workup, excellent yields of ortho-substituted benzaldehydes (Review Pt. 2 Scheme 13). It was considered that reaction of N-t-butyl-benzaldimine complexes with a suitable vinyl carbanion could lead to the isoquinoline skeleton as shown below (eqns. 3 - 6).



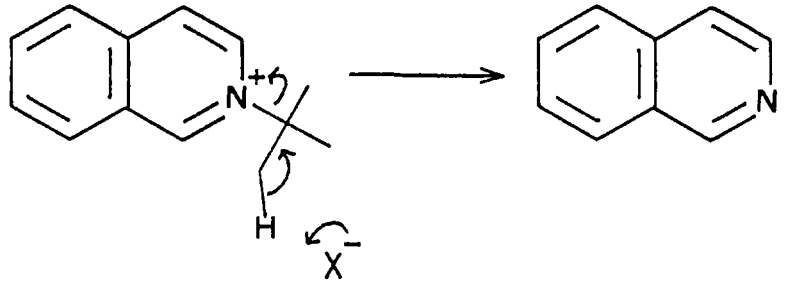
(3)



(4)



(5)



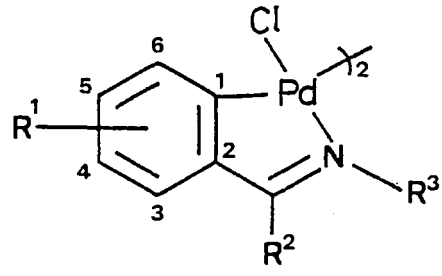
(6)

Alternatively, as vinylation of palladated aromatics is a well known process, the possibility of using an olefin as a C_2 unit was considered and from the above scheme, olefins such as methyl vinyl ether and vinyl acetate would appear to be suitable candidates.

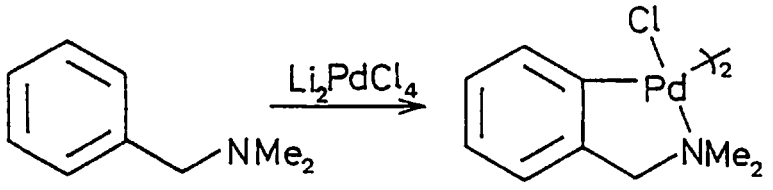
In the remainder of this section the work is organised as outlined in the introduction, the preparation of the complexes is dealt with first, followed by the attempted reactions of these complexes with both carbanions and subsequently with olefins.

PREPARATION OF CYCLOPALLADATED SCHIFF BASES

For the reaction of carbanions with cyclopalladated imines,[17,18] the complexes required are of the general type illustrated below:-

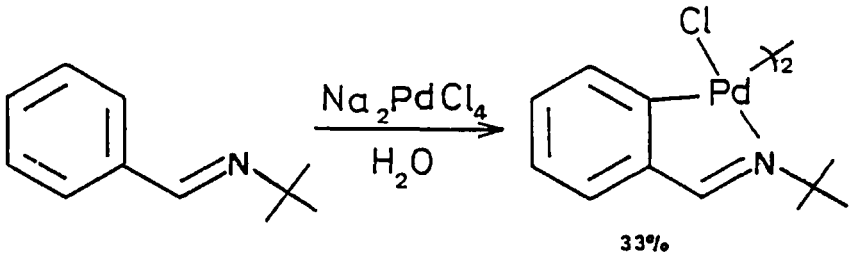


In the literature the most successful method for preparing complexes of this type was that of Onoue and Moritani,[19] who treated the imine with palladium acetate in acetic acid to obtain high yields of the corresponding acetate-bridged complexes, subsequent treatment of which with chloride ion readily gave the chloro-bridged complexes.[19] However, it was thought to be more desirable if the chloro-bridged complexes could be prepared directly in a single step from the parent imines. This was known to be possible for N,N-dimethylbenzylamines which on reaction with Li_2PdCl_4 in the presence of triethylamine yielded the ortho-palladated products[20,21] (e.g. eqn. 7).



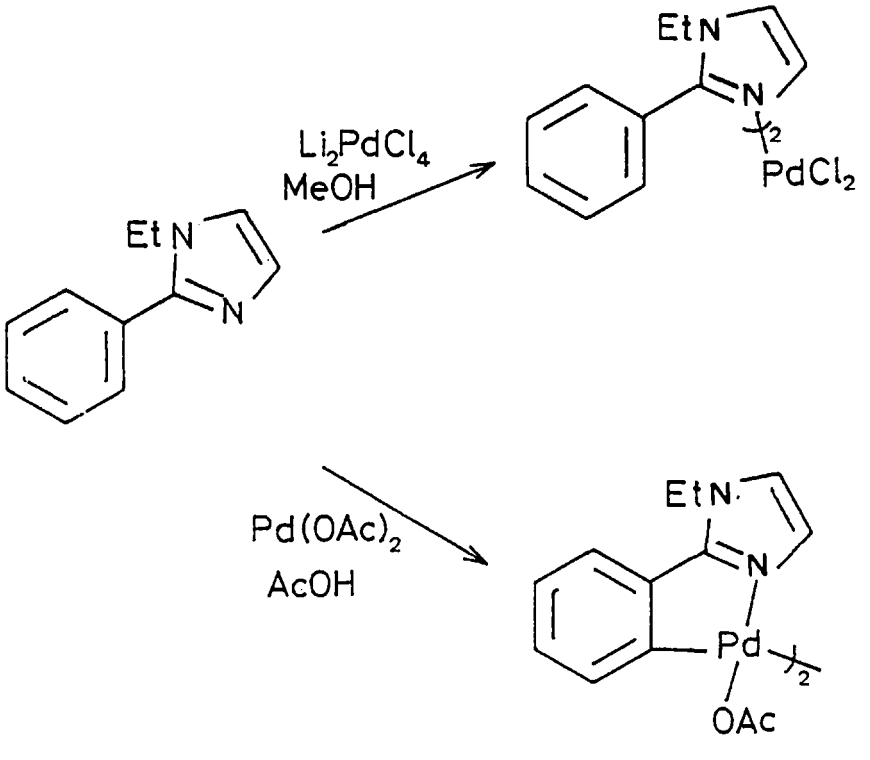
(7)

It had also been claimed, by Molnar and Orchin,[22] that reaction of $PdCl_2(PhCN)_2$ with a number of N-benzylidene-anilines produced high yields of the corresponding chloro-bridged ortho-palladated aromatic imines, the full characterisation of which was not reported. However, other workers[19,23] could not repeat these results. Instead when N-benzylidene-aniline was treated with $PdCl_2(PhCN)_2$ in methanol the major product obtained was the bis-aniline complex, $PdCl_2(PhNH_2)_2$ with only a small amount of the ortho-palladated complex being formed. Other attempts[24,25] at preparing the chloro-bridged cyclopalladated imines using Li_2PdCl_4 in hydroxylic solvents produced only low yields of the desired complexes (e.g. eqn. 8). Presumably the hydrolysis of the imine was of a comparable rate to the electrophilic attack by palladium onto the aromatic ring. If no base is added to remove the HCl produced by the electrophilic substitution not only will the rate of imine hydrolysis be increased but the electrophilic substitution will also be retarded.



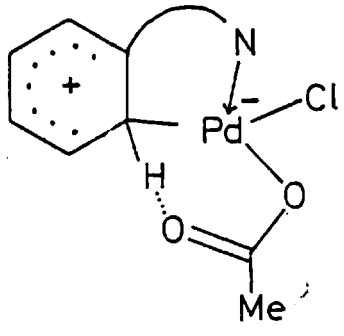
(8)[24]

Palladium acetate is known to be superior to palladium chloride for the electrophilic substitution of aromatics,[26] and this is exemplified by the reactions of Li_2PdCl_4 and $Pd(OAc)_2$ with 1-ethyl-2-phenylimidazole,[27] shown below (eqn. 9).



(9)

Although palladium chloride itself is not a powerful electrophile in the presence of sodium acetate[28,29] its reactivity is greatly increased, this has been attributed to the fact the acetate ion is a weaker ligand than the chloride ion, and in part, displaces the chloride to provide a more reactive species. It has been suggested[30] that the acetate ion could play a more active role in the electrophilic substitution reactions by palladium, by assisting in the removal of a proton from the aromatic ring, as is schematically represented below.



From the above work it was concluded that the best approach to the desired complexes would be by treatment of the imine with palladium chloride in glacial acetic acid in the presence of an excess of sodium acetate under a nitrogen atmosphere. Under the above conditions it was in theory possible that either chloro- or acetate-bridged complexes would be obtained. In the event only the chloro- bridged complexes were obtained; the chloride ligand being more strongly bound to the palladium than the acetate and also as

the chloro- bridged complexes are less soluble than the corresponding acetate-bridged complexes, the chloro- bridged complexes precipitate out of the reaction mixture. The sodium acetate, added to facilitate the electrophilic substitution, circumvented the requirement for the presence of an additional base by acting as a buffer, effectively removing the HCl produced by the electrophilic substitution.

In the ortho-palladated complexes the imine function is present in the trans- configuration, the free imines can adopt either the cis or trans configurations, normally only a trace of the cis isomer is present.[14] Even if a larger percentage of the cis isomer was present, it should not present a problem as the acetic acid mixture would be capable of isomerising any cis-imine to the desired trans isomer.

The imines used for the preparation of the ortho-palladated complexes are listed in Table 1. The preparation of imines of this type is trivial and is dealt with in the experimental section.

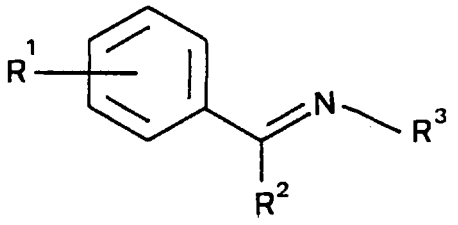


TABLE 1

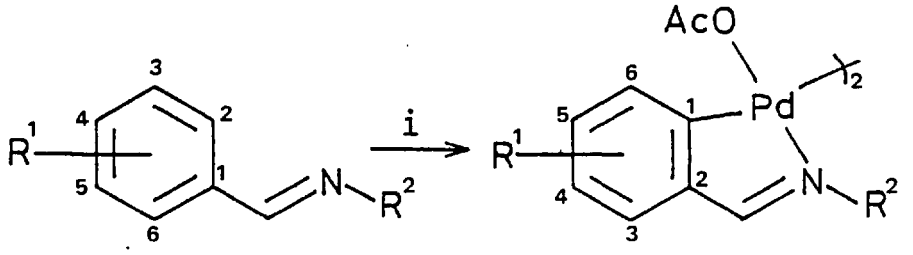
IMINE

Cpd No.	(R^1=)	(R^2=)	(R^3=)	(Yield %)
1	H	H	Me	(86)
2	H	H	Ph	(93)
3	H	H	n-Bu	(88)
4	H	H	i-Pr	(98)
5	H	H	t-Bu	(72)
6	H	Me	n-Bu	(83)
7	3,4-$(MeO)_2$	H	Me	(68)
8	3,4-$(MeO)_2$	H	t-Bu	(82)
9	2-MeO	H	t-Bu	(78)
10	3-MeO	H	t-Bu	(84)
11	4-MeO	H	t-Bu	(86)
12	4-Me	H	t-Bu	(79)
13	4-Cl	H	t-Bu	(79)
14	4-Me_2N	H	t-Bu	(73)
15	4-O_2N	H	t-Bu	(86)

The imines (1-15) can be prepared in high yields; they are generally low melting solids or liquids and can be readily purified by distillation or recrystallisation.

In order to assess the general properties of the ortho-palladated Schiff bases, i.e. spectral characteristics, solubility in organic solvents, stability and ease of handling, several acetate-bridged complexes (cpds. 16,17,18) were prepared by treatment of the imine with palladium acetate in acetic acid following the method of Onoue and Moritani[19] (Scheme1, Table 2).

Scheme 1



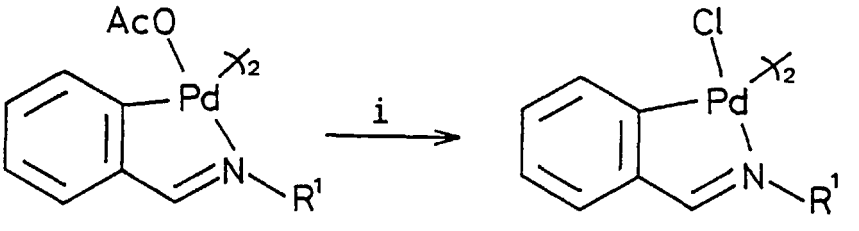
i, $Pd(OAc)_2$; AcOH

TABLE 2

IMINE			COMPLEX			
Cpd No.	(R^1=)	(R^2=)	Cpd No.	(R^1=)	(R^2=)	(Yield %)
1	H	Me	16	H	Me	(92)
2	H	Ph	17	H	Ph	(88)
7	3,4-$(MeO)_2$	Me	18	4,5-$(MeO)_2$	Me	(79)

The complexes (16,17,18) were found to be air stable, yellow crystalline solids, soluble in many common organic solvents. Of the complexes prepared 16 and 17 were known, their spectral data was in good agreement with that cited in the literature.[19] The acetate-bridged complexes 16 and 17 were converted to the known chloro-bridged dimers by treatment with sodium chloride in aqueous acetone (Scheme 2, Table 3), providing authentic samples for comparison with the complexes prepared using palladium chloride in acetic acid in the presence of sodium acetate.

Scheme 2



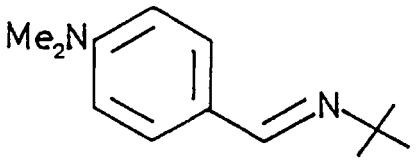
i, NaCl; $(CH_3)_2CO$; H_2O.

TABLE 3

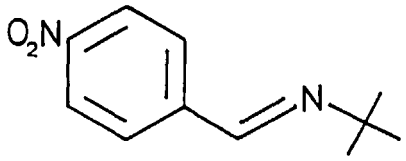
Acetate-Bridged Complex Cpd No.	(R^1=)	Chloro Bridged Complex Cpd No.	(R^1=)	(Yield %)
16	Me	19	Me	(89)
17	Ph	20	Ph	(90)

Like the acetate-bridged complexes, the chloro-bridged complexes were air stable, yellow, crystalline solids, but they were far less soluble in organic solvents, dissolving well only in the presence of complexing ligands such as pyridine and triphenylphosphine, or in complexing solvents such as DMSO.

Having carried out these preliminary investigations, the preparation of the chloro-bridged complexes directly by the proposed method was attempted. The best results were obtained by using the following conditions. A mixture of acetic acid (dry),and sodium acetate (anhydrous, 15-20 eq) was purged with nitrogen at 60° for 20 to 30 minutes, to this was added palladium chloride (1 eq) the mixture was further purged for 10 minutes during which time some of the palladium chloride dissolved to give a deep brown solution. To this mixture the imine (1.2-1.5 eq) was added, the temperature was raised to 80° and the mixture efficiently stirred under nitrogen until the solid palladium chloride had all been replaced by a yellow precipitate, and the mother liquor had also discharged its brown colour. Usually this process took 1-2 hours. Finely ground palladium chloride is essential for a fast reaction as its rate of dissolution is fairly slow. The yellow precipitate of the complex was sometimes slightly green in colour due to the inclusion of palladium metal in the crystals. Workup was a simple



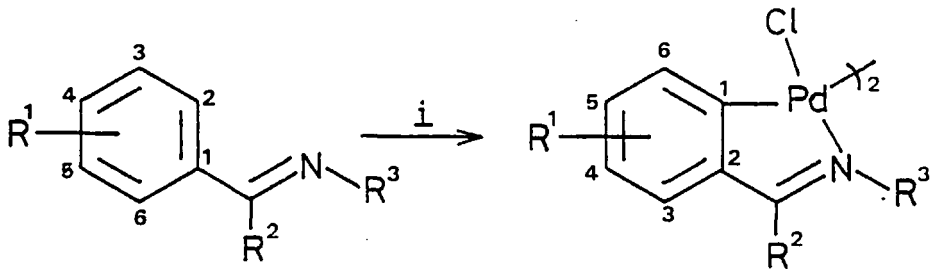
14



15

matter of dilution with water to precipitate out any dissolved complex, which was then filtered off, washed with water and recrystallised from THF/water or DMSO/THF/water mixtures. Complexes containing large alkyl groups were, not unexpectedly, generally more soluble in organic solvents. In most cases good yields of the complexes were obtained (Scheme 3, Table 4), except for the p-N,N-dimethylamine and p-nitro substituted imines (cpds. 14 and 15 resp.) where none of the ortho-palladated product was obtained. This was expected in the case of the p-nitro derivative (15), as p-nitro-N, N-dimethylbenzylamine had been reported[31] not to undergo electrophilic substitution by palladium. However, the p-N,N-dimethylamino-substituted imine (14) was expected to palladate readily. In the event a mixture of products was obtained, in which the ortho-palladated complex could not be found. There are several reports[32,33] in the literature of N,N-dialkylanilines giving abnormal reaction products on reaction with palladium (II) salts, possibly via an electron transfer mechanism (Review Pt. 1 eqn. 105).

Scheme 3



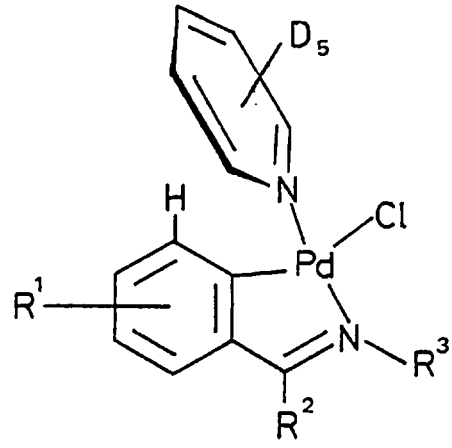
i, $PdCl_2$; NaOAc; AcOH; 80°; 1-2 hrs.

TABLE 4

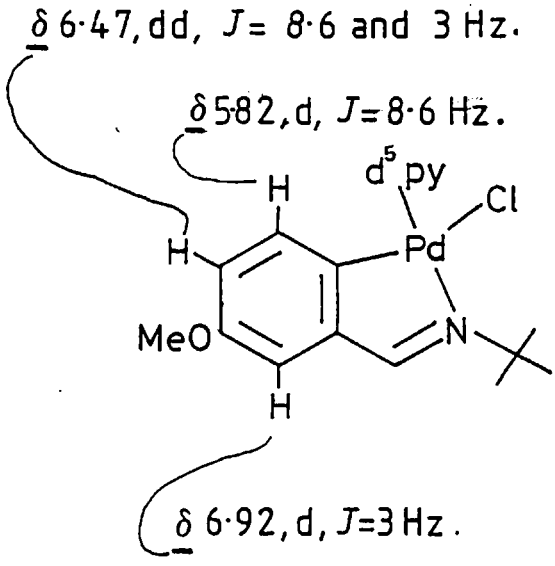
Cpd No.	IMINE (R^1=)	(R^2=)	(R^3=)	Cpd No.	COMPLEX (R^1=)	(R^2=)	(R^3=)	(Yield) %
1	H	H	Me	19	H	H	Me	(82)
2	H	H	Ph	20	H	H	Ph	(92)
3	H	H	n-Bu	21	H	H	n-Bu	(91)
4	H	H	i-Pr	22	H	H	i-Pr	(94)
5	H	H	t-Bu	23	H	H	t-Bu	(95)
6	H	Me	n-Bu	24	H	Me	n-Bu	(63)
8	3,4-$(MeO)_2$	H	t-Bu	25	4,5-$(MeO)_2$	H	t-Bu	(89)
9	2-MeO	H	t-Bu	26	3-MeO	H	t-Bu	(81)
10	3-MeO	H	t-Bu	27	4-MeO	H	t-Bu	(96)
11	4-MeO	H	t-Bu	28	5-MeO	H	t-Bu	(95)
12	4-Me	H	t-Bu	29	5-Me	H	t-Bu	(89)
13	4-Cl	H	t-Bu	30	5-Cl	H	t-Bu	(88)
14	4-Me_2N	H	t-Bu	31	5-Me_2N	H	t-Bu	-
15	4-O_2N	H	t-Bu	32	5-O_2N	H	t-Bu	-

The complexes 19 and 20 prepared by this method were identical to the samples prepared previously (Scheme 2, Table 2) and their spectral characteristics in good agreement with those reported by Onoue and Moritani.[19]

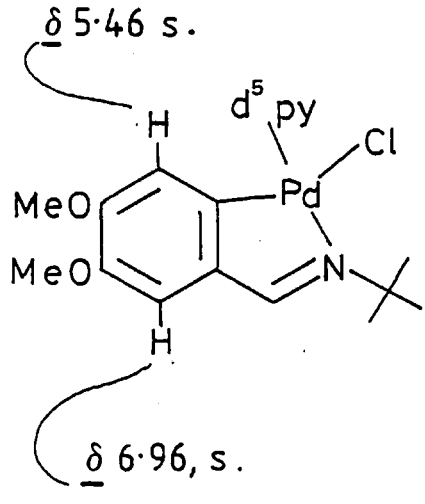
The infrared spectra of the complexes were as expected, the C $=$ N stretch of the parent imine (1640 - 1625 cm^{-1}) had shifted to a lower wavenumber (1620 - 1600 cm^{-1}). The NMR spectra were also in good agreement with the proposed structures, although the poor solubility of complexes was, in some cases, a problem. To overcome this d^5 pyridine was added, apart from splitting the chloro-bridged dimers to give the more soluble monomers it also had the advantage of greatly simplifying the aromatic region of the spectrum. The co-ordination of the d^5 pyridine shifted the resonance of the proton H-6 upfield by 1-2 ppm, allowing the resonances and splitting patterns of aromatic protons to be more clearly seen. In most cases complete assignment of every proton in the spectrum was possible (see experimental), thus the site of palladation could be precisely defined. This result can be rationalised by assuming that the pyridine co-ordinates <u>trans</u> to the imino-nitrogen ligand, and is at 90° to the plane of the complex, as shown below, putting H-6 into the shielding cone of the pyridine ring.



The imines 8 and 10 possess two possible sites for ortho-palladation. From the NMR spectra, of the complexes obtained, in the presence of d^5 pyridine, the sites of palladation could be unambiguously assigned as:-



Cpd. 27

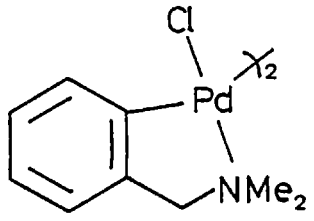


Cpd. 25

For both of these imines only these isomers were obtained. Presumably palladation ortho to a methoxy substituent was too sterically demanding.

The chloro-bridged N,N-dimethylbenzylamine complex 33, prepared by literature[20] methods was used for preliminary studies of the reactions of the complexes with anions. This

complex does not contain the imine function and so any side reactions due to nucleophilic attack of the imine function can be ruled out, thus allowing the evaluation of the



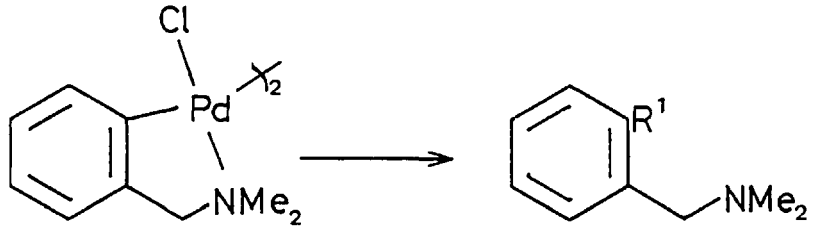
33

reaction of an anion with the palladium-carbon bond in an ortho-palladated complex.

REACTIONS OF THE CYCLOPALLADATED COMPLEXES

As was outlined in the introduction the first reactions of these complexes to be examined were to be with carbanions. Preliminary studies were carried out with the N,N-dimethyl benzylamine complex 33, the reaction of methyl-lithium with this complex has previously been reported[18] and was carried out to check the method. Phenyl magnesium bromide was also found to react in reasonable yield (Scheme 4, Table 5). Whilst the above work was being carried out, the reactions of Schiff base complexes with aryl Grignards had been investigated and found to proceed smoothly.[34]

Scheme 4

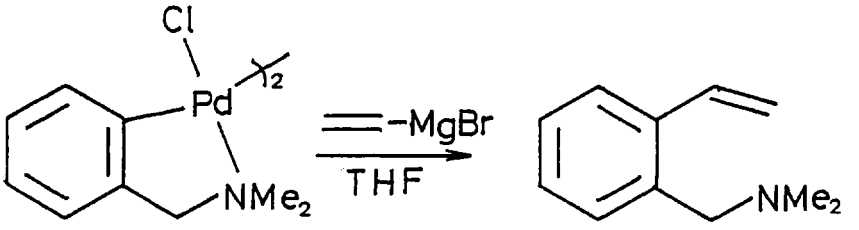


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TABLE 5

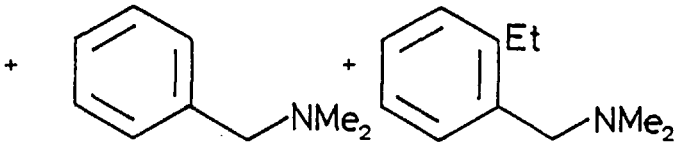
Carbanion	Phosphine	Benzylamine Derivative Cpd No.	(R^1 =)	(Yield %)
MeLi	PPh_3, 4eq	34	Me	(70)
PhMgBr	PPh_3, 4eq	35	Ph	(58)

These results indicated that the method should be satisfactory for the introduction of a vinyl group into the ortho-position of a Schiff base. The only report[18] of the reaction of a vinyl anion with an ortho-palladated complex was that shown below. A mixture of products had been obtained,



31%

(11)



43% 13%

but no triphenylphosphine, which has been claimed to greatly improve the reaction,[18] had been added. With this in mind attempts were made to react the imine complexes, shown in Table 4, with vinyl magnesium bromide in THF in the presence of triphenylphosphine. The reactions did not look promising. From the mass spectra of the product mixture a small peak corresponding to the $M^{+\cdot}$ of the ortho-vinyl Schiff bases was seen, but this is by no means a firm identification. Comparison of the mass spectra of the product mixture with that of the corresponding pure imines, indicated that a large proportion of the product was the parent imine. The β-alkoxy

vinyl anions, required for the proposed isoquinoline synthesis shown in the introduction, are themselves difficult and time consuming to prepare,[35] therefore it was decided to find an alternative method for the introduction of the acetaldehyde equivalent.

As was seen in the review, olefins generally react smoothly with palladated aromatics to produce vinylated arenes. Some of the simplest olefins which constitute acetaldehyde equivalents are vinyl ethers and for this reason it was considered worthwhile to attempt the vinylation of an ortho-palladated aromatic complex using a simple vinyl ether. However, it must be noted that the reactions of vinyl ethers with simple palladated aromatics are not usually clean (Review Pt. 1 eqns. 56 and 57) and no reports of their reactions with ortho-palladated aromatic complexes have been made.

The first attempts at this reaction were made using methyl vinyl ether. Treatment of the complex with methyl vinyl ether in a variety of organic solvents, compatible with the enol ether function (THF, toluene, Et_2O) at room temperature under nitrogen in the presence of triethylamine gave no reaction. Heck had reported that the reaction between ortho-palladated Schiff bases and the olefin, methyl acrylate required elevated temperatures as no reaction occurred at room temperature, although the products he isolated were somewhat unusual (Review Pt. 2 eqn. 133).

Based on this work the higher boiling, n-butyl vinyl ether was employed. The complex, excess n-butyl vinyl ether

and triethylamine were refluxed in toluene under nitrogen. Over 2 - 3 days metallic palladium was slowly deposited, but no products indicating the formation of the arylated vinyl ether were found. In a blank experiment, where the complex was refluxed in toluene in the presence of triethylamine alone, the rate of deposition of palladium metal was found to be the same as that in the presence of the vinyl ether. Vinyl acetate, which was considered to be less electron rich, compared to the alkyl vinyl ethers, was also unreactive.

The vinylation of an aryl iodide with N-vinyl phthalimide in the presence of palladium had been reported to proceed in moderate yield (Review Pt. 1 eqn. 59). On this basis reaction of N-vinyl-2-pyrrolidinone with the imine complexes in the presence of triethylamine in refluxing toluene was tried; again the results were not promising.

At this point it was decided to try to react the Schiff base complexes with an olefin that was known to react reasonably well with palladated aromatics, and preferably cyclopalladated aromatics. ortho-palladated N,N-dialkylbenzylamine complexes had been reported to react with styrenes, acrylates and α,β-unsaturated ketones in reasonable yields [Review Pt. 2 (iv)]. Brisdon et al found they could react chloro-bridged ortho-palladated N,N-dimethylbenzylamine complexes with styrenes in CH_2Cl_2/ACOH mixtures to produce the corresponding stilbenes in good yields[36] (Review Pt. 2 eqn. 135). Following this method the Schiff base complex 23 was treated with styrene, no reaction occurred and the starting

material was recovered. Holton had reported[37] that the presence of acid enhanced the reactions of α, β-unsaturated enones with ortho-palladated N,N-dimethylbenzylamines. With this in mind the complex 23 was treated, in a mixture of trifluoroacetic acid/acetic acid, under a nitrogen atmosphere, with styrene. After an aqueous workup 2-formylstilbene was obtained in a 95% yield based on palladium. The results for this complex and others are summarised in Scheme 5, Table 6. The NMR spectra of the stilbenes indicated the presence of the trans isomer only. High yields of the 2-formylstilbenes were obtained with no pronounced effects due to the presence of ring substituents being seen. Interestingly, the choice of the N-alkyl group seemed fairly critical, the N-methyl complex 19 gave no reaction at all. This could be attributed to its very poor solubility in acetic acid. With the complexes 21 - 23 it was noted that the N-t-butyl imine ortho-palladated complex reacted the fastest, the order being n-Bu<i-Pr<t-Bu, which is also that of increasing steric bulk.

Scheme 5

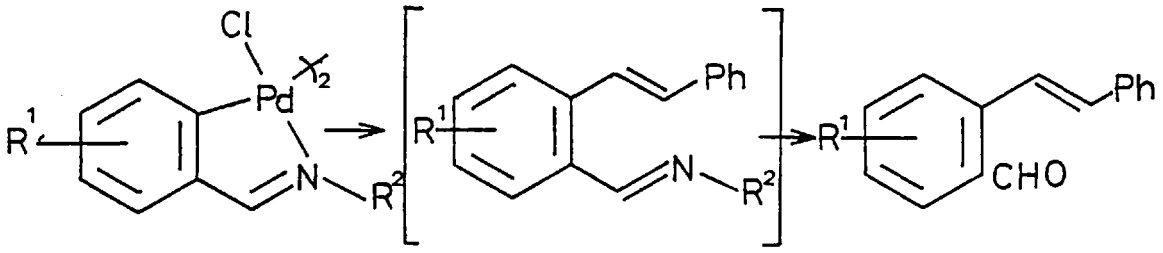
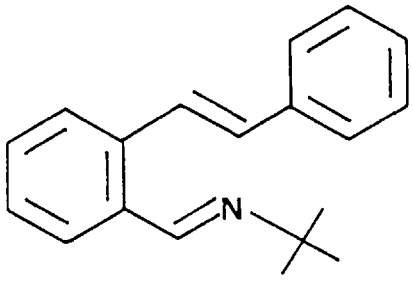


TABLE 6

Complexes			Stilbene Aldehyde		
Cpd No.	(R^1 =)	(R^2 =)	Cpd No.	(R^1 =)	(Yield %)
19	H	Me	36	H	(0)
21	H	n-Bu	36	H	(45)
22	H	i-Pr	36	H	(74)
23	H	t-Bu	36	H	(90)*
25	4,5-$(MeO)_2$	t-Bu	37	4,5-$(MeO)_2$	(91)
26	3-MeO	t-Bu	38	3-MeO	(67)
27	4-MeO	t-Bu	39	4-MeO	(81)
28	5-MeO	t-Bu	40	5-MeO	(75)
29	5-Me	t-Bu	41	5-Me	(74)
30	5-Cl	t-Bu	42	5-Cl	(85)

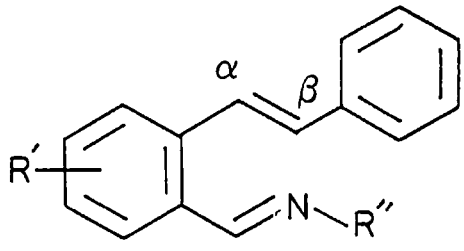
* Cpd 43 was also prepared by refluxing complex 23 with excess styrene, in toluene in the presence of triethylamine in 78% yield.



43

Although the effects of substituents on the aryl ring of the styrene were not examined the results of Brisdon et al (Review Pt. 2 eqn. 135) indicate that a wide range of functional groups could be tolerated.[36]

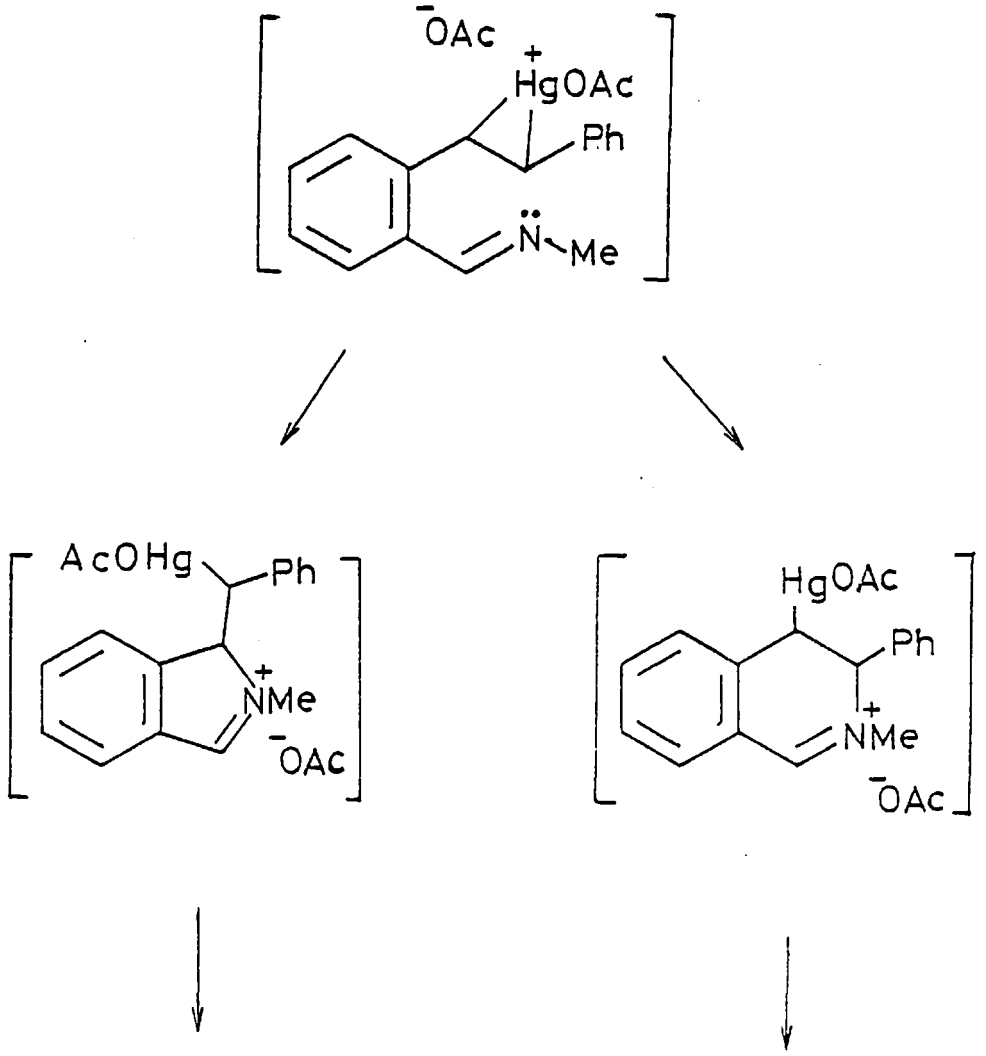
This method allows the construction of a wide range of unsymmetrical trans-2-formylstilbenes, the conventional synthesis of these compounds[38-42] are more lengthy and often give mixtures of the cis and trans isomers. 2-formylstilbenes themselves have been used as precursors to heterocyclic rings, principally benzodiazepines.[43,44] It was decided to convert the 2-formylstilbenes, which were now readily available, into 3-arylisoquinoline derivatives, conversion of the aldehyde to the imine function would introduce the nitrogen, and formation of a carbon-nitrogen bond between the imine nitrogen and the β-carbon of the olefin would yield the isoquinoline skeleton. A metal ion mediated attack by the

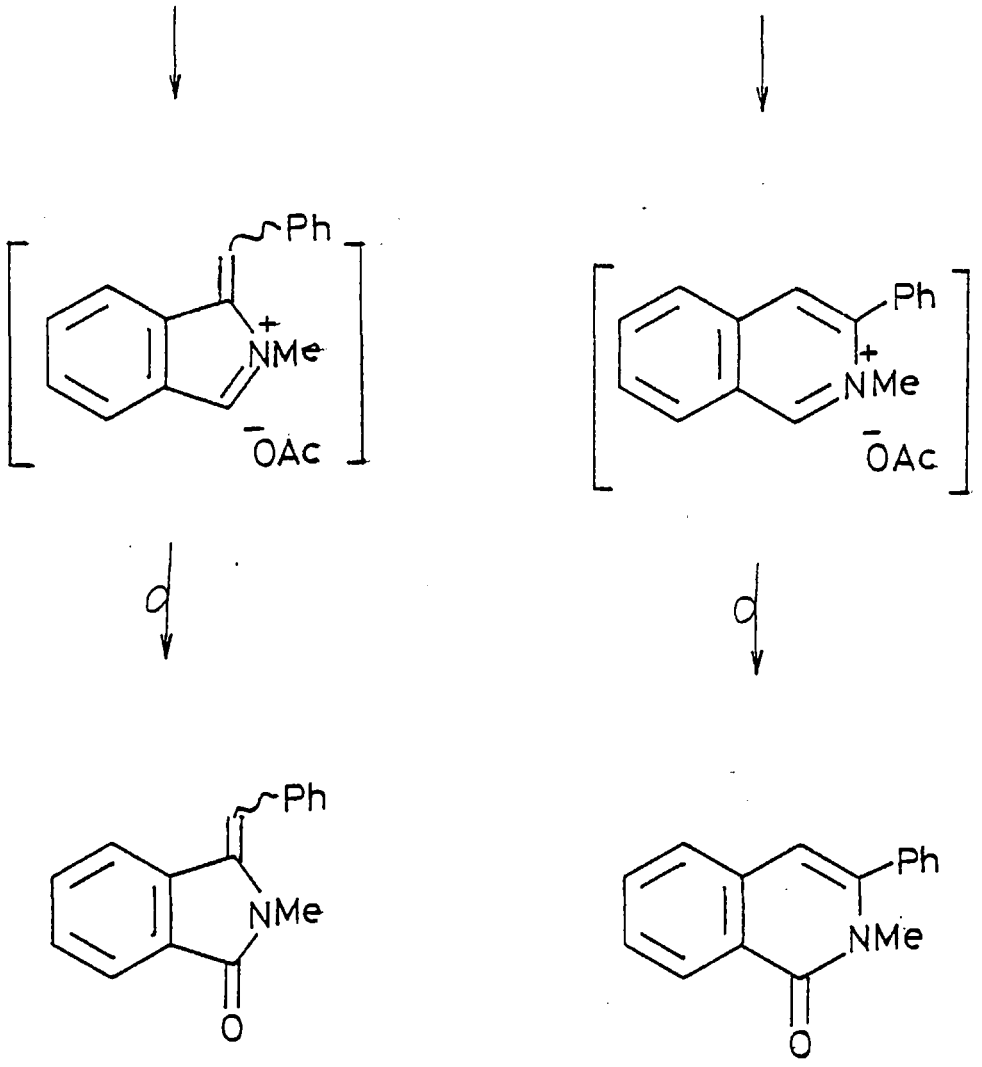


nitrogen onto the olefin seemed the most reasonable. Oxymercuration of olefins is a well documented process,[45] the oxygen nucleophile has in several cases been replaced by an amine nucleophile.[46] For the proposed 3-arylisoquinoline synthesis it was envisaged the imino-nitrogen would act as the nucleophile in an intramolecular fashion to form the

isoquinoline ring.

The aldehydes were converted to their N-methyl imine derivatives, and without purification were treated with mercuric acetate (2eq) in refluxing toluene to produce the cyclised products. The mercury (II) mediated cyclisation can, in principle, give rise to both 5 and 6 membered rings, as shown below.





On the basis of spectral evidence, and comparison of data reported for the phthalimidine[47,48] and isoquinolone[49,51] derivatives, where possible, the structure of the cyclised products were determined to be the 2-methyl-3-phenylisoquinolone derivatives as shown in Scheme 5, Table 7.

Following the successful reaction of styrene with the Schiff base complexes, the reaction of methyl acrylate with the ortho-palladated N-t-butyl imine complex 23 under the same conditions was attempted. On workup a complex mixture of products was obtained, the NMR spectrum indicated a small

amount of 2-formyl-methylcinnamate was present in the mixture.

Scheme 6

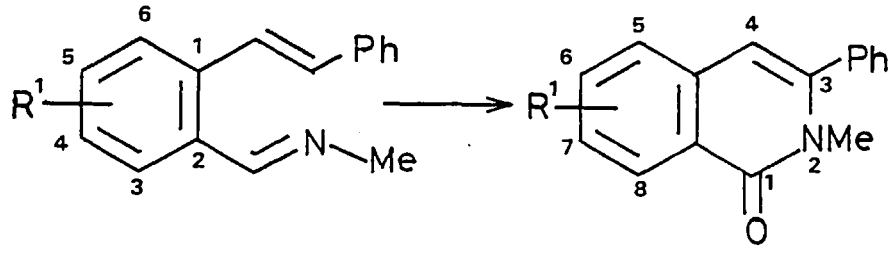


TABLE 7

Stilbene Aldehyde Cpd No.	(R^1 =)	Imine Cpd No.	Isoquinolone Cpd No.	(R^1 =)	(Yield %)*
36	H	44	50	H	(43)
37	4,5-$(MeO)_2$	45	51	6,7-$(MeO)_2$	(62)
38	3-MeO	46	52	8-MeO	(33)
39	4-MeO	47	53	7-MeO	(32)
40	5-MeO	48	54	6-MeO	(59)
42	5-Cl	49	55	6-Cl	(41)

* yields based on stilbene aldehydes.

As an alternative to using these highly acidic conditions the ortho-palladated N-t-butyl imine complex 23 was refluxed with excess methyl acrylate, in toluene, in the presence triethylamine, under a nitrogen atmosphere, giving the N-t-butyl imine of 2-formyl-methylcinnamate in 84% yield. The 4,5-dimethoxy and 5-methyl substituted complexes (cpds. 25 and 29 resp.) also reacted smoothly with methyl acrylate to

produce the corresponding cinnamate derivatives (Scheme 7, Table 8). These imines (cpds. 56-58) were found to be remarkably stable to hydrolysis; to hydrolyse the 5-methyl derivative 58 it was found to be necessary to use aqueous acetic acid, as the normal hydrolysis conditions using Et_2O/water mixtures and a catalytic amount of acid resulted in a slow rate of conversion.

Scheme 7

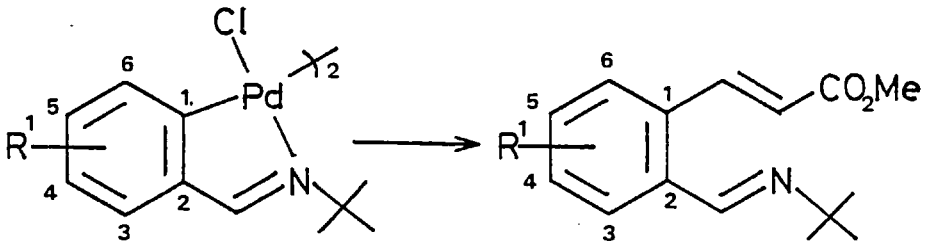
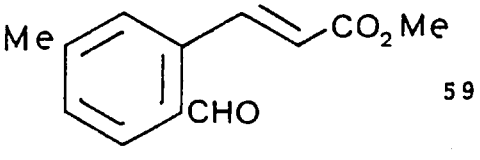


TABLE 8

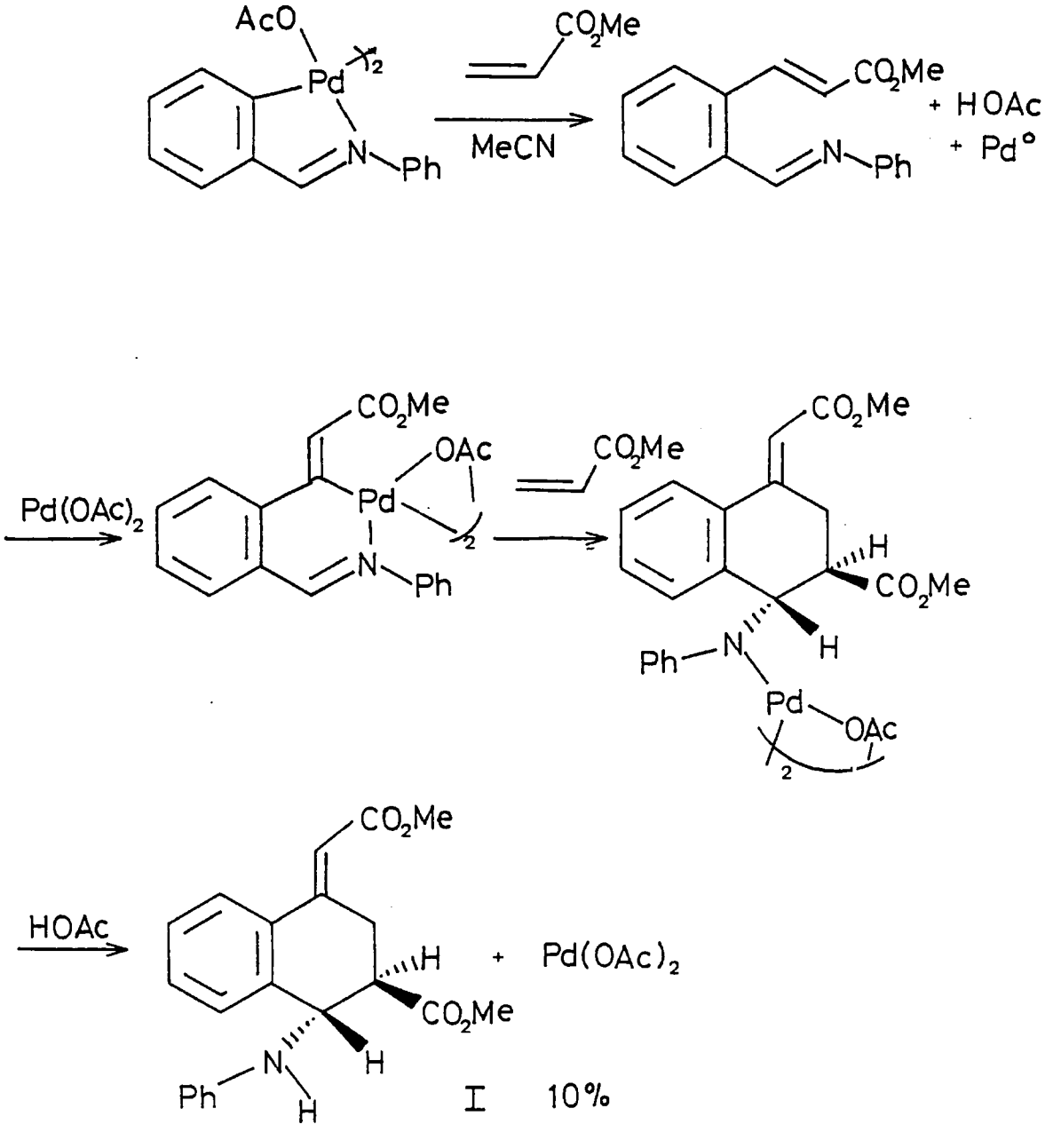
Cpd No.	Complex (R^1=)	Cpd No.	Cinnamate (R^1=)	(Yield %)
23	H	56	H	(84)
25	4,5-$(MeO)_2$	57	4,5-$(MeO)_2$	(86)
29	5-Me	58	5-Me	(79)*

* this cpd. was hydrolysed to the aldehyde derivative 59 in 81% yield.

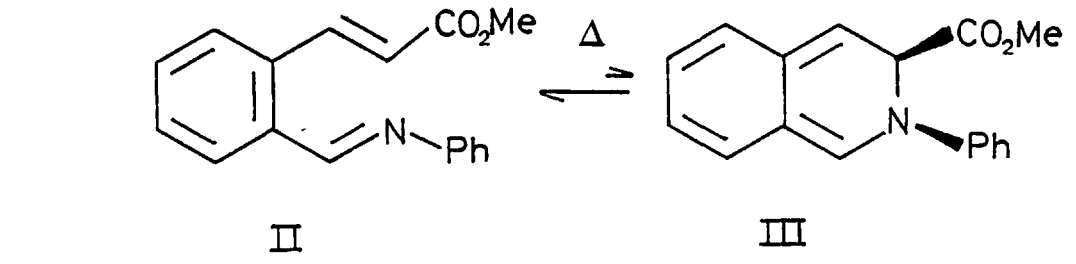


59

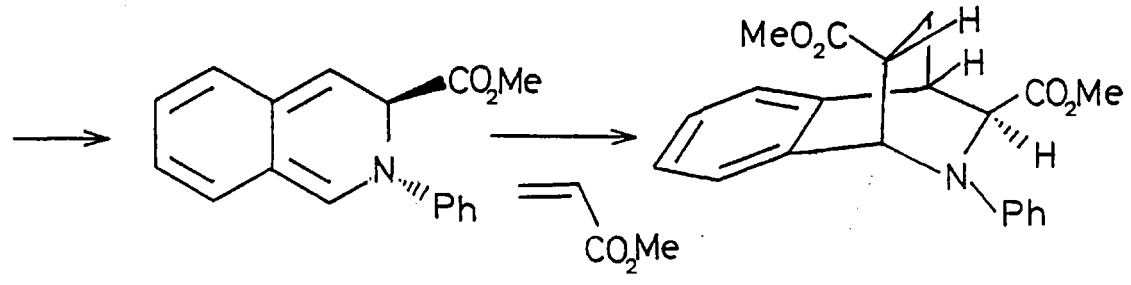
It is interesting to compare these results with those reported[16] by Heck, who found that on reacting the acetate-bridged benzylideneaniline complex with excess methyl acrylate in acetonitrile at a temperature of 100-150°, a low yield of an unexpected product was obtained. This product was shown to be, by X-ray analysis, the tetralin derivative (I). The mechanism proposed[16] by Heck for its formation is shown below.



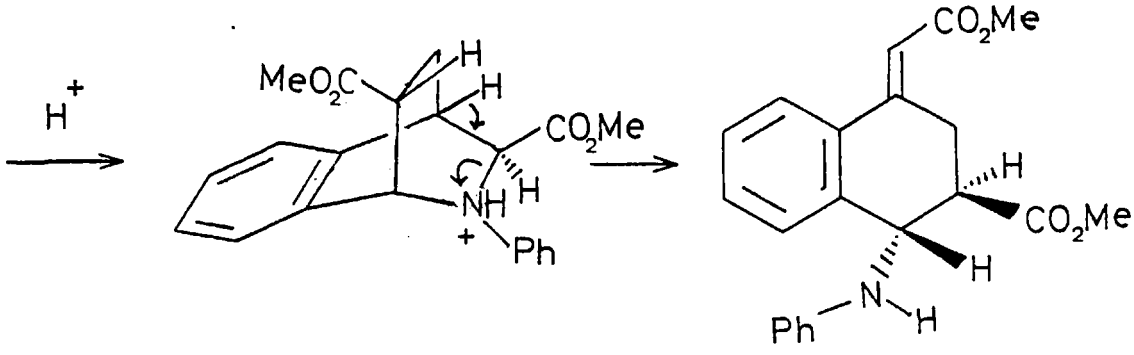
The palladium acetate required for the vinylic palladation, was said to have been generated by reversal of the Schiff base palladation with acetic acid formed in the first insertion step. An alternative mechanism is as follows:-



II III



IV V

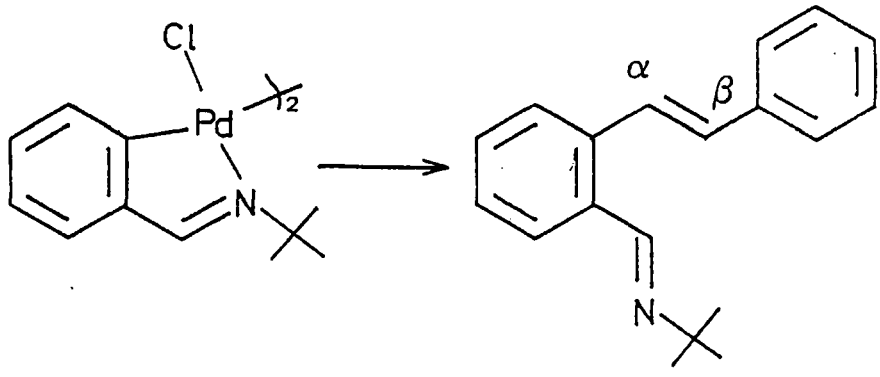


VI I

In this alternative mechanism, palladium acetate is not required. The initial ring closure is a thermal electrocyclic reaction[52,53] in which the imino styrene (II) is in equilibrium with the closed form (III). The equilibrium would be predominantly to the left, but in the presence of excess methyl acrylate the closed form (IV) is trapped by the acrylate in a 4 + 2 cyclo-addition reaction[54,55] to give the bridged species (V). It is in this step that the stereo and regiochemistry of the final product is determined. The olefin adds, as expected, across the most reactive diene, favourably re-aromatizing the benzene ring. Addition of the acrylate with the carbomethoxy group syn to the aromatic ring is the preferred pathway.[55] The polarisation of both the diene and olefin[56] define the regiochemistry of the product. Finally, of the two faces of the diene, the acrylate adds to the least hindered face which is cis to the carbomethoxy group, the N-phenyl having adopted a trans relationship to the carbomethoxy group by inversion of the N (III $\longrightarrow$ IV).

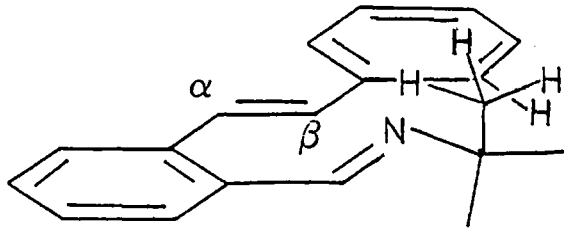
From the above mechanism it can be seen that in the first step the isoquinoline ring structure is formed and by using an electrocyclic ring closure it was envisaged that the imino nitrogen could be incorporated directly into the isoquinoline ring. In the previous route to 3-arylisoquinolones, using a mercury mediated ring closure, the original imino nitrogen could not be used.

It was found that the complex 23 reacts with styrene in refluxing toluene in the presence of triethylamine to yield the ortho-imino stilbene 43. From the highly acidic medium

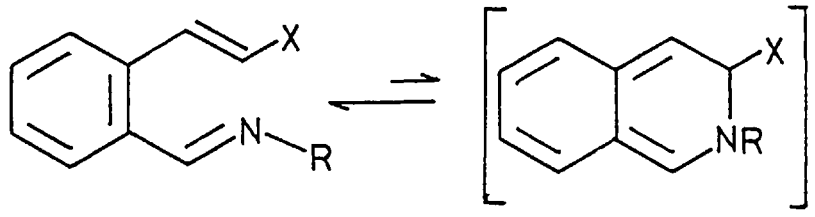


23 43

used earlier, the ortho-imino stilbenes could not be isolated, the ortho-formyl stilbenes being isolated as the products of reaction. Treatment of the ortho-imino stilbene 43 with mercuric acetate (2 eq) in refluxing toluene did not yield the ring closed product. Presumably the steric interactions between the N-t-butyl and β-phenyl group are too large to allow the required conformation to be obtained.

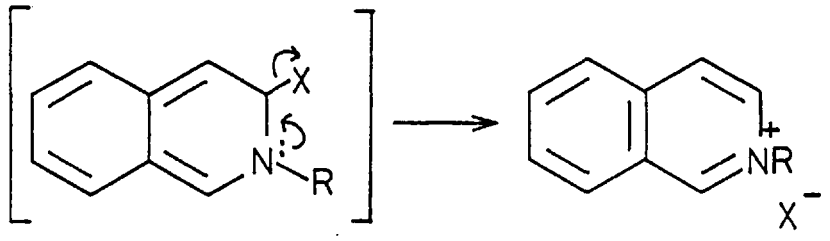


The first electrocyclic reaction can be written schematically (eqn. 12).



(12)

In the absence of excess olefin the closed form would either return to iminostyrene or if X was a suitable leaving group an irreversible aromatisation step would occur (eqn. 13).

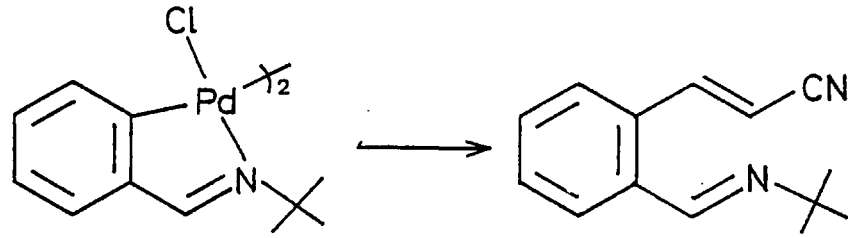


(13)

For this process to be accomplished an olefin $CH_2=CHX$ would be required where X is a suitable leaving group. Vinyl acetate and vinyl ethers (where X = OAc, OR resp.) are unsuitable as they do not undergo the insertion process. From the results obtained and the general pattern exhibited in the literature[57-63] the insertion process appears to be favoured in the cases where X is either a weakly polarising or electron withdrawing group. An olefin which satisfies both these criteria is acrylonitrile, the nitrile function is both electron withdrawing and a leaving group, it is also cheap,

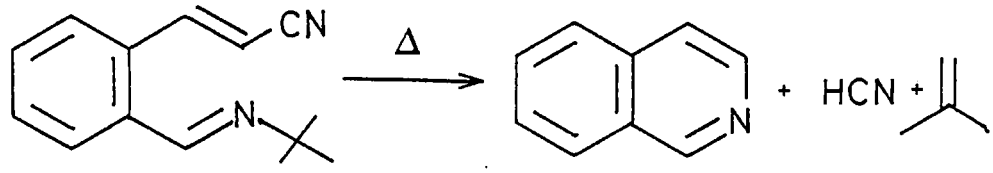
readily available and easy to handle.

Treatment of the imine complex 23 with acrylonitrile in the presence of triethylamine in refluxing toluene gave the crude isolated imine 60 in 78% yield.



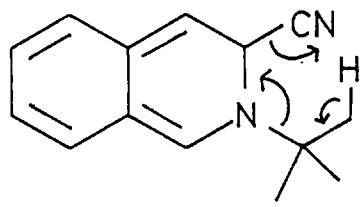
23 60

The imine 60 was heated in an inert solvent (mesitylene) at 160° to yield isoquinoline 61 in 24% overall yield based on the complex 23.

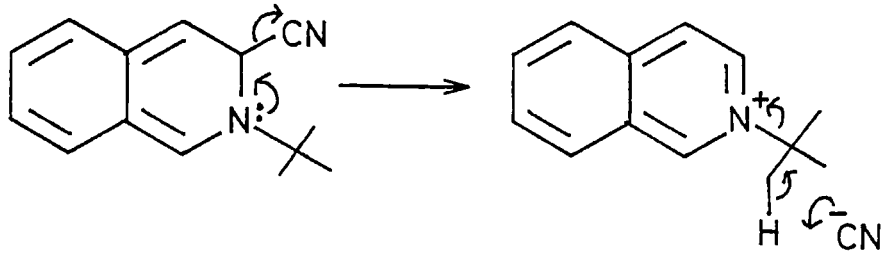


60 61

The aromatization can be written as a concerted process, for which similar pathways have been reported,[64]



or as an ionic process (see below).



By using diphenyl ether/mesitylene (95:5) as solvent, the entire procedure could be carried out without isolation of the intermediate imine. Typically, the complexes were treated with excess acrylonitrile in the presence of triethylamine in diphenyl ether/mesitylene at 80-110° under nitrogen for 8 - 12 hrs. The excess triethylamine and acrylonitrile were removed <u>in vacuo</u> and the precipitated palladium and triethylamine hydrochloride filtered off. The solution was then heated to 180-200° under nitrogen for 8 - 13 hrs to yield the isoquinolines (Scheme 8, Table 9).

Scheme 8

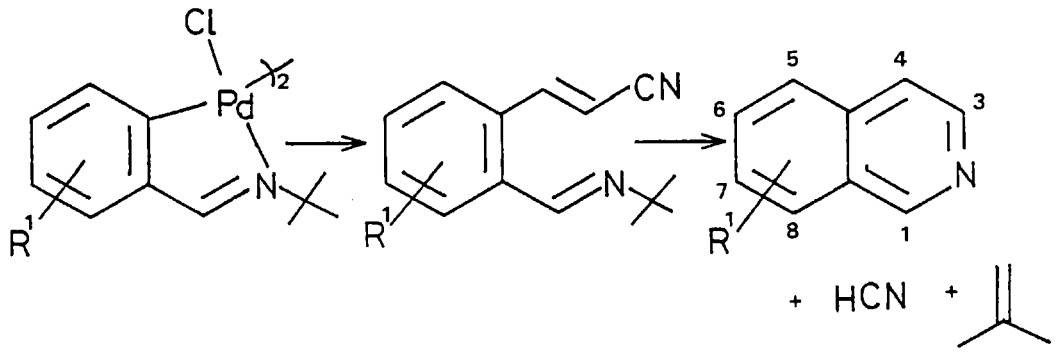


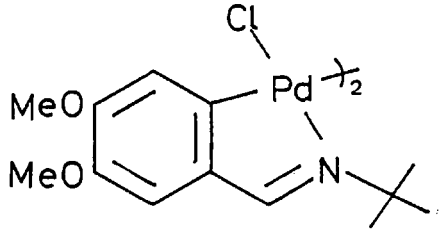
TABLE 9

COMPLEX Cpd No.	(R^1 =)	Stage 1 °C	Hr	Stage 2 °C	Hr	ISOQUINOLINE Cpd No.	(R^1 =)	(Yield %)*
23	H	110	9	190-5	13	61	H	(47)
25	4,5-$(MeO)_2$	100	12	180	8	62	6,7-$(MeO)_2$	(10)
26	3-MeO	95	14#	—		—		
27	4-MeO	110	12	200	8	63	7-MeO	(42)
28	5-MeO	110	8#	—		—		
29	5-Me	100	12	190	12	64	6-Me	(56)
30	5-Cl	110	8#	—		—		

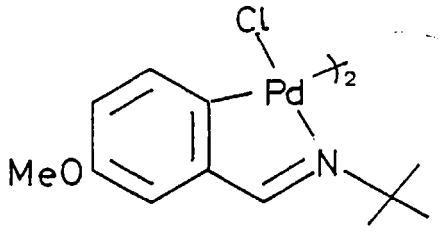
* Yields based on starting complex

\# These reactions were repeated using toluene as the solvent with excess acrylonitrile in the presence of triethylamine and it was found that the olefin insertion had not occured

Unlike the styrene insertion reactions reported earlier (Scheme 5, Table 6), in the reactions with acrylonitrile a pronounced substituent effect can be seen.



25



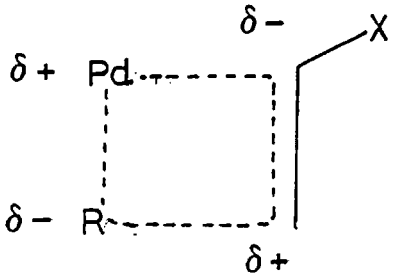
27

The complexes 25 and 27 contain a π-donor substituent <u>para</u> to the palladium atom which allowed the insertion to

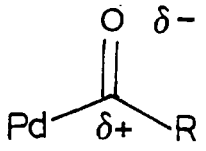
take place. Here the π-donor substituent increases the nucleophilic character of the carbon σ bonded to palladium. It is generally assumed[65] that the palladium-carbon σ bond is polarised with positive charge residing on palladium and that the insertion occurs via a



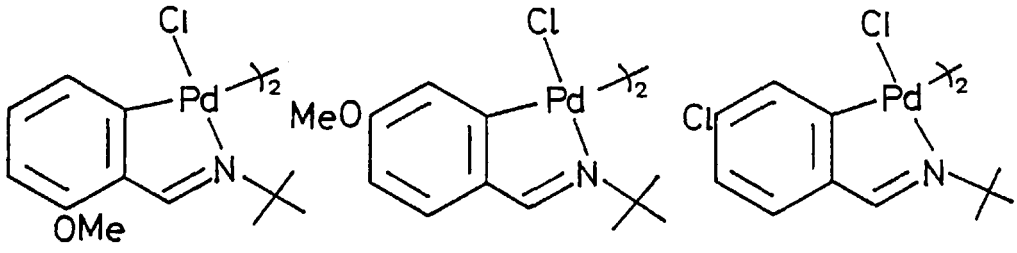
4-centre concerted process[65] (as shown below), although little



mechanistic work has been carried out on this reaction in comparison with its importance.[66] Polarisation of the palladium-carbon σ bond in the above manner appears to be essential. Examples of olefin insertions into the palladium-carbon σ bond of acyl palladium species where the carbon is electrophilically disposed, are extremely scarce.[67]



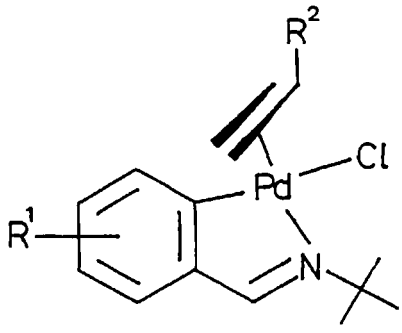
In contrast to the complexes 25 and 27, the complexes 26, 28 and 30 did not undergo the insertion reaction with acrylonitrile.



26 28 30

These complexes contain a π-donor substituent ortho- or para- to the imine function and this would be expected to increase the electron donating power of the imino nitrogen ligand. This increases the electron density on palladium and gives rise to two effects.

(i) Preceding the insertion, the olefin must be co-ordinated[68] cis to the palladium carbon σ bond as shown below



Strong donation by the imino-nitrogen ligand trans to the olefin would be expected to strengthen the metal olefin interaction by increased back bonding.[69] This may hinder the rotation[70] of the olefin, however, in this case its effect on the insertion would be small.

(ii) Increased electron density on palladium reduces its positive character, altering the polarisation of the palladium-carbon σ bond. The insertion reaction is expected to be facilitated by an increase in the positive character of the palladium[71] and inhibited by a decrease. From our results it would appear that the rate determining step in the acrylonitrile insertion process is the actual insertion itself.

The insertion of acrylonitrile into the palladium-carbon σ bond of these cyclometallated aromatic imines appears to be remarkably sensitive to the donor power of the imino-nitrogen ligand. This is also possibly true for styrene*, although to a much lesser extent, but is implied by the order of reactivity found for the N-alkyl group on the imine i.e. n-Bu<i-Pr<t-Bu. The t-butyl group being bulkiest, reduces electron donation from the imino-nitrogen to the palladium and facilitates the insertion reaction.

* The reactions with styrene were carried out under different conditions and a direct comparison may not be valid. However, the N-n-butyl imine complex 21 did not undergo the insertion reaction with acrylonitrile in refluxing toluene in the presence of triethylamine whereas the N-t-butyl imine complex 23 reacted smoothly.

CONCLUSION

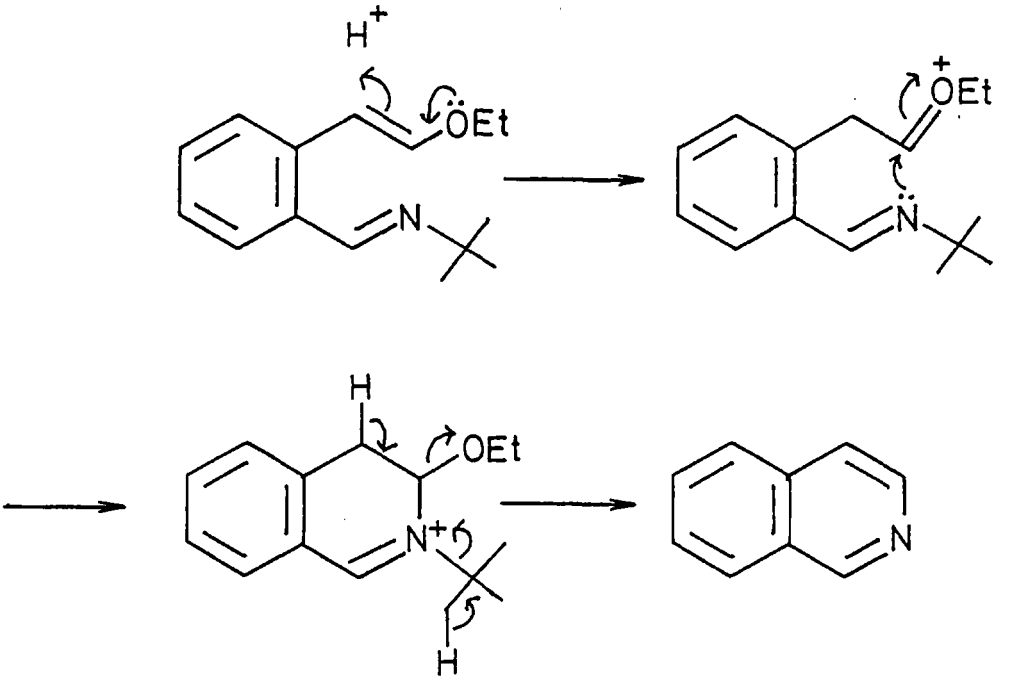
Cyclopalladated aromatic imines could provide an interesting tool for the investigation of the olefin insertion reaction. The stability of these complexes allows a complete characterisation of the starting palladated aromatic to be carried out which is not always possible for palladated aromatics generated *in situ*.

The "inserting olefin" must co-ordinate *trans* to the imino nitrogen, which is necessarily *cis* to the aryl ligand, thus the ligand positions are well defined.

The donating power of the imino nitrogen ligand can be easily varied by altering the substitutents on the palladated aryl ring, as was seen in the work presented here (cplxs. 23-30), or if *N*-aryl imines are used, substituents on the *N*-aryl ring will also influence the donating power of the imino-nitrogen.

The work presented here represents the first successful report of the reaction of olefins with *ortho*-palladated aromatic imine complexes, providing a route to *ortho*-vinylated aromatic aldehydes, which are useful precursors to heterocyclic ring systems. Direct conversion of *ortho*-palladated aromatic imines to isoquinolines was achieved using acrylonitrile as the olefin, recent work with vinyl boranes,[72] particularly β-ethoxy vinyl borane $(EtOCH{=}{=}CH)_3B$ (Review Pt. 1 eqns.

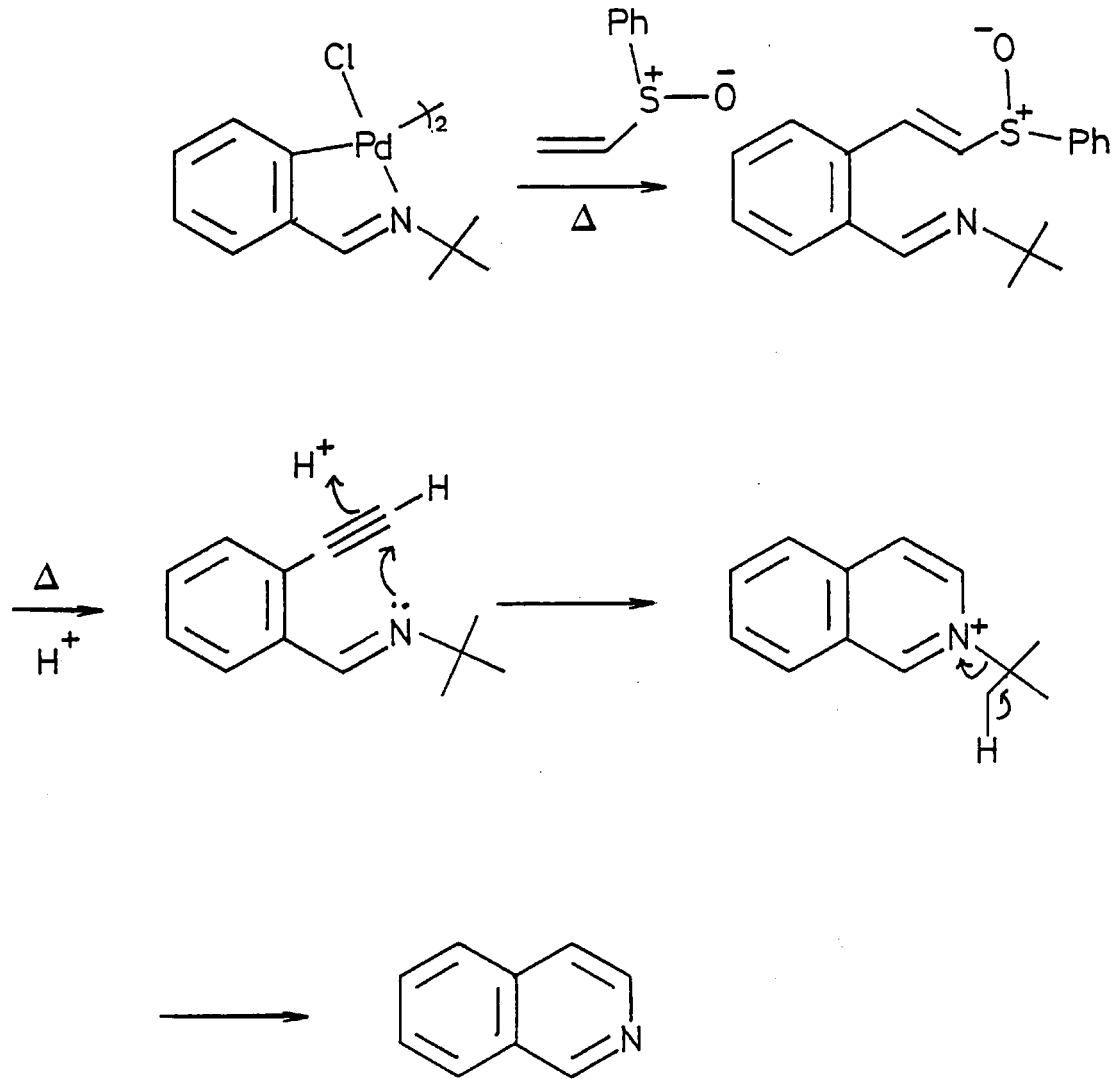
32 and 33), should allow the smooth introduction of the vinyl ether group ortho- to the imine which on treatment with catalytic acid should provide a mild route to isoquinolines as shown below.



However acrylonitrile is a more easily obtainable reagent when compared to the vinyl boranes.

The use of an acetylene as a C_2 unit was considered. The known[73] reactions of acetylenes with cyclopalladated complexes and preliminary investigations using phenyl acetylene did not appear promising. Recent work involving the reaction of copper acetylide intermediates with palladated aromatics (Review Pt. 1 eqn. 25-28) perhaps indicates this approach may be useful. An interesting but perhaps more speculative possibility, is the use of an olefin, such as a vinyl sulphoxide, as a masked acetylene.[74,75] Insertion, followed by thermal rearrangement to the acetylene with concomitant ring closure would be an efficient and elegant route to

isoquinolines.



EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer. ^{1}H Nuclear magnetic resonance spectra were recorded on a Varian EM360A machine, in deuterochloroform using tetramethylsilane as the internal standard (unless otherwise stated). Mass spectra were measured on a V. G. Micromass 7070B instrument operating at 70eV.

Microanalyses were carried out by the microanalytical laboratory, Imperial College.

Organic extracts were dried over an appropriate desiccant (magnesium sulphate, sodium sulphate or sodium carbonate).

Solvents used for chromatographic separations and recrystallizations were redistilled before use. Tetrahydrofuran and diethyl ether used for the Grignard and organolithium reactions were freshly distilled from potassium benzophenone ketyl. Toluene, mesitylene and diphenyl ether were dried over and distilled from sodium.

Sodium acetate supplied as anhydrous was baked at 250° for 24-48 hours. Acetic acid was refluxed with acetic

anhydride and chromium trioxide* followed by distillation.

Other general reagents and starting materials were purified by literature methods.[76]

Chromatographic absorbents refer to Merck products.

All reactions involving palladated complexes or intermediates were carried out using degassed solvents under dry nitrogen.

General preparation of Imines (1-15).— This was achieved by the simple condensation of the appropriate aromatic aldehyde and primary amine under mildly dehydrating conditions. Essentially the method used to remove the water of condensation depended on the volatility of the amine. Two methods were employed; (i) with amines boiling at greater than 80°C the water was removed azeotropically with benzene and (ii) with more volatile amines the water was removed with a suitable desiccant.

Method (i)

Equimolar amounts of the aldehyde and amine were

* The acetic acid and acetic anhydride were gently warmed and chromium trioxide added in small portions (ca. 0.1-0.2g), on the addition of too large a portion a vigorous reaction occurs, otherwise the method is much the same as that given in reference 76.

refluxed in benzene until the calculated amount of water had been collected in a Dean-Stark trap. The benzene solution was dried (sodium carbonate), the benzene removed under vacuum and the imine distilled or recrystallized as required.

Method (ii)

The aldehyde (1 eq.) and amine (2 eq.) were stirred together over molecular sieves (3A)* at room temperature in a suitable solvent, usually ether.# The reaction was conveniently followed by infrared spectroscopy.+

N-Benzylidene-methylamine (1).— Method (ii); (86%), b.p. 41-2°/3mm (lit.,[77] 89°/30mm); ν_{max}(neat) 1648, 755, and 695 cm^{-1}; $\delta(CDCl_3)$ 8.12 (1H,s,CH=N), 7.8-7.6 (2H,m,ArH), 7.4-7.2 (3H,m,ArH), and 3.42 (3H,s,NMe).

N-Benzylidene-aniline (2).— Method (i); (93%) m.p. 50° (from light petroleum ether) (lit.,[78] 54°); ν_{max}(nujol) 1624, 760, 755, and 690 cm^{-1}; $\delta(CDCl_3)$ 6.91(1H,s,CH=N), 6.3 (2H,m,ArH), and 6.0-5.6 (8H,m,ArH).

* It was found that sodium sulphate or magnesium sulphate could also be used.

\# The reactions involving methylamine were carried out in ethanol, as the amine is supplied as an ethanolic solution.

\+ The disappearance of the carbonyl stretching band at ~1690cm^{-1} indicated completion of reaction. Also from the infrared spectrum it could easily be seen if more desiccant or amine was required to drive the reaction to completion.

N-Benzylidene-n-butylamine (3).— Method (i); (88%) b.p. 58-62°/1mm (lit.,[79] 112-113°/14mm); ν_{max}(neat) 1640, 755, and 695 cm^{-1}; $\delta(CDCl_3)$ 8.21 (1H,s,CH=N), 7.8-7.1 (5H,m, ArH), 3.54(2H,t,J5Hz, NCH_2-), and 1.8-0.8 (7H,m,$-CH_2CH_2CH_3$); m/e: 161 (M+·).

N-Benzylidene-2-propylamine (4).— Method (ii); (98%) b.p. 64°/2.5mm (lit.,[77] 116°/24mm); ν_{max}(neat) 1639, 750, and 690 cm^{-1}; $\delta(CDCl_3)$ 8.2 (1H,s,CH=N), 7.77-7.2(5H,m,ArH), 3.42 (1H,septet,J6Hz, $(Me)_2CHN$), and 1.24 (6H,d,J6Hz, $(Me)_2CHN$); m/e: 147 (M+·).

N-Benzylidene-t-butylamine (5).— Method (ii); (72%) b.p. 61-2°/2mm (lit.,[80] 59-63°/1mm); ν_{max}(neat) 1639, 750, and 690 cm^{-1}; $\delta(CDCl_3)$ 8.32 (1H,s,CH=N), 7.92-7.3 (5H,m,ArH), and 1.34 (9H,s,$NC(Me)_3$); m/e: 161 (M+·).

N-(α-Methylbenzylidene)-n-butylamine (6).— Method (ii); (83%) b.p. 87-91°/3mm (lit.,[81] 83-84°/0.38mm); ν_{max}(neat) 1630, 765, and 700 cm^{-1}; $\delta(CDCl_3)$ 7.85-7.5 (2H,m,ArH), 7.35-7.05 (3H,m,ArH), 3.36 (2H,t,J6Hz, NCH_2-), 2.04 (3H,s, Ar(Me)C=N), and 1.9-0.7 (7H,m,$-CH_2-CH_2-CH_3$).

N-(3,4-Dimethoxybenzylidene)-methylamine (7).— Method (ii); (68%) m.p. 55-55.5°(from 40-60 petroleum ether-ether) (lit.,[82] 56°); ν_{max}(nujol)1640, and 745 cm^{-1}; $\delta(CDCl_3)$ 8.05 (1H,d, J1.5Hz, CH=N), 7.39 (1H,d,J1.8Hz, H-2), 7.04 (1H,dd,J7.5 and 1.8Hz,H-6), 6.74 (1H,d,J7.5Hz, H-5),3.86(3H,s,OMe), 3.78 (3H,s,OMe), and 3.4 (3H,d,J1.5Hz,NMe). (Found: C,67.03; H, 7.37; N,7.76: Calc. for $C_{10}H_{13}NO_2$: C,67.02; H,7.31; N,7.82%).

N-(3,4-Dimethoxybenzylidene)-t-butylamine (8).— Method (ii); (82%) m.p. 73-73.5°(needles from 40-60 petroleum ether) (lit.,[82] 73°); ν_{max}(nujol) 1640 cm^{-1}; $\delta(CDCl_3)$ 8.16 (1H,s, CH=N), 7.41 (1H,d,J2Hz, H-2), 7.13 (1H,dd,J8,and 2Hz,H-6), 6.78 (1H,d,J8Hz, H-6) 3.88 (3H,s,OMe), 3.82 (3H,s,OMe), 1.28 (9H,s,$NC(Me)_3$); m/e: 221 (M+·); (Found: C,70.74; H, 8.78; N,6.34: Calc. for $C_{13}H_{19}NO_2$: C,70.56; H,8.65; N, 6.34%).

N-(2-Methoxybenzylidene)-t-butylamine (9).— Method (ii); (78%) b.p. 102°/4.5mm; ν (neat) 1635 (C=N) cm^{-1}; $\delta(CDCl_3)$ 8.67 (1H,s,CH=N), 7.9 (1H,dd,J7.8 and 2Hz, H-6), 7.38-6.61 (3H,m,ArH), 3.72 (3H,s,OMe), and 1.25 (9H,s,$NC(Me)_3$); m/e: 191 (M+·); (Found: C,75.47; H,9.05; N,7.03. $C_{12}H_{17}NO$ requires: C,75.35; H,8.96; N,7.32%).

N-(3-Methoxybenzylidene)-t-butylamine (10).— Method (ii); (84%) b.p. 144-6°/35mm; ν(neat) 1640 (C=N) cm^{-1}; δ($CDCl_3$) 8.26 (1H,s,CH=N), 7.4-6.8(4H,m,ArH) 3.82 (3H,s,OMe), and 1.3 (9H,s,$NC(Me)_3$); m/e: 191 (M+·); (Found: C, 75.08; H, 8.99; N,7.24: $C_{12}H_{17}NO$ requires: C,75.35; H, 8.96; N, 7.32%).

N-(4-Methoxybenzylidene)-t-butylamine (11).— Method (ii); (86%) m.p. 28.5-30°; b.p. 115/7.5mm (lit.,[83] 110°/2.1mm); ν(melt) 1640 (C=N) cm^{-1}; δ($CDCl_3$) 8.15 (1H,s,CH=N), 7.63 (2H,d,J8Hz, ArH), 6.83 (2H,d,J8Hz, ArH), 3.78 (3H,s,OMe), and 1.23 (9H, s, $NC(Me)_3$); m/e: 191 (M+·); (Found: C, 75.11; H,8.78; N, 7.12: Calc. for $C_{10}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32%).

N-(4-Methylbenzylidene)-t-butylamine (12).— Method (ii); (79%) b.p. 81°/2mm (lit.,[83] 83-84°/1.4mm); ν(neat) 1638 (C=N) cm^{-1}; δ ($CDCl_3$) 8.13 (1H,s,CH=N), 7.56 (2H,d,J8Hz, ArH), 7.04 (2H,d,J8Hz, ArH), 2.27 (3H,s,Me), and 1.26 (9H,s,$NC(Me)_3$); m/e:175 (M+·); (Found: C, 82.18; H, 10.03; N,7.69: Calc. for $C_{12}H_{17}N$: C, 82.22; H,9.78; N,7.99%).

N-(4-Chlorobenzylidene)-t-butylamine (13).— Method (ii); (79%) m.p. 31-4° (from 40-60 petroleum ether) (lit.,[84] 33-5°), b.p. 90°/0.9mm with some sublimation (lit.,[83] 89-90°/1mm); ν(neat) 1640 (C=N) cm^{-1}; δ ($CDCl_3$) 8.19 (1H,s, CH=N), 7.66 (2H,d,J8Hz, ArH), 7.3 (2H,d,J8Hz, ArH), and 1.3 (9H,s,$NC(Me)_3$); m/e: 195 ($M^{+\cdot}$); (Found; C,67.68; H, 7.19; Cl, 17.93; N,7.14: Calc. for $C_{11}H_{14}ClN$: C,67.52; H,7.2; Cl,18.12; N,7.16%).

N-(4-N′,N′-Dimethylaminobenzylidene)-t-butylamine (14).— Method (ii); (73%) b.p. 110-14°/2mm (lit.,[85] 143-145°/7.5mm); ν (neat) 1653 (C=N) cm^{-1}; δ($CDCl_3$) 8.2(1H,s,CH=N), 7.65 (2H,d,J8Hz, ArH), 6.67 (2H,d,J8Hz,ArH), 2.97 (6H,s,$N(Me)_2$), and 1.35 (9H,s,$NC(Me)_3$).

N-(4-Nitrobenzylidene)-t-butylamine (15).— Method (ii); (86%) m.p. 74.5-75.5° (from 40-60 petroleum ether-ether) (lit.,[83] 72-75°); ν(melt) 1645 (C=N) cm^{-1}; δ($CDCl_3$) 8.34 (1H,s,CH=N), 8.24 (2H,d,J9Hz,ArH), 7.88 (2H,d,J9Hz,ArH), and 1.33 (9H,s,$NC(Me)_3$); m/e: 206 ($M^{+\cdot}$).

PREPARATION OF THE ORTHO-PALLADATED COMPLEXES

General Preparation of the acetate-bridged complexes.(16-18) — These were prepared by reacting the appropriate imine (1,2 and 7 resp.) with palladium acetate in acetic acid following the method of Onoue and Moritani.[19] The yields and data for these complexes are listed below.

Di-μ-acetatobis [2-(N-methyliminomethyl)phenyl]-1, N-dipalladium (II) (16).— (92%) m.p. 221° (yellow crystals from CH_2Cl_2-cyclohexane) (lit.,[19] 222-5°); ν(nujol) 1624 (C=N), and 1570 (COO^-) cm^{-1}; δ($CDCl_3$) 7.6 (1H,d,J1.5Hz, CH=N), 7.3 (5H,m,ArH), 3.2 (3H,d,J1.5Hz, NMe), and 2.5(3H,s,$MeCOO^-$).

Di-μ-acetatobis [2-(N-phenyliminomethyl)phenyl]-1,N-dipalladium (II) (17).— (88%) m.p. 208-14°(darkening at 200°) (yellow crystals from CH_2Cl_2-hexane) (lit.,[19] 210-20°); ν (nujol) 1575 (broad peak contg. CH=N, Arom.C=C, and COO^-str.) cm^{-1}; δ ($CDCl_3$) 7.68 (1H,s,CH=N), 7.3-6.6(9H,m, ArH), and 1.78(3H,s,$MeCOO^-$).

Di-μ-acetatobis [2-(N-methyliminomethyl)-4,5-dimethoxyphenyl] -1,N-dipalladium (II) (18).— (79%) m.p. 212-15° decomp. (yellow crystals from chloroform); ν(nujol) 1575 (broad peak contg. C=N, Arom. C=C, and COO^-str.) cm^{-1}; δ ($CDCl_3$) 7.32 (1H,s,CH=N), 6.74 (1H,s,ArH), 6.62(1H,s,ArH) 3.92 (3H,s,OMe), 3.87 (3H,s,OMe), 2.91 (3H,s,NMe), and 2.21 (3H, s,$MeCOO^-$); (Found: C,42.0; H,4.41; N, 3.89 $C_{22}H_{30}N_2O_8Pd_2$ requires: C,41.9; H,4.4; N, 4.08%).

General preparation of the chloro-bridged complexes 19-30. — these were prepared by treatment of the imine with palladium chloride in the presence of sodium acetate in acetic acid in the following manner: a magnetically stirred solution of sodium acetate (anhydrous, 15-20 eq) in acetic acid (dry, 80 ml) was purged with nitrogen at 60° for 20-30 minutes, to this was added finely ground palladium chloride (0.708g, 0.004 mol), the mixture was purged for a further 5-10 minutes during which time a small amount of the palladium chloride dissolved to give a brown solution. To this mixture was added the imine (1.2-1.5 eq), the temperature was raised to 80° and the mixture efficiently stirred for a further 1 - 2 hours until the solid palladium chloride had been replaced by a yellow precipitate, and the mother liquor had discharged its brown colouration. The mixture was allowed to cool and diluted with water to precipitate out any dissolved complex. The complex was then filtered off, washed with water, and allowed to air dry. Recrystallization from tetrahydrofuran-water or DMSO-water mixtures yielded the complexes as yellow, crystaline solids. The complexes prepared by this method, their yields and data are listed below:-

Di-μ-chlorobis [2-(N-methyliminomethyl)phenyl]-1,N-dipalladium (II) (19)*.— (82%) m.p. 268-70° decomp. (yellow crystals from THF-H_2O) (lit.,[19] 271-2°); ν(nujol) 1620 (C=N) cm^{-1}; δ (d^6DMSO) 8.3 (1H,d,J1.5Hz,CH=N), 7.8 (1H,m,ArH) 7.4 (1H,m,ArH), 7.1(2H,m,ArH), and 3.4(3H,br s, NMe); δ ($CDCl_3$-d^5pyridine) 7.81(1H,br s, CH=N), 7.31-6.73(3H,m,ArH), 6.21 (1H,m,H-6), and 3.51 (3H,br s, NMe); (Found: C,37.3; H,3.14; Cl,13.68; N,5.38: Calc. for $C_{16}H_{16}Cl_2N_2Pd_2$: C,36.96; H,3.1; Cl, 13.64; N,5.39%).

Di-μ-chlorobis[2-(N-phenyliminomethyl)phenyl]-1,N-dipalladium (II) (20)*. — (92%) m.p. 276° decomp. (yellow crystals from DMSO - H_2O) (lit.,[19] 281-3°); ν(nujol) 1599 (C=N) cm^{-1}; δ (d^6DMSO) 8.2 (1H,s,CH=N), and 7.8-7.01 (9H,m,ArH).

Di-μ-chlorobis[2-(N-n-butyliminomethyl)phenyl]-1,N-dipalladium (II) (21). — (91%) m.p. 225-7° (darkening at 220°) (yellow crystals from THF-DMSO-H_2O); ν(nujol) 1612 (C=N) cm^{-1} δ ($CDCl_3$) 7.9 (1H,s,CH=N), 7.85-6.7 (4H,m,ArH), 3.5 (2H,t, J5Hz,NCH_2-), and 1.7-0.7 (7H,m,-$CH_2CH_2CH_3$); δ($CDCl_3$-d^5pyridine) 8.0 (1H,s,CH=N), 7.8-6.9 (3H,m,ArH), 6.35 (1H,m,H-6), 3.91 (2H,t,J6.8Hz,NCH_2-), and 2.2-0.9 (7H,m,-$CH_2CH_2CH_3$); (Found: C,43.53; H,4.64; Cl, 11.90; N,4.55: $C_{22}H_{28}Cl_2N_2Pd_2$ requires: C,43.74; H,4.67; Cl, 11.74; N,4.64%).

* The complexes 19 and 20 were also prepared, in 89 and 90% yields respectively, by treatment of the corresponding acetate-bridged complexes (16 and 17 respectively) with chloride ion in aqueous acetone, as described by Onoue and Moritani.[19]

Di-μ-chlorobis[2-(N-iso-propyliminomethyl)phenyl]-1,N-dipalladium (II) (22).— (94%) m.p. 240-1° (darkening at 230°) (yellow crystals from THF-H_2O); ν(nujol) 1605 (C=N) cm^{-1}; δ ($CDCl_3$-d^6DMSO) 8.05 (1H,s,CH=N), 7.8-6.85 (4H,m,ArH), 4.2 (1H,m,$(Me)_2\underline{C}H\underline{N}$), and 1.4 (6H,d,J6.2Hz, $(\underline{Me})_2CHN$); δ ($CDCl_3$-d^5 pyridine) 8.0 (1H,s,CH=N), 7.4-6.7 (3H,m,ArH),6.13 (1H,m, H-6), 4.6 (1H, septet, J6.1Hz, $(Me)_2\underline{C}H\underline{N}$), and 1.4 (6H,d, J6.1Hz, $(\underline{Me})_2CHN$); (Found: C,41.96; H,4.22; Cl, 12.25; N, 4.84: $C_{20}H_{24}Cl_2N_2Pd_2$ requires: C,41.7; H,4.2; Cl, 12.3; N, 4.9%).

Di-μ-chlorobis [2-(N-t-butyliminomethyl)phenyl]-1, N-dipalladium (II) (23).— (95%) m.p. 252-3° (darkening at 230°) (yellow crystals from THF-H_2O) (lit.,[24] decomposed gradually from 230°); ν(nujol) 1604 (C=N) cm^{-1}; δ ($CDCl_3$) 7.81 (1H,s, CH=N), 7.5-6.8(4H,m,ArH), and 1.51 (9H,s,$NC(Me)_3$); δ ($CDCl_3$-d^5pyridine) 7.86 (1H,s,CH=N), 7.49-6.67 (3H,m,ArH), 5.92 (1H,apparent dd, J6 and 2Hz, H-6), and 1.66 (9H,s,$NC(Me)_3$); (Found: C, 44.01; H,4.68; Cl,11.78; N,4.60: Calc. for $C_{22}H_{28}Cl_2N_2Pd_2$: C, 43.74; H,4.67; Cl, 11.74; N,4.63%).

Di-μ-chlorobis[2-[α-methyl(N-n-butyliminomethyl)]phenyl]-1, N-dipalladium (II) (24).— (63%) m.p. 205-6° decomp. (yellow crystals from THF-H_2O); ν (nujol) 1600 br (C=N, ArC=C) cm^{-1}; δ ($CDCl_3$) 7.5-6.8 (4H,m,ArH), 3.6(2H,m,NCH_2-), 2.23 (3H,s, Ar(Me)C=N), and 2.1-0.8 (7H,m,$-CH_2CH_2CH_3$); δ ($CDCl_3$-d^5 pyridine) 7.4-6.8 (3H,m,ArH), 6.15 (1H,m,H-6), 3.9(2H,t,J6.5Hz NCH_2-), 2.2 (3H,s,Ar(Me)C=N), and 2.0-0.8 (7H,m,$-CH_2CH_2CH_3$); (Found: C,45.52; H, 4.84; N, 4.46: $C_{24}H_{32}Cl_2N_2Pd_2$ requires: C, 45.59; H, 5.1; N, 4.43%).

Di-μ-chlorobis [2-(N-t-butyliminomethyl)-4, 5-dimethoxyphenyl]-1, N-dipalladium (II) (25).— (89%) m.p. 270-2° (darkening at 230-40° (yellow crystals from THF-H_2O); ν(nujol)1603 (C=N) cm^{-1}; δ ($CDCl_3$) 7.98 (1H,s,CH=N), 7.23 (1H,s,ArH), 7.0 (1H,s, ArH), 4.05 (3H,s,OMe), 3.98 (3H,s,OMe), and 1.6 (9H,s,$NC(Me)_3$); δ ($CDCl_3$-d^5pyridine) 7.9 (1H,s,CH=N), 6.96 (1H,s,H-3), 5.46 (1H,br s, H-6), 3.77 (3H,s,OMe-4), 3.46(3H,s,OMe-5), and 1.64(9H,s,$NC(Me)_3$); (Found: C, 43.37; H, 4.98; Cl, 9.99; N, 3.64: $C_{26}H_{36}Cl_2N_2O_4Pd_2$ requires: C, 43.12; H,5.01; Cl; 9.79; N, 3.87%).

Di-μ-chlorobis[2-(N-t-butyliminomethyl)-3-methoxyphenyl]-1, N-dipalladium (II) (26).— (81%) m.p. >300° (darkening at 250-265°) (yellow crystals from THF-DMSO-H_2O); ν (nujol) 1595 (C=N) cm^{-1};δ*($CDCl_3$/d^6DMSO) 8.2 (1H,s,CH=N), 7.4-6.4 (3H, m,ArH), 3.82 (3H,s,OMe), and 1.45 (9H,s,$NC(Me)_3$); δ ($CDCl_3$-d^5 pyridine) 8.29(1H,s,CH=N), 6.82 (1H, br t, J7.5Hz, H-5), 6.46 (1H,br d, J7.5Hz,H-4), 5.45 (1H,br d, J7.5Hz, H-6), 3.78 (3H,s,OMe), and 1.62 (9H,s,$NC(Me)_3$); (Found: C,43.55; H, 4.83; Cl, 10.75; N, 4.17; $C_{24}H_{32}Cl_2N_2O_2Pd_2$ requires: C, 43.4; H, 4.86; Cl, 10.68; N, 4.22%).

* Due to the very poor solubility of this complex in either d^6 dimethylsulphoxide or deuterochloroform the chemical shifts quoted maybe slightly inaccurate. However, the complex was completely soluble in the d^5 pyridine-chloroform mixture.

Di-μ-chlorobis[2-(N-t-butyliminomethyl)-4-methoxyphenyl]-1, N-dipalladium (II) (27).— (96%) m.p. 254-6° (darkening at 195-215°) (yellow crystals from THF-H_2O); ν (nujol) 1607 (C=N) cm^{-1}; δ ($CDCl_3$) 7.8 (1H,s,CH=N), 7.25 (1H,d,J2Hz,H-3), 6.8-6.45 (2H,m,ArH), 3.73 (3H,s,OMe), and 1.53 (9H,s,NC(Me)$_3$); δ ($CDCl_3$-d^5pyridine) 7.91 (1H,s,CH=N), 6.92 (1H,d,J3Hz,H-3), 6.47 (1H,dd,J8.6, and 3Hz, H-5), 5.82 (1H,d,J8.6Hz, H-6), 3.65 (3H,s,OMe), and 1.6 (9H,s,NC(Me)$_3$); (Found: C,43.76; H, 4.92; Cl, 10.61; N, 4.16: $C_{24}H_{32}Cl_2N_2O_2Pd_2$ requires: C, 43.4; H, 4.86; Cl, 10.68; N, 4.22%).

Di-μ-chlorobis[2-(N-t-butyliminomethyl)-5-methoxyphenyl]-1, N-dipalladium (II) (28).— (95%) m.p. 262° (darkening at 220-235°) (yellow crystals from THF-H_2O); ν (nujol) 1604 (C=N) cm^{-1}; δ ($CDCl_3$) 7.68 (1H,s,CH=N), 7.15-6.94 (2H,m, ArH), 6.34 (1H,dd,J8.4, and 2Hz, H-4), 3.63 (3H,s,OMe), and 1.33 (9H,s,NC(Me)$_3$); δ ($CDCl_3$-d^5pyridine) 7.83 (1H,s,CH=N), 7.17 (1H,d,J8.2Hz,H-3), 6.43(1H,dd,J8.2 and 2.5Hz, H-4), 5.36(1H,d,J2.5Hz, H-6), 3.42 (3H,s,OMe), and 1.51 (9H,s, NC(Me)$_3$); (Found: C,43.96; H, 4.89; Cl, 10.62; N, 4.18: $C_{24}H_{32}Cl_2N_2O_2Pd_2$ requires: C, 43.4; H, 4.86; Cl, 10.68; N, 4.22%).

Di-μ-chlorobis[2-(N-t-butyliminomethyl)-5-methylphenyl]-1, N-dipalladium (II) (29).— (89%) m.p. 232-4° decomp. (yellow crystals from THF*-H_2O); ν (nujol) 1604 (C=N) cm^{-1}; δ ($CDCl_3$) 7.76(1H,s,CH=N), 7.3-6.7(3H,m,ArH), 2.28 (3H,s,Me), and 1.51 (9H,s,$NC(Me)_3$); δ ($CDCl_3$-d^5pyridine) 7.88 (1H,s,CH=N), 7.18 (1H,d,J7.5Hz, H-3), 6.81 (1H,br d,J7.5Hz, H-4), 5.7 (1H,br s, H-6), 2.09(3H,s,Me), and 1.64 (9H,s,$NC(Me)_3$); (Found: C,45.53; H, 5.03; Cl, 11.41; N, 4.39: $C_{24}H_{32}Cl_2N_2Pd_2$ requires: C, 45.59; H,5.1; Cl, 11.22; N, 4.43%).

Di-μ-chlorobis [2-(N-t-butyliminomethyl)-5-chlorophenyl-]-1, N-dipalladium (II) (30).— (88%) m.p. 282-4° (darkening at 240°) (yellow crystals from THF-H_2O); ν (nujol) 1604 (C=N) cm^{-1}; δ ($CDCl_3$) 7.74 (1H,s,CH=N), 7.5-7.01 (3H,m,ArH), and 1.57 (9H,s,$NC(Me)_3$); δ ($CDCl_3$-d^5pyridine) 7.83 (1H,s,CH=N), 7.23 (1H,d,J8Hz, H-3), 6.98 (1H, dd, J8 and 2Hz, H-5), 5.87 (1H,br s, H-6) and 1.64 (9H,s,$NC(Me)_3$); (Found: C, 39.58; H, 4.04; Cl^+, 20.34; N, 3.92: $C_{22}H_{26}Cl_4N_2Pd_2$ requires: C, 39.26; H, 3.9; Cl, 21.07; N, 4.16%)

* To remove residual tetrahydrofuran from the crystals, extended periods (1-2 weeks) in vacuum were needed. This problem could be avoided by recrystallization from ether alone, although the solubility of the complex in ether is not high.

\+ Several analyses of this complex were carried out, the elements carbon hydrogen and nitrogen were always present in the correct percentages the chlorine content being repeatably low. This could be due to the presence of both anionic chlorine and co-valently bound chlorine in the complex, interfering with the analytical technique.

Di-μ-chlorobis[2-(N,N-dimethylaminomethyl)phenyl]-1,N-dipalladium (II) (33).— Following the method of Holton and Davis,[20] N,N-dimethylbenzylamine was treated with lithium tetrachloropalladate in methanol containing excess triethylamine to give the product (33) in 74% yield. m.p. 181-184° decomp. (yellow crystals from THF-H_2O) (lit.,[31] 183-185° decomp.); $\nu_{max.}$(nujol) 1564, 1280, 1040, 1020, 980, 964, 860, 840, and 724 cm^{-1}; δ($CDCl_3$) 7.4-6.8 (4H,m,ArH), 4.05 (2H,s,NCH_2-), and 2.94 (6H,s,$N(Me)_2$).

Reactions of the ortho-palladated complexes:o-Methyl-N,N-dimethylbenzylamine (34).— A mixture of the complex (33) (0.522g, 0.001mol) and triphenylphosphine (1.044g, 0.004mol) was dissolved in THF. To this mixture was added MeLi (1.5 eq in ether), after stirring overnight at room temperature the palladium black was filtered off, the solution was diluted with ether, acidified (HCl) and the amine hydrochloride extracted into water. The aqueous layer was washed with several portions of ether, before being made alkaline (KOH) to liberate free amine, which was extracted into ether and dried. Removal of the ether under vacuum gave the title compound (34) as a colourless liquid in 70% yield. ν_{max}(neat) 2970, 2810, 2780, 1455, 1020, and 740 cm^{-1}; δ(CCl_4) 7.5-7.1 (4H, m,ArH), 3.5 (2H,s,NCH_2-), 2.45 (3H,s,Me), and 2.2 (6H,s, $N(Me)_3$); m/e: 149 (M+·)

Picrate salt m.p. 112-13° (yellow needles from EtOH) (lit.,[86] 112.5-13°).

o-Phenyl-N,N-dimethylbenzylamine (35).— A mixture of the complex (33) (0.522g, 0.001 mol) and triphenylphosphine (1.044g, 0.004 mol) was dissolved in THF. To this mixture was added a THF solution of phenyl magnesium bromide (4ml, 0.004 mol) [prepared by treatment of bromobenzene (1.57g, 1.0 eq) with magnesium (0.267g, 1.1 eq) in THF, then the total volume made up to 10 ml with THF]. After 1 hour the precipitated palladium metal was filtered off and the product (35) was extracted in the same manner as was described for compound (34) to give o-phenyl-N,N-dimethylbenzylamine (35) as a colourless oil in 58% yield. ν_{max} (neat) 2820, 2760, 1450, 1250, 1170, 1025, 750, and 705 cm^{-1}; δ ($CDCl_3$) 7.7-7.3 (9H,m,ArH), 3.45 (2H,s,NCH_2-), and 2.2 (6H,s,$N(Me)_2$); m/e: 211 (M+·), and 210 (M-1).

Picrate salt m.p. 166-166.5° (yellow leaflets from MeOH) (Found: C,57.27; H,4.53; N, 12.74: $C_{21}H_{20}N_4O_7$ requires: C, 57.27; H, 4.58; N, 12.72%).

General preparation of the o-Formylstilbenes (36-42).— Styrene (2ml, excess) was added over 10 minutes, to a magnetically stirred suspension of the complex* (0.002 mol) in trifluoroacetic acid-acetic acid (1:3[+], 35 ml) at 0-5°. The mixture was allowed to warm to room temperature and stirring continued for a further 24-36 hours until the yellow suspension of the complex had been replaced by palladium metal. The precipitated palladium was filtered off, the solution diluted with water, neutralized (Na_2CO_3) and the organic products were extracted into ether. The ethereal layer was then washed with water and dried. Removal of the ether and excess styrene under vacuum followed by column chromatography over silica H60 (eluant 40-60 petroleum ether-ether) to yield the 2-formylstilbenes 36-42, the data for which are listed below.

trans-2-Formylstilbene (36).— (45,74, and 90% from the complexes 21,22 and 23 resp.) Colourless oil (lit.,[38] m.p. 83°); ν_{max}(neat) 1690, 1594, 1295, 1280, 960, 760, and 690 cm^{-1}; δ($CDCl_3$) 10.27 (1H,s,CH=O), 8.02 (1H,d,J16Hz, CH=CH, trans), 7.8-7.2 (9H,m,ArH), and 6.96 (1H,d,J16Hz, CH=CH, trans); m/e: 208 (M+·); (Found: C, 86.64; H, 6.02: Calc. for $C_{15}H_{12}O$: C, 86.51; H, 5.81%).

* To determine the stability of the complexes in such acidic media, a suspension of the N-t-butylbenzaldimine complex (23) was stirred for 48 hrs in trifluoroacetic acid-acetic acid (1:1), after which the complex (23) was recovered in 96% yield with only a trace of decomposition.

\+ The amount of trifluoroacetic acid is not critical, it was found that trifluoroacetic acid-acetic acid mixtures ranging from 1:5 to 1:2 gave satisfactory results.

trans-4,5-Dimethoxy-2-formylstilbene (37).— (91%) m.p. 150-151° (needles from 40-60 petroleum ether-ether); ν_{max}(nujol) 1670, 1590, 1515, 1285, and 1275 cm^{-1}; δ ($CDCl_3$) 10.3 (1H,s, CH=O), 7.85 (1H,d,J16Hz, CH=CH, trans), 7.6-7.15 (7H,m,ArH), 6.85(1H,d,J16Hz, CH=CH, trans), 3.95 (3H,s,OMe), and 3.87 (3H,s,OMe); m/e: 268 (M+·) and 204 (100%); (Found: C, 75.90; H, 5.96: $C_{17}H_{16}O_3$ requires: C, 76.1; H, 6.01%).

trans-2-Formyl-3-methoxystilbene (38).— (67%) m.p. 120-121° melting again at 124-5° (prisms from 40-60 petroleum ether-ether); ν_{max}(nujol) 1675, 1565, 1070, 975 and 785 cm^{-1}; δ ($CDCl_3$) 10.65 (1H,s,CH=O), 8.06 (1H,d,J16Hz, CH=CH trans), 7.6-6.7 (9H,m,ArH + olefinic H), and 3.76 (3H,s,OMe); m/e: 238 (M+·, 100%); (Found: C, 80.67; H, 5.93: $C_{16}H_{14}O_2$requires: C, 80.65, H, 5.92%).

trans-2-Formyl-4-methoxystilbene (39).— (81%) m.p. 59.5° (needles from 40-60 petroleum ether-ether); ν_{max}(nujol) 1675, 1595, 1240, 1160, 1025, 958, 755, 720, and 690 cm^{-1}; δ ($CDCl_3$) 10.24 (1H,s,CH=O), 7.82 (1H,d,J16Hz, CH=CH, trans), 7.6-7.0 (8H, m,ArH), 6.8 (1H,d,J16Hz, CH=CH, trans), and 3.72 (3H,s,OMe); m/e: 238 (M+·, 100%); (Found: C, 80.70; H, 5.93; $C_{16}H_{14}O_2$ requires: C, 80.65; H, 5.92%).

trans-2-Formyl-5-methoxystilbene (40).- (75%) m.p. 46-7° (prisms from 40-60 petroleum ether-ether); ν_{max}(nujol) 1685, 1600, 1550, 1120, 1040, 990, 810, and 765 cm^{-1}; δ ($CDCl_3$) 10.14 (1H,s,CH=O), 8.0 (1H,d,J16Hz, CH=CH, trans), 7.7-6.6 (9H,m, ArH + one olefinic H), and 3.8 (3H,s,OMe); m/e: 238 (M+·,80%)and 105 (100%); (Found: C, 80.59; H, 5.93: $C_{16}H_{14}O_2$requires: C, 80.65; H, 5.92%).

trans-2-Formyl-5-methylstilbene (41)[87].- (74%) colourless oil; ν_{max}(neat) 1690, 1600, 1195, 955, and 900 cm^{-1}; δ ($CDCl_3$) 10.1 (1H,s,CH=O), 7.96 (1H,d,J16Hz, CH=CH, trans), 7.7-7.0 (8H,m,ArH), 6.9 (1H,d,J16Hz, CH=CH, trans), and 2.32 (3H,s, Me); m/e: 222 (M+·), 178, 105, and 77 (100%).

trans-5-Chloro-2-formylstilbene (42).- (85%) m.p. 63-4° (needles from 40-60 petroleum ether-chloroform); ν_{max}(nujol) 1690, 1590, 1550, 960, 820, 755, and 690 cm^{-1}; δ ($CDCl_3$) 10.1 (1H,s,CH=O), 7.83 (1H,d,J16Hz, CH=CH, trans), 7.67-7.04 (8H,m,ArH), and 6.83 (1H,d,J16Hz, CH=CH, trans); m/e: 242 (M+·, 100%), 207, and 178; (Found: C, 74.30; H, 4.61; Cl, 14.62: $C_{15}H_{11}ClO$ requires: C, 74.23; H, 4.57; Cl, 14.61%).

2-(N-t-Butyliminomethyl)-trans-stilbene (43).— The complex (23) (0.0015 mol), styrene (2ml) and triethylamine were refluxed together in toluene under a nitrogen atmosphere. After 10 hours the precipitated palladium metal and triethylamine hydrochloride were filtered off and removal of the toluene, excess styrene and triethylamine gave the product as an oil in 78% yield. ν*(neat) 1646 (C=N) cm^{-1}; δ*($CDCl_3$) 8.6 (1H,s,CH=N), 8.1-7.0 (10H,m,ArH + olefinic H), and 1.5 (9H,s,$NC(Me)_3$); m/e: 263 ($M^{+\cdot}$).

General preparation of the N-methyl imino compounds (44-49).— These N-methyl imine derivatives were prepared from the corresponding 2-formylstilbenes by reaction with methylamine using the procedure+ described previously for the preparation of the benzaldimines. On completion of reaction, as judged by infrared spectroscopy, the solids were filtered off, the ethanol removed under vacuum and the product imines were used without further purification for the mercuric acetate mediated cyclisations; listed below are the spectral characteristics of the crude imine derivatives 44-49.

2-(N-Methyliminomethyl)-trans-stilbene (44).— ν(neat) 1650 (C=N) cm^{-1}; δ($CDCl_3$) 8.7 (1H,d,J2Hz, CH=N), 8.0-7.17 (10H,m,ArH + olefinic H), 6.9 (1H,d,J16.5Hz, CH=CH, trans), and 3.54 (3H,d,J2Hz, NMe); m/e: 221.1198 (M+·): $C_{16}H_{15}N$

* In both the infrared and NMR spectra of the compound small peaks at 1690 cm^{-1} and δ 10.3 corresponding to the aldehyde function could be seen. Hydrolysis with acetic acid-damp ether gave the known 2-formylstilbene (36).

\+ Method (ii) page 165.

requires 221.1183.

4,5-Dimethoxy-2-(N-methyliminomethyl)-trans-stilbene (45).— ν (neat) 1630 (C=N) cm^{-1}; δ ($CDCl_3$) 8.64 (1H,d,J2Hz, CH=N), 7.6-6.5 (9H,m,ArH + olefinic H), 3.92 (3H,s,OMe), 3.88 (3H, s,OMe), and 3.51 (3H,d,J2Hz, NMe); m/e: 281(M+·).

3-Methoxy-2-(N-methyliminomethyl)-trans-stilbene (46).— ν (neat) 1640 (C=N) cm^{-1}; δ ($CDCl_3$) 8.74 (1H,d,J1.5Hz,CH=N), 7.96 (1H,d,J17Hz, CH=CH, trans), 7.6-6.65 (9H,m,ArH + olefinic H), 3.72 (3H,s,OMe), and 3.56 (3H,d,J1.5Hz, NMe); m/e: 251.1308 (M+·): $C_{17}H_{17}NO$ requires: 251.1310.

4-Methoxy-2-(N-methyliminomethyl)-trans-stilbene (47).— ν (neat) 1645 (C=N) cm^{-1}; δ ($CDCl_3$) 8.65 (1H,d,J1.7Hz, CH=N), 7.65-6.74 (9H,m,ArH + olefinic H), 6.73 (1H,d,J16.5Hz, CH=CH, trans), 3.76 (3H,s,OMe), and 3.49 (3H,d,J1.7Hz, NMe); m/e: 251.1310 (M+·): $C_{17}H_{17}NO$ requires: 251.1310.

5-Methoxy-2-(N-methyliminomethyl)-trans-stilbene (48).— ν (neat) 1640 (C=N) cm^{-1}; δ ($CDCl_3$) 8.5 (1H,d,J2Hz,CH=N), 7.85-6.65 (10H,m,ArH + olefinic H), 3.74 (3H,s,OMe), and 3.42 (3H,d,J2Hz,NMe); m/e: 251.1303 (M+·): $C_{17}H_{17}NO$ requires: 251.1310.

5-Chloro-2-(N-methyliminomethyl)-trans-stilbene (49).— ν (neat) 1635 (C=N) cm^{-1}; δ ($CDCl_3$) 8.57 (1H,d,J2Hz, CH=N), 7.85-7.04 (9H,m,ArH + olefinic H), 6.87 (1H,d,J16Hz, CH=CH, trans), and 3.5(3H,d,J2Hz,NMe).

General preparation of the 2-Methyl-3-phenyl-1(2H)isoquinolone derivatives (50-55).— The imines (44-49) (1eq*) were treated with mercuric acetate (2.2 eq*) in refluxing toluene#. On completion of reaction+ (2-3 hrs) the mercury metal was removed, the toluene solution washed with several portions of water, dried and toluene removed under vacuum. Chromatography over silica H60 (eluant 40-60 petroleum ether-ether) gave the 2-methyl-3-phenyl-1(2H)-isoquinolones which were further purified by recrystallization if necessary. The data and yields‡ for these compounds are listed below.

2-Methyl-3-phenyl-1(2H)-isoquinolone (50).— (43%) m.p. 65-68° (from 40-60 petroleum ether) (lit.,[50] 68.5-70.5°) ν (nujol) 1642 (C=O) cm^{-1}; δ ($CDCl_3$) 8.7-8.3 (1H,m,H-8), 7.7-7.2 (8H,m,ArH), 6.44 (1H,s,H-4), and 3.4 (3H,s,NMe). m/e: 235 (M^+, 100%).

* These amounts are based on the starting 2-formylstilbenes.

\# For a reaction involving 300mg of imine 50 ml of toluene was used.

\+ The 6,7-dimethoxy-N-methyl-3-phenyl-1(2H)-isoquinolone (51) was found on several occasions to have precipitated out of the reaction mixture.

‡ Yields are based on the starting 2-formylstilbenes.

6,7-Dimethoxy-2-methyl-3-phenyl-1(2H)-isoquinolone (51).— (62%) m.p. 232° (from ether-chloroform) (lit.,[50] 229-231°); ν(nujol) 1635 (C=O) cm^{-1}; δ($CDCl_3$) 7.94 (1H,s,H-8), 7.53-7.2 (5H,m,ArH), 6.8 (1H,s,H-5), 6.36 (1H,s,H-4), 4.0 (3H,s, OMe), 3.95 (3H,s,OMe), and 3.42 (3H,s,NMe); m/e: 295 (M+·,100%); (Found: C, 73.22; H, 5.84; N, 4.72: Calc. for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8; N, 4.74%).

8-Methoxy-2-methyl-3-phenyl-1(2H)isoquinolone (52).— (33%) m.p. 140-141° (from 40-60 petroleum ether-ether); ν(nujol) 1650 (C=O) cm^{-1}; δ($CDCl_3$) 7.6-7.25 (6H,m,ArH), 7.1-6.72 (2H,m,ArH), 6.29 (1H,s,H-4), 3.98 (3H,s,OMe), and 8.35 (3H, s,NMe); m/e: 265 (M+·); (Found: C, 77.06; H, 5.44; N, 5.29: $C_{17}H_{15}NO_2$ requires: C, 76.96, H, 5.7; N, 5.28%).

7-Methoxy-2-methyl-3-phenyl-1(2H)-isoquinolone (53).— (32%) m.p. 137-9° (from 40-60 petroleum ether-ether); ν (nujol) 1644 (C=O) cm^{-1}; δ($CDCl_3$) 7.86 (1H,d,J2Hz, H-8), 7.6-7.1 (7H,m,ArH), 6.39 (1H,s,H-4), 3.91 (3H,s,OMe), and 3.42 (3H, s,NMe); m/e: 265 (M+·, 100%); (Found: C, 76.88; H, 5.7; N, 5.25: $C_{17}H_{15}NO_2$ requires: C, 76.96; H, 5.7; N, 5.28%)

6-Methoxy-2-methyl-3-phenyl-1(2H)-isoquinolone (54).— (59%) m.p. 126-128° (needles from 40-60 petroleum ether-ether); ν (nujol) 1648 (C=O) cm^{-1}; δ ($CDCl_3$) 8.39 (1H,d,J8Hz, H-8), 7.45 (5H,m,ArH), 7.04 (1H,dd,J8 and 2.5Hz, H-7), 6.81 (1H, d,J2.5Hz, H-5), 6.34 (1H,s,H-4), 3.84 (3H,s,OMe), and 3.40 (3H,s,NMe); m/e: 265 (M+·, 100%): (Found: C, 77.09; H, 5.73; N, 5.27: $C_{17}H_{15}NO_2$ requires: C, 76.96; H,5.70; N, 5.28%).

6-Chloro-2-methyl-3-phenyl-1(2H)-isoquinolone (55).— (41%) m.p. 150-151° (from 40-60 petroleum ether-ether); ν (nujol) 1640 (C=O) cm^{-1}; δ ($CDCl_3$) 8.35 (1H,d,J9Hz, H-8), 7.5-7.2 (7H,m,ArH), 6.32 (1H,s,H-4), and 3.41 (3H,s,NMe); m/e: 269 (M+·); (Found: C, 71.20; H, 4.49; Cl, 13.30; N, 5.19: $C_{16}H_{12}ClNO$ requires: C, 71.25; H, 4.48; Cl, 13.14; N, 5.19%).

General Preparation of the Cinnamate derivatives (56-58).— The complex (0.0015 mol),methyl acrylate (2-3ml, excess) and triethylamine (2-3 ml, excess) were brought to reflux in toluene under a nitrogen atmosphere. After 10-24 hours when all the complex had been consumed, as judged by the disappearance of the yellow colour of the solution, the precipitated palladium metal and triethylamine hydrochloride crystals were filtered off. The toluene, excess styrene and excess triethylamine were removed under vacuum to yield the cinnamates. The spectral data and yields obtained for the compounds are as follows.

Methyl 2-(N-t-butyliminomethyl)-trans-cinnamate (56).— (84%) b.p. 110-115°/0.04 mm; ν_{max}(neat) 2960, 1720, 1634, 1435, 1320, 1277, 1200, 1170, and 766 cm^{-1}; $\delta(CDCl_3)$ 8.56 (1H,s,CH=N), 8.42 (1H,d,J16.5Hz, CH=CH, trans), 7.9-7.1 (4H,m,ArH), 6.27 (1H,d,J16.5Hz, CH=CH, trans), 3.77 (3H, s,COOMe), and 1.32 (9H,s,NC(Me)$_3$); m/e: 245 (M+·); (Found: C, 73.42; H, 8.07; N, 5.71: $C_{15}H_{19}NO_2$ requires: C, 73.44; H, 7.81; N, 5.71%).

Methyl 2-(N-t-butyliminomethyl)-4,5-dimethoxy-trans-cinnamate (57).— (86%) m.p. 107° (needles from 40-60 petroleum ether); ν_{max}(nujol) 1710, 1630, 1590, 1510, 1394, 1380, 1168, and 1104 cm^{-1}; $\delta(CDCl_3)$ 8.66 (1H,s,CH=N), 8.33 (1H,d,J16Hz, CH=CH, trans), 7.49 (1H,s,ArH), 7.04 (1H,s,ArH), 6.29 (1H,d,J16Hz, CH=CH, trans), 3.96 (3H,s,OMe), 3.92 (3H, s,OMe), 3.81 (3H,s,OMe), and 1.35 (9H,s,NC(Me)$_3$); m/e: 305 (M+·); (Found: C, 66.88; H, 7.65; N, 4.61: $C_{17}H_{23}NO_4$ requires: C, 66.86; H, 7.59; N, 4.59%).

Methyl 2-(N-t-butyliminomethyl)-5-methyl-trans-cinnamate (58).— (79%) unstable yellow oil; ν_{max}(neat) 2960, 1712, 1628, 1312, 1268, 1220, 1190, and 1165 cm^{-1}; $\delta(CDCl_3)$ 8.53 (1H,s,CH=N), 8.32 (1H,d,J16Hz, CH=CH, trans), 7.69 (1H,d,J7Hz,ArH-3), 7.4-7.05 (2H,m,ArH), 6.27 (1H,d,J16Hz,CH=CH, trans), 3.8(3H,s,COOMe), 2.37 (3H,s,Me), and 1.32 (9H,s,NC(Me)$_3$); m/e: 259 (M+·). To allow a full characterisation to be carried out the compound (58) was hydrolysed, by treatment with aqueous acetic acid at room temperature overnight, to give methyl 2-formyl-5-methyl-cinnamate (59) in 81% yield.

M.p. 60-60.5° (plates from 40-60 petroleum ether); ν_{max}(nujol) 1710, 1694, 1630, 1325, 1290, 1230, 1195, 1180, and 830 cm^{-1}; $\delta(CDCl_3)$ 10.22 (1H,s,CH=O), 8.7 (1H,d,J16Hz, CH=CH, trans), 7.74 (1H,d,J7Hz, H-3), 7.47-7.2 (2H,m,ArH), 6.34 (1H,d,J16Hz, CH=CH, trans), 3.81 (3H,s,COOMe), and 2.45 (3H,s,Me); m/e: 204 (M+·); (Found: C, 70.74; H, 5.92: $C_{12}H_{12}O_3$ requires: C, 70.58; H, 5.92%).

Reaction of acrylonitrile with the N-t-butylbenzaldimine complex (23).— The complex (0.0015 mol), acrylonitrile (2 ml, excess) and triethylamine (2ml, excess) were refluxed together in toluene under a nitrogen atmosphere. After 8 hours, the complex had been consumed. The precipitated palladium metal and triethylamine hydrochloride were filtered off. The toluene, excess acrylonitrile and excess triethylamine were removed under vacuum to give 2-(N-t-butyl-iminomethyl)-trans-cinnamonitrile (60) in 78% yield: $\delta(CDCl_3)$ 8.46(1H,s,CH=N), 8.28 (1H,d,J16.5Hz, CH=CH, trans),7.75-7.1 (4H,m,ArH), 5.7 (1H,d,J16.5H_3, CH =CH, trans) and 1.32 (9H,s,NC(Me)$_3$). The compound (60) was not further characterised and was used without further purification for the next reaction.

Thermolysis of compound (60).— The compound (60) was dissolved in mesitylene (40ml) and refluxed for 8 hours under nitrogen. On completion, the mesitylene solution was diluted with water, the aqueous layer acifified (HCl) and washed with several portions of ether. The aqueous layer was then made alkaline and the free bases extracted into ether. The ethereal layer was then washed with water, dried and the ether removed under

vacuum. Column chromatography of the residual oil over silica H60 (eluant 40-60 petroleum ether-ether) gave isoquinoline (61) as a colourless liquid in 24% overall yield based on the complex 23. The spectral data obtained are as follows: ν_{max}(neat) 3020, 1622, 1582, 1567, 1377, 1272, 943, 827, and 745 cm^{-1}; $\delta(CDCl_3)$ 9.26 (1H,s,H-1), 8.51 (1H,d,J6Hz, H-3), and 8.04-7.15 (5H,m,ArH). The spectra were identical to those measured using an authentic sample of isoquinoline. Picrate m.p. 222-225° (yellow needles from EtOH) (lit.,[88] 226°).

Preparation of the isoquinolines 61-64 without isolation of the intermediate cinnamonitriles.— The complex (0.0015 mol), triethylamine (5ml, excess), and acrylonitrile (5ml, excess) were heated to 100-110° in diphenyl ether-mesitylene (95:5*, 40-50 ml) for 9-12 hours, until the yellow solution became colourless. The mixture was allowed to cool overnight, during which time the remainder of the triethylamine hydrochloride crystallized out. The mixture was then filtered to remove the precipitated palladium metal and triethylamine hydrochloride. Excess triethylamine and acrylonitrile were removed under vacuum (ca. 3mm) and the resulting solution heated at

* The 5% of mesitylene was added to prevent crystallization of the diphenyl ether, which otherwise hindered filtration.

180-200° for 8-13 hours to effect the thermal cyclisation. The reaction was worked up as described for the conversion of 2-(N-t-butyliminomethyl)-trans-cinnamonitrile (60) to isoquinoline (61), column chromatography over silica H60* (eluant ether-petroleum ether) gave the product isoquinolines 61-64 whose yields and spectral data are listed below.

Isoquinoline (61).— (47%) data as previously described

6,7-Dimethoxyisoquinoline (62).— (10%) m.p. 89-91° (from 40-60 petroleum ether-ether) (lit.,[89] 90-91); ν_{max}(nujol) 1502, 1250, 1140, 1002, and 850 cm^{-1}; $\delta(CDCl_3)$ 9.1 (1H,s, H-1), 8.43 (1H,d,J6Hz,H-3), 7.51 (1H,d,J6Hz,H-4), 7.21 (1H, s,ArH), 7.09 (1H,s,ArH), and 4.03 (6H,s,$(OMe)_2$); Picrate m.p. 223-5° (yellow needles from EtOH) (lit.,[89,90] 215-220°, 226° resp.).

7-Methoxyisoquinoline (63).— (42%) m.p. 48-49° (from 40-60 petroleum ether) (lit.,[88] 49°); ν_{max}(nujol) 1626, 1590, 1565, 1504, 1263, 1214, 1148, 1018, 864, and 850 cm^{-1}; $\delta(CDCl_3)$ 9.2 (1H,s,H-1), 8.46 (1H,d,J5.5Hz,H-3), 7.8-7.1(4H,m,ArH) and 3.89 (3H,s,OMe); m/e: 159 ($M^{+\cdot}$); (Found: C, 75.29; H, 5.69; N, 8.78: Calc. for $C_{10}H_9NO$: C, 75.45; H, 5.7; N, 8.8%). Picrate m.p. 203-5° (yellow crystals from EtOH) (lit.,[88] 194-5°).

* 6,7-Dimethoxyisoquinoline was chromatographed on alumia H60 as it was found to decompose on silica.

6-Methylisoquinoline (64).— m.p. 85-87° (from 40-60 petroleum ether) (lit.,[88] 83°); ν_{max}(nujol) 1630, 1276, 1215, 890, and 840 cm^{-1}; $\delta(CDCl_3)$ 9.19 (1H,s,H-1), 8.49 (1H,d,J6Hz, H-3), 7.92-7.25 (4H,m,ArH), and 2.5 (3H,s,Me); m/e: 143 ($M^{+\cdot}$, 100%). Picrate m.p. 216° (yellow needles from EtOH) (lit.,[88] 212°).

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APPENDIX

ABBREVIATIONS USED

Ac	acetyl, CH_3CO
acac	acetylacetonate
Ar	aryl or arene (ArH)
Bu	butyl (superscript n, i, s, or t, normal, iso, secondary or tertiary butyl)
Cp	cyclopentadienyl, C_5H_5
diphos	1,2-bis(diphenylphosphino)ethane, dppe
DMF	N,N-dimethylformamide, $HCONMe_2$
DMSO	dimethylsulphoxide, Me_2SO
dppe	1,2-bis(diphenylphosphino)ethane,
dppf	1,1'-bis(diphenylphosphino)ferrocene
dR	desoxyribosyl
Et	ethyl
HMPT	hexamethylphosphoric triamide, $OP(NMe_2)_3$
L	ligand
Me	methyl
OAc	acetate ion
Pent	pentyl
Ph	phenyl, C_6H_5
TFA	trifluoroacetate, CF_3COO
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl, $SiMe_3$
w.r.t.	with respect to

ABBREVIATIONS USED TO DESCRIBE SPECTRA

s	singlet
d	doublet
dd	double doublet
t	triplet
br	broad
q	quartet