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Functionalisation of heterocycles by Ni- and Pd-catalysed reactions

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ABSTRACT. The review covers carbon–carbon bond formation at heterocyclic ring positions by Ni- and Pd-catalysed cross-coupling, alkenylation and alkynylation. The influence of the catalyst and the metal of the organometallic component on the facility of cross-coupling has been analysed, and the limitations emphasised.

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I. Introduction

The substitution of heterocyclics is a key step in the synthesis of many physiologically active compounds. A carbon–carbon bond can be formed conveniently by reacting lithiated heterocyclics with sufficiently reactive electrophiles, such as alkyl halides.[1] However, the method cannot be used for coupling aryl, alkenyl and heterocyclic halides where the halogen is at an sp^2-hybridised carbon atom, since here the halogen is not reactive enough.

Cross-coupling is defined as a process where a simple carbon–carbon bond is formed between two carbon radicals. The reaction of organometallic compounds with organic halides or other electrophiles falls in this category:[2]

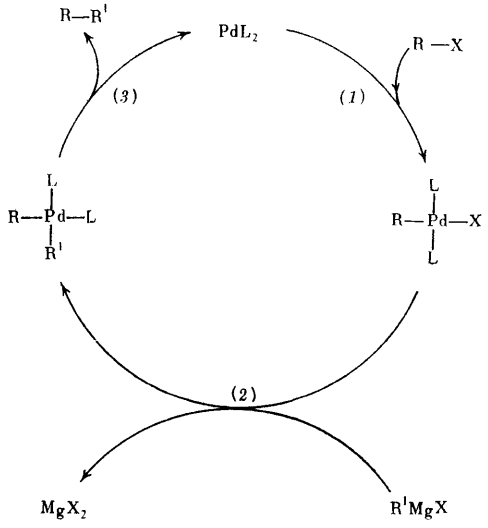
$$R^1M+R^2X\rightarrow R^1—R^2+MX.$$

Although the above scheme appears simple, this type of cross-coupling is complicated by side-reactions. The classical Wurtz synthesis is a variation on this theme, where a halogen-metal exchange is followed by homo-coupling. If the halide has a branched alkyl group, α- and β-elimination takes place. Uncatalysed cross-coupling does not take place with unsaturated halides where the halogen is bonded to an sp^2- or *sp*-carbon atom.

In 1972 Corriu and Masse[3], and Kumada et al.,[4] introduced nickel-catalysed cross-coupling between reactive Grignard compounds and organic halides. Later, palladium and other Group VIII complexes were found to catalyse this reaction. The main advantages of using Ni and Pd complexes for such catalysed cross-coupling are the higher selectivity of the reaction, the mild conditions, and the possibility of using unsaturated halides. As a result, synthetic organic chemistry has benefited significantly.

Organolithium compounds have rarely been used in catalysed cross-coupling. The use of Grignard reagents in this capacity has been limited to some extent by their reducing properties towards transition metal salts. Organo-zinc, -boron and -aluminium compounds are more compatible with complex metal catalysis and are highly reactive towards organic halides. The same is true of organotin compounds in view of their high stability and the potential of introducing functionalised residues. The following catalysts are usually used for cross-coupling: $Ni(acac)_2$, $M(PPh_3)_4$, $MCl_2(PPh_3)_2$, MCl_2(dppe), MCL_2(dppp), MCl_2(dppb), MCl_2(dppf)† (where M = Ni or Pd), $Pd(OAc)_2[P(o\text{-}Tol)_3]_2$ and others. Usually the zero-valent complexes, M(0), are generated from the corresponding M(II) complexes *in situ*. Palladium catalysts are the more widespread. The catalytic cycle is based on the redox couple, Pd(0) ⇄ Pd(II), and comprises the following three stages: (*1*) oxidative addition, (*2*) transmetallation, and (*3*) reductive elimination, as shown below.[5]

Scheme 1



Cross-coupling is complicated if the transferred alkyl group has a β-hydrogen atom since here transfer of β-hydrogen in the Pd-intermediate is dominant with the formation of a Pd–H complex on elimination of olefin. Catalysed cross-coupling is most effective with alkenyl, aryl and heterocyclic halides.

General aspects of catalysed cross-coupling have already been reviewed[6–9] or covered in monographs.[5,10–13] However, cross-coupling with heterocyclic compounds has not been adequately surveyed. Negishi's review[14] is based on literature published up to 1982.

† dppe = $Ph_2PCH_2CH_2PPh_2$, dppp = $Ph_2PCH_2CH_2CH_2PPh_2$, dppb = $Ph_2P(CH_2)_4PPh_2$, dppf = $(\pi\text{-}Ph_2PC_5H_4)_2Fe$.

The present review covers cross-coupling with heterocyclic systems in the presence of Ni and Pd complexes. It focusses on cross-coupling with heterocyclic organometallic derivatives and heterocyclic halides. There is also a section on the reactions of heterocyclic halides with alkenes and terminal acetylenes which lead to vinyl- and alkenyl-heterocyclics under metal complex catalysis. Homo-coupling of heterocyclic halides is considered separately.

In discussing the data, the accent is placed on synthetic aspects of cross-coupling and preparative applications.

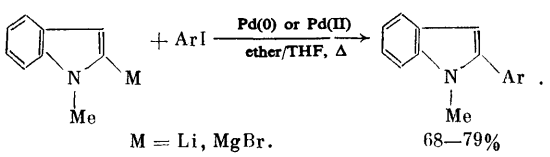
II. Cross-coupling between heterocyclic halides and heterocyclic organometallic derivatives

For the synthesis of substituted heterocyclic compounds by catalysed cross-coupling, one can consider three possible routes: a) cross-coupling of heterocyclic organometallic compounds with organic halides, b) cross-coupling of organometallic compounds with heterocyclic halides, and c) cross-coupling of heterocyclic organometallic compounds with heterocyclic halides.

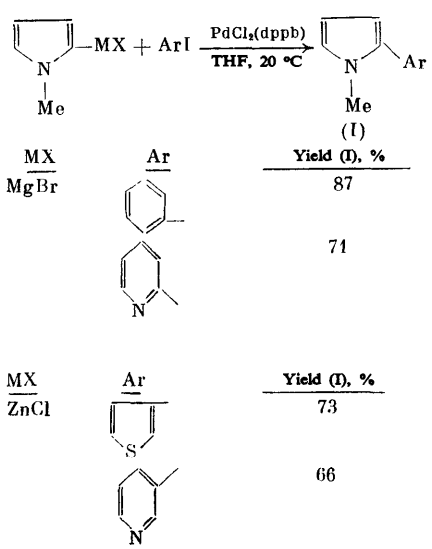
1. Organo-lithium, -magnesium and -zinc compounds

Organolithium compounds are not normally used in cross-coupling. As a rule, they are used as precursors of other organometallic compounds, e.g. organo-zinc, -boron and -tin compounds, etc.

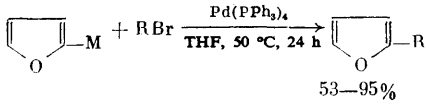
1-Methylindol-2-yl-lithium and -magnesium bromide readily react with aryl iodides in the presence of Pd(0) or Pd(II) complexes to give 2-arylindoles.[15,16]



1-Methyl-2-pyrrolyl-magnesium bromide and -zinc chloride react with aromatic or heterocyclic halides in the presence of palladium phosphine complexes to give the corresponding 2-substituted pyrroles:[15]

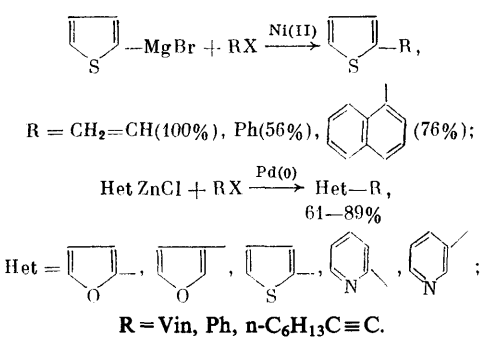


2-Furyl-lithium and -zinc chloride readily interact with aryl, benzyl and cinnamyl bromide in the presence of Pd(0).[17]

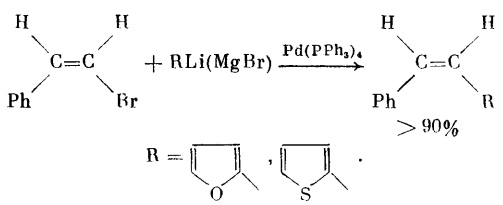


R = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-$O_2NC_6H_4$, $PhCH_2$, $PhCH{=}CHCH_2$.

Unsaturated groups may be introduced at heterocyclic ring positions by cross-coupling of the corresponding heterocyclic organomagnesium[18] or -zinc[19] compounds with vinyl chloride or bromide, bromo- or iodo-benzene, bromonaphthalene, and with 1-bromooct-1-yne in the presence of a Ni or Pd catalyst.

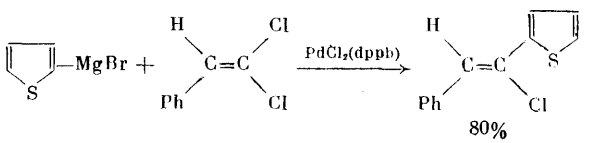


β-Styrylheteroarenes can conveniently be prepared by interaction of β-styryl bromide with 2-furyllithium, 2-thienyllithium and 2-furylmagnesium bromide in the presence of a Pd(0) catalyst.[20]

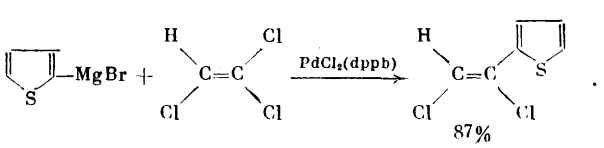


Reaction proceeds with complete retention of configuration, *trans*-β-styryl bromide affording the corresponding *trans*-β-styryl-heteroarene.

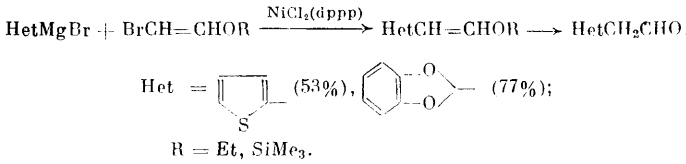
The reaction between 1,1-dichloroalkenes with 2-thienyl-magnesium bromide also proceeds with high stereoselectivity.[21]



The corresponding *cis*-dichloroalkenes are obtained with trichloroethylene:

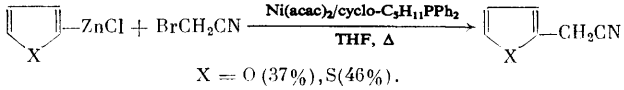


A one-pot bishomologisation of heterocyclic Grignard compounds can be achieved by cross-coupling with β-bromovinyl ethers.[22,23]

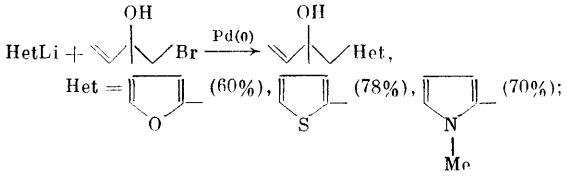


As the resulting vinyl ethers are readily hydrolysed to aldehydes, the above cross-coupling may be viewed as a formylmethylation of Grignard compounds.

2-Furyl- and 2-thienyl-zinc chloride react with bromoacetonitrile to give the corresponding cyanomethyl derivatives in the presence of a Ni catalyst:[24]

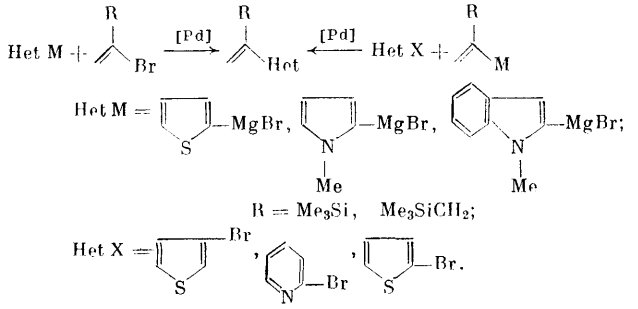


Characteristically, lithiated heterocyclics react with ispropene bromhydrin in the presence of a Pd catalyst to give the corresponding unrearranged allyl alcohol with complete regioselectivity.[25]

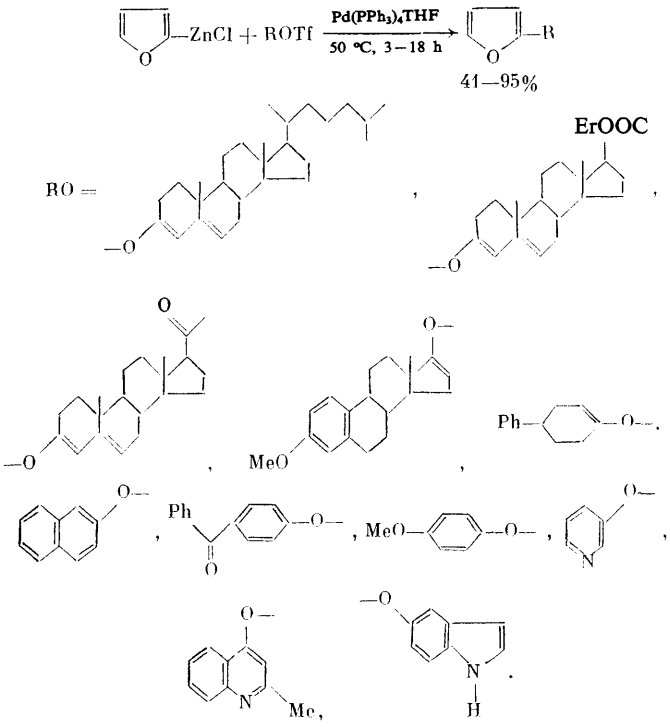


In contrast, alkyl and aryl Grignard compounds react with allyl rearrangement.[26]

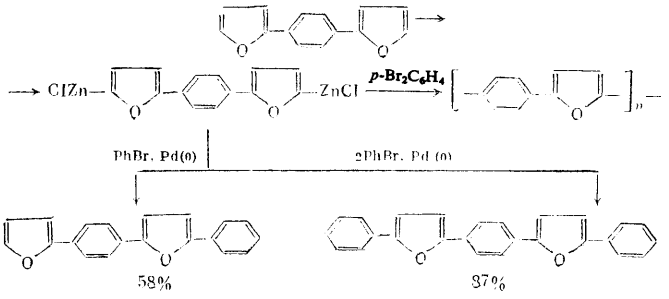
Palladium-catalysed cross-coupling of 1-halogenovinyl- or 2-halogenoallyl-silanes with heterocyclic organo-magnesium or -zinc compounds affords the corresponding heterocyclic vinyl- or allyl-silanes in high yield. Alternatively, these products can be obtained by cross-coupling of heterocyclic halides with the corresponding silylated organometallic compounds:[27]



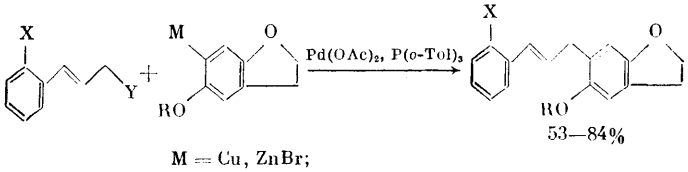
Triflates (ROTf) may be used in place of halides for cross-coupling. Thus 2-substituted furans are readily formed by coupling 2-furylzinc chloride with various vinyl and aryl triflates:[28]



The bis(2-furylzinc chloride) obtained from 1,4-bis(2-furyl)benzene reacts with bromobenzene or 1,4-dibromobenzene to give oligomers or polymers:[29]

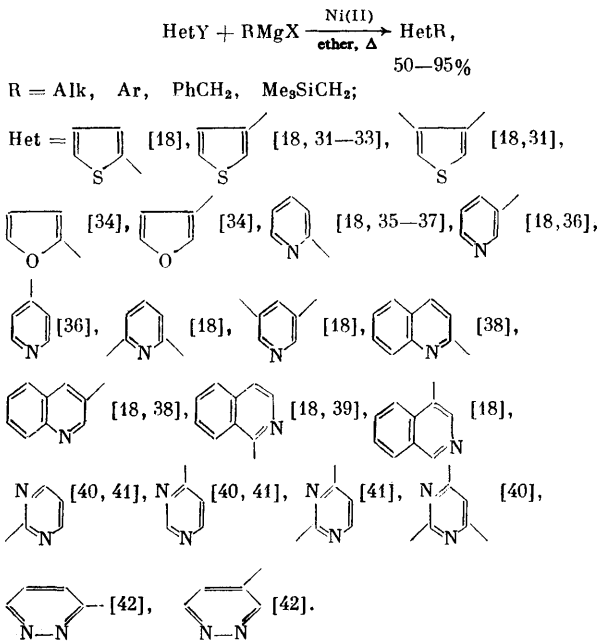


Palladium-catalysed allylic alkylation of organometallic derivatives of dihydrobenzofuran with cinnamyl bromides or acetates leads to the corresponding cinnamyl derivatives which are of interest as antipyretic agents.[30]



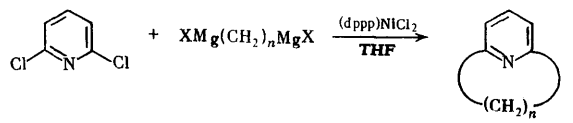
Various types of heterocyclic halides couple with Grignard compounds in the presence of nickel catalysts to give the

corresponding substituted heterocyclics in high yield:



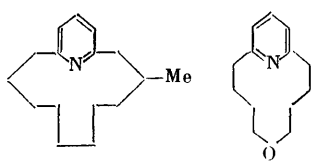
Extension of cross-coupling to heterocyclic dihalides and trihalides leads to the corresponding di- and tri-alkyl or di- and tri-aryl derivatives. Best results have been obtained with catalysts having a bidentate phosphine ligand—dppe, dppp, dppb and dppf.

Interestingly, cycloalkylation takes place on coupling 2,6-dichloropyridine with bis(Grignard compounds) to give 2,6-pyridophanes:[43]



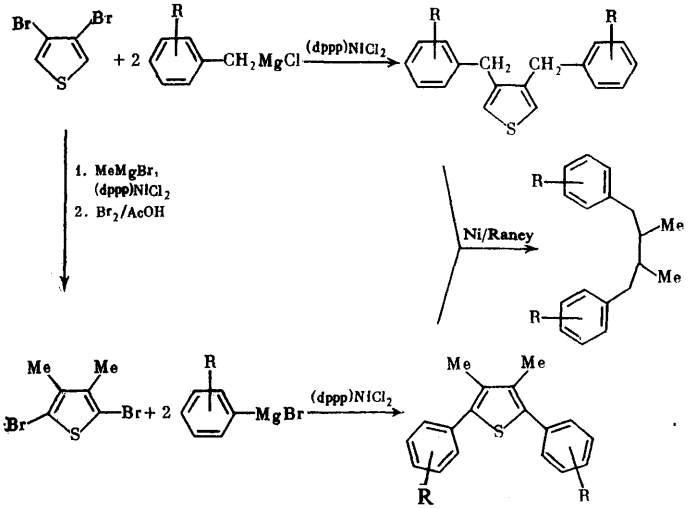
p=6 (11%), 7 (10%), 8 (16%), 9 (15%), 10 (33%), 12 (26%).

Racemic muscopyridine (II) and the oxapyridophane (III) have also been prepared by this route:

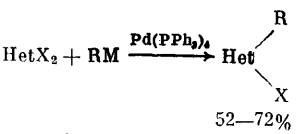


(II), 20% (III), 20%

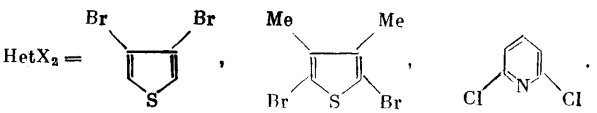
The thiophene molecule has been used as a four-carbon synthon in the synthesis of 2,3-disubstituted butanes, the basic structure of certain ligands. The key step is the cross-coupling of the appropriate dihalogenothiophene with Grignard or organozinc compounds in the presence of a nickel or palladium catalyst:[44]



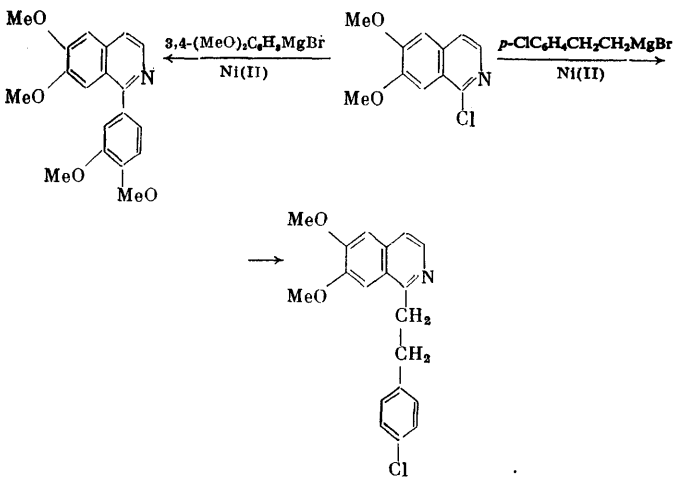
It is also possible to prepared unsymmetrically substituted heterocyclics by Pd-catalysed mono-benzylation or -arylation of the corresponding heterocyclic polyhalides:[45]



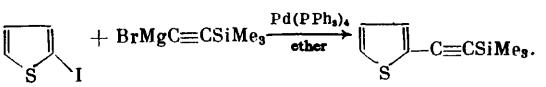
M = MgX, ZnX; R = Ph, $PhCH_2$;



The reaction of 1-chloro-6,7-dimethoxyisoquinoline with 3,4-di-methoxyphenylmagnesium bromide and *p*-chlorophenylethyl-magnesium bromide leads to intermediates *en route* to pharmacologically active isoquinoline alkaloids.[18]

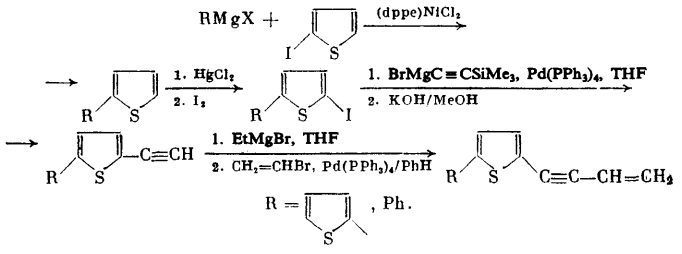


2-Iodothiophene cross-couples with trimethylsilylethynyl-magnesium bromide:[46]

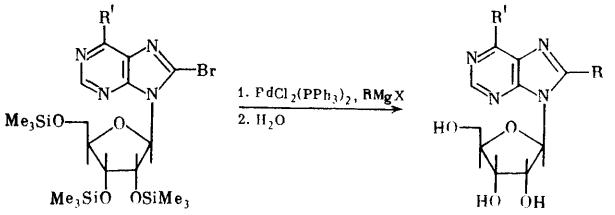


98%

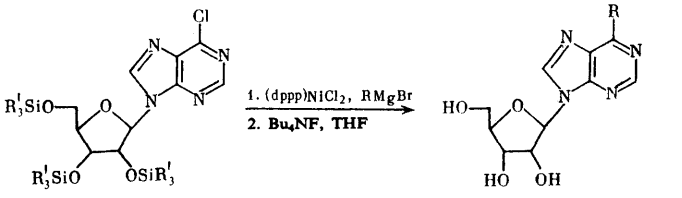
This reaction has been used for the synthesis of natural products containing a thiophene residue, which possess nematocidal activity.[47] One such route is based on a sequential cross-coupling using both nickel and palladium catalysts:



Silyalated 8-bromopurine nucleosides and 8-bromoadenosine-3′,5′-cyclic monophosphate cross-coupling with Grignard compounds in the presence of a Pd catalyst to give the corresponding 8-substituted derivatives;[48]

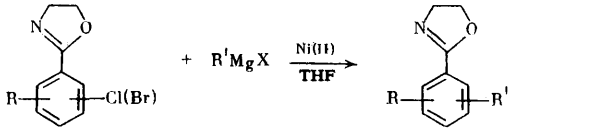


Biologically active 6-substituted purine nucleosides may be obtained similarly by nickel-catalysed cross-coupling of the corresponding 6-chloropurine nucleoside with Grignard compounds:[49]



R = Et, cyclo-C_6H_{11}, Ph, $PhCH_2CH_2$, $PhCH_2CH_2CH_2$, $Me_2C{=}CHCH_2CH_2$.

It has been shown that a halogen atom at the 2-, 3- or 4-position of (Δ^2-oxazolin-2-yl)arenes is readily replaced by an alkyl or aryl group in high yield:[50]



With (Δ^2-oxazolin-2-yl)dichlorobenzenes there is the possibility of regioselective introduction of one or two substituents into the benzene ring, depending on the relative proportion of Grignard compound and substrate.

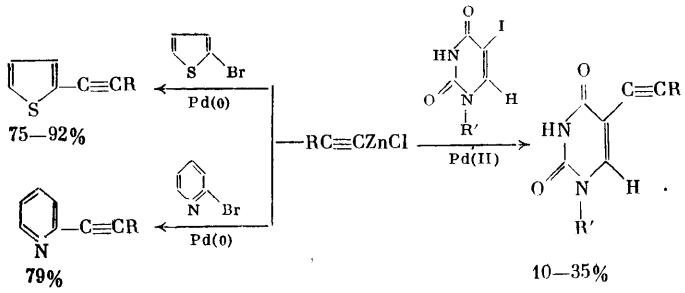
Both simple and functionalised organozinc compounds participate in Pd-catalysed cross-coupling with heterocyclic halides. Thus, 2-, 3- and 4-halogenopyridines, 2, 4- and 5-halogenopyrimidines, and 2-halogenoquinolines readily couple with functionalised organozinc compounds, including the Reformatskii reagent:[51,52]

$$HetX + IZn(CH_2)_nX \xrightarrow{Pd} Het(CH_2)_nX, \quad \sim 95\%$$

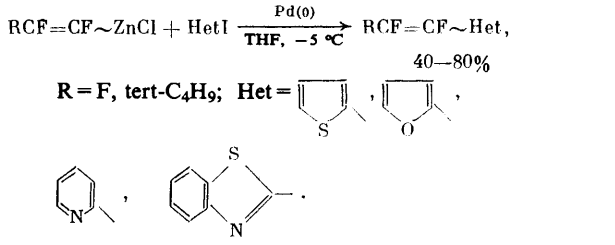
$p = 2, 3, 4$; X = Cl, CO_2Et.

The 2- and 4-halogenopyridines are more active than 3-halogenopyridines in this reaction.

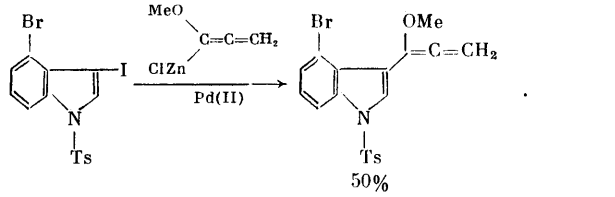
Alkynylzinc chlorides also couple smoothly with 2-bromo- or 2-iodo-thiophene[53] and with 2-bromopyridine[19], and react with 5-iododeoxyuridines to give the corresponding 5-alkenyl derivatives:[54]



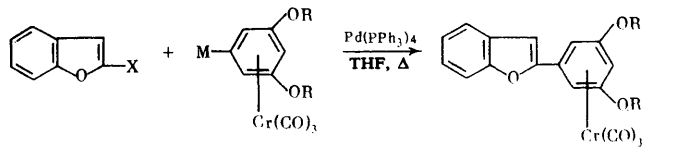
Perfluorovinylzinc compounds cross-couple effectively with a variety of heterocyclic halides:[55,56]



Allenylzinc chlorides have been used to introduce an unsaturated function at the 3-position of the indole ring.[57]



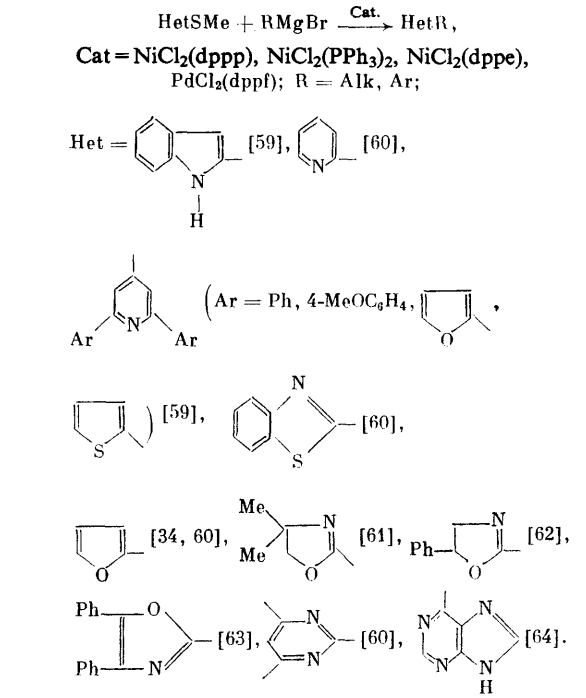
Moracin, a member of a family of biologically active compounds[58], has also been prepared by cross-coupling. The strategy involves Pd-catalysed cross-coupling of two aromatic systems: 2-metallated (or 2-halogenated) benzofurans and 5-halogenated (or-metallated) resorcinols, the latter as their chromium tricarbonyl complexes:



X = I, Br, $ZnBr$, $SnMe_3$,
M = $ZnBr$, I, Cl; R = H, SiR_3', Me.

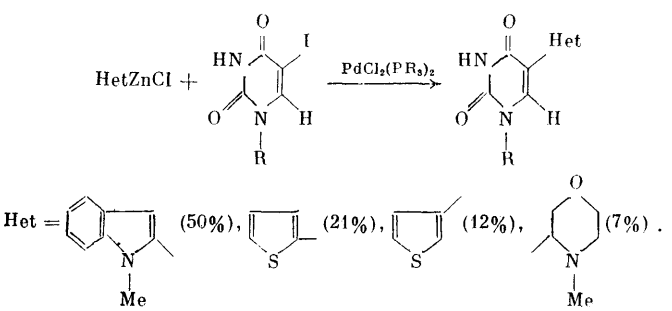
Alkylthio derivatives may be used in place of halides for cross-coupling. Thus, methylthio-substituted *N*-, *O*-, and *S*-heterocyclics undergo Ni- and Pd-catalysed cross-coupling with Grignard

compounds to give the corresponding alkyl- or aryl-heterocyclics.



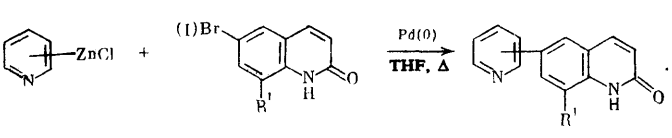
Alkyl- and aryl-derivatives of indole, pyridine, furan, benzothiazole, oxazoline, oxazole, pyrimidine and purine have all been prepared by this route.

Various biheterocyclics are generally available by catalysed cross-coupling of heterocyclic Grignard or organozinc compounds with heterocyclic halides. Thus, interaction of 5-iododeoxyuridines with HetZnCl affords a low yield of the corresponding nucleoside with a heterocyclic substituted in the 5 position:[65]

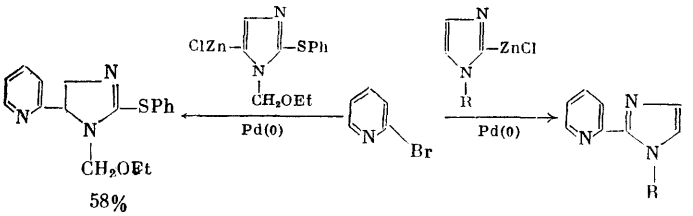


The above reactions proceed in the presence of a Pd catalyst.

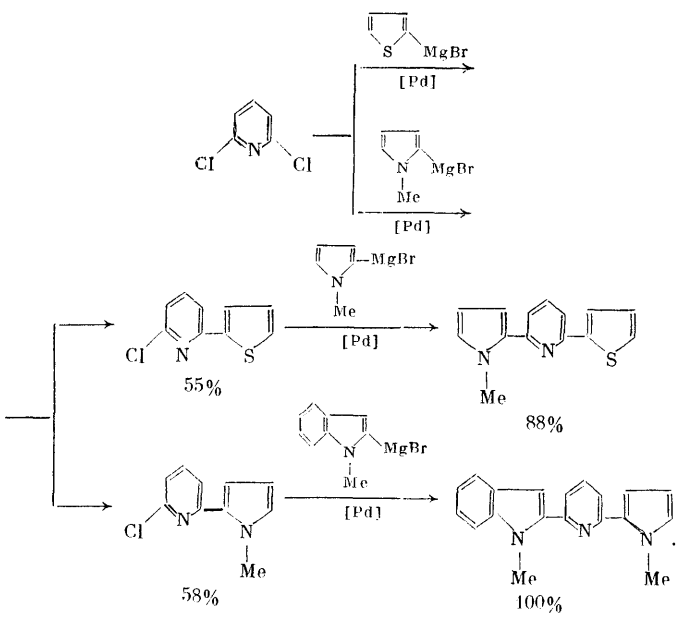
Cross-coupling of pyridylzinc chlorides with 6-halogeno-2(1*H*)-quinolines is a convenient method of preparing 6-pyridyl-2-(1*H*)-quinolines:[66,67]



2-Bromopyridine readily reacts with *N*-substituted 2- and 5-imidazolylzinc chlorides in the presence of a Pd(0) catalyst to give the corresponding imidazolylpyridines:[68]

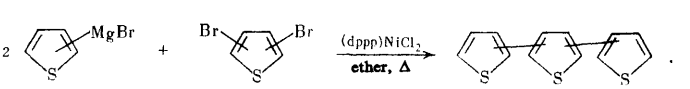


Reactions of dihalogenopyridines with 2-thienyl-, 2-pyyrolyl-, and 2-indolyl-magnesium bromides can be preformed in a variety of sequences to give the corresponding tri-nuclear systems,[69] e. g.



This is the basis of a method of preparing linear polyheterocyclic compounds.

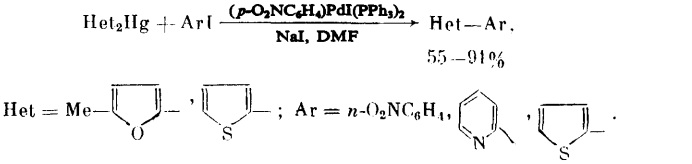
Nickel- or palladium-catalysed cross-coupling of 2- and 3-thienylmagnesium bromides with 2- and 3-bromothiophenes or isomeric dibromothiophenes (in varying proportions) leads to bi-, ter- and oligo-thienyls:[18,70–72]



Biheterocyclics of the type furan-thiophene[46] and thiophene-uracil[73] have also been synthesised.

2. Organo-mercury and -copper compounds

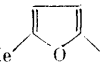
In addition to the organometallic compounds mentioned in section 1, cross-coupling with heterocyclic derivatives can also be achieved with organomercury compounds. Thus, symmetrical diorganomercury compounds react with aryl and heteroaryl iodides in the presence of a Pd-catalyst:[74]

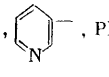


Heterocyclic ketones have been prepared by acyldemetallation of organomercury compounds in the presence of a Pd complex.[75] Thus, the reaction of diorganomercurials, R_2Hg, with acyl chlorides proceeds readily in acetone at 20 °C during 5–30 min in the presence of a Pd(II) salt:

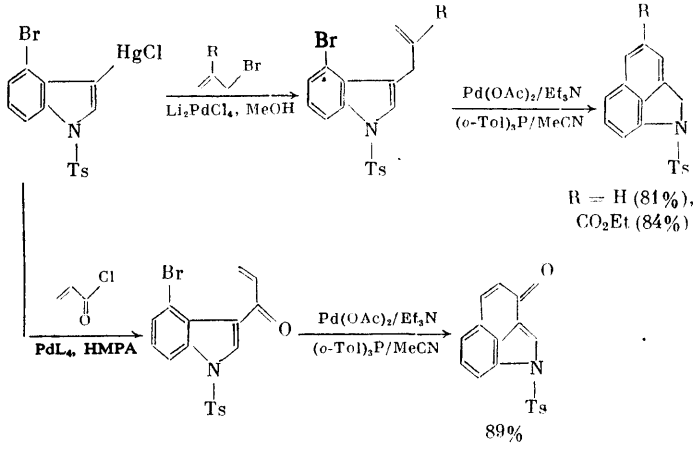
$$R_2Hg + 2R'COCl \xrightarrow[20\ ^\circ C,\ acetone]{Pd(II),\ I^-} 2RCOR' + R_2,$$

$>70\%$

R = , n-C_3H_7, , Ph;

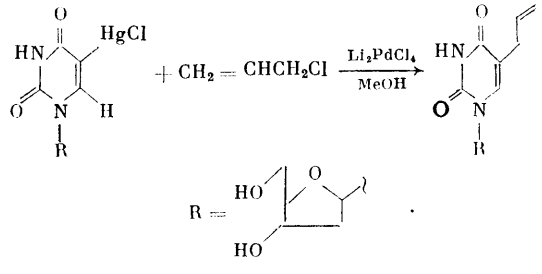
R' = *p*-$O_2NC_6H_4$, , , Ph.

Palladium catalysts have been used in the synthesis of indole derivatives.[76] Thus, 3-substituted indoles are obtained in high yield by treatment of 3-chloromercuri-4-bromoindole derivatives with allyl halides in the presence of Li_2PdCl_4. Feaction proceeds via Hg → Pd transmetallation, followed by insertion of the olefin group into the resulting indolylpalladium complex then elimination of β-halogen. The products readily undergo intramolecular Heck reaction with simultaneous isomerisation of the formed tricyclic indole into the thermodynamically more stable benz[*c*,*d*]indole system.[57]



Similarly, 3-chloromercuriindole reacts with acryloyl chloride in the presence of Pd(0) to give the corresponding 3-acylindole which cyclises into a tricyclic ketone in high yield.

5-Chloromercuri-2-deoxyuridine condenses with allyl chloride in the presence of 20 mol% Li_2PdCl_4 to give the corresponding 5-allyl derivative:[77]



The use of substituted allyl chlorides in this reaction leads to a mixture of regioisomers.[78]

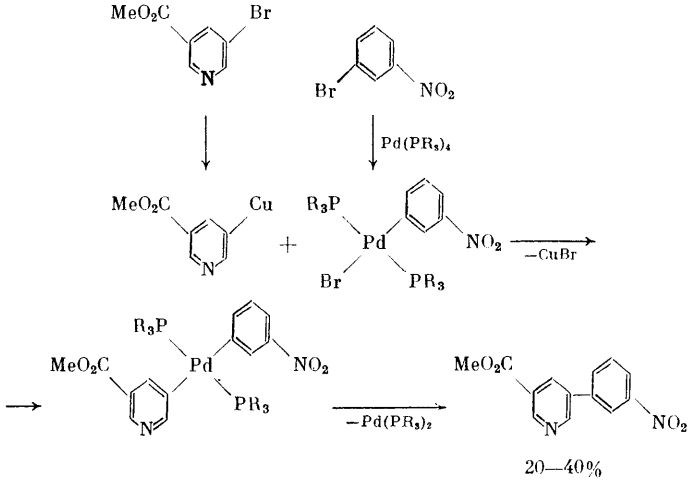
Beletskaya et al.[79] showed that cuprous phenylacetylide reacts quite readily with 2-iodothiophene and 2-iodopyridine to give the corresponding 2-alkynylheterocyclics:

$$Het{-}I + PhC{\equiv}CCu \xrightarrow[HMPA,\ 20\ ^\circ C]{Pd(II),\ Bu_4NI} Het{-}C{\equiv}CPh,$$

Het =  (94%),  (67%).

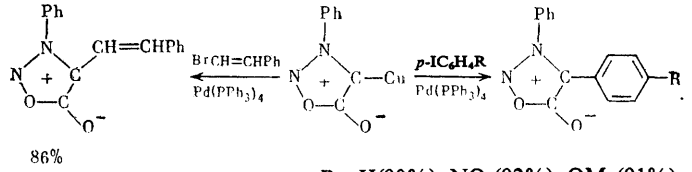
Tetra-π-butylammonium iodide, which increases the solubility of CuI (used for the preparation of the acetylide), has a significant effect on the rate of reaction and the yield of product.

Coupling 5-bromonicotinates with *m*-bromonitrobenzene in the presence of Cu and a Pd(0) catalyst affords the corresponding 5-arylnicotinates which have been used in the synthesis of physiologically active compounds.[80] The mechanism of the reaction is thought to involve formation of a 5-cupronicotinate which couples with the palladium compound formed by oxidative addition of Pd(0) to *m*-bromonitrobenzene; reductive elimination then takes place in the final step:



$Pd(PR_3)_4 = Pd(PPh_3)_4$, $Pd[P(Tol\text{-}o)_3]_4$.

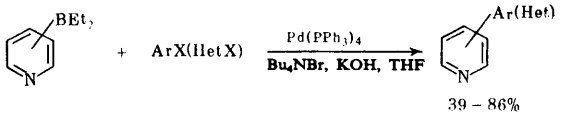
Palladium-catalysed cross-coupling of 4-cuprosydnone with aryl and vinyl halides is the basis of a general method of introducing a 4-substituent into the 3-phenylsydnone ring.[81]



R = H(90%), NO_2(92%), OMe(91%).

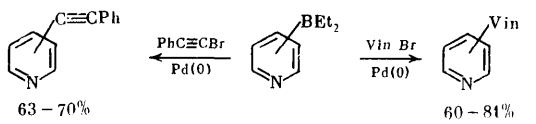
3. Organo-boron, -aluminium and -zirconium compounds

Three-coordinate boron compounds have also been used in cross-coupling. 3-Pyridyl- and 4-pyridyl-boranes react efficiently with various bromo- or iodo-arenes and heterocyclic halides in the presence of a Pd(0) catalyst:[82–84]

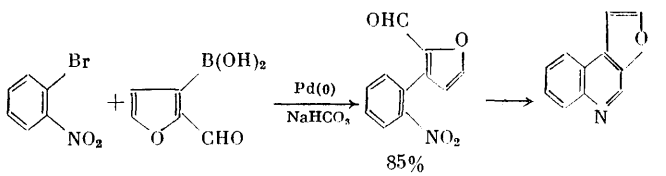


Reaction has been carried out with a wide variety of aryl halides having different functional groups and with a number of heterocyclics, such as substituted pyridines, quinolines, thiophenes, benzoaxoles, pyrimidines and indoles.

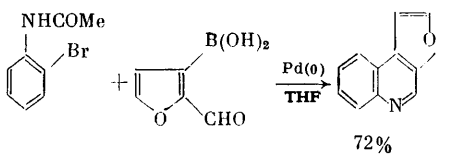
Vinyl and alkynyl bromides couple readily with 3- and 4-pyridyldiethylboranes to give the corresponding vinyl- and alkynylpyridines:[85]



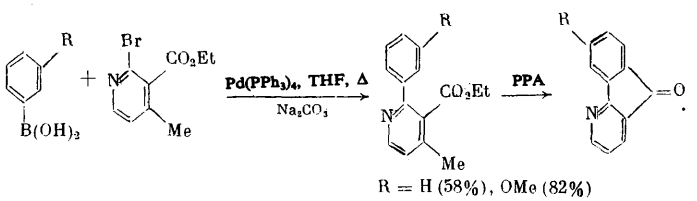
Cross-coupling has been applied in a multi-step route to pharmaceutically interesting furoquinoline alkaloids. Thus, 2-formyl-3-furylboronic acid couples with 2-bromonitrobenzene to produce 2-formyl-3-(2′-nitrophenyl)furan:[86]



A more effective route is based on coupling 2-bromoacetanilides with 2-formyl-3-furylboronic acid, which leads directly to the desired furoquinoline:



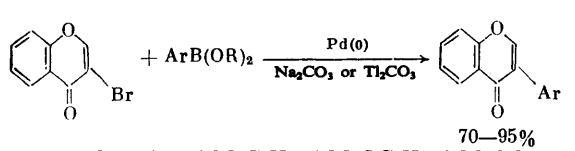
An interesting application of cross-coupling between arylboronic acids and heterocyclic halides has been reported in the synthesis of alkaloids with the azafluorenone skeleton.[87] Palladium-catalysed coupling of arylboronic acids with 2-bromonicotonic acid esters affords dimeric products which subsequently cyclise to give the desired alkaloids.



R = H (58%), OMe (82%)

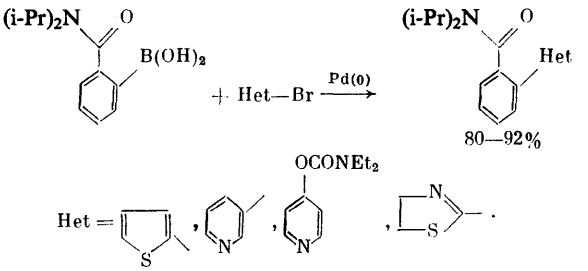
However, in this case, the best results have been achieved with arylstannanes.[87]

Cross-coupling of 3-bromochromones with arylboronic acids or their esters in the presence of a Pd catalyst provides a convenient preparative route to isoflavones:[88]

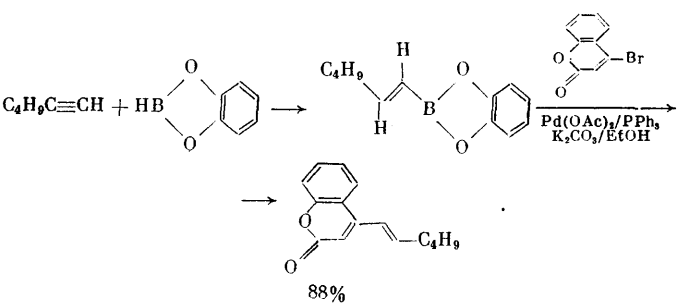


R = H, n-Bu; Ar = 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$, Ph, 4-FC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 1-C$_{10}$H$_7$, 2,4,6-Me$_3$C$_6$H$_2$.

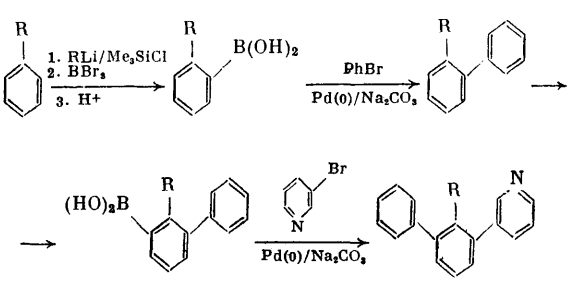
Heterocyclic residues can effectively be incorporated into unsaturated systems by cross-coupling of aryl- and vinyl-boronic acids with heterocyclic halides.[80,89,90] Thus:



2-Alkenyl-1,3,2-benzodioxaboroles, readily formed by hydroboration of acetylenes with catecholborane, are suitable synthons for preparing 2,4-alkadienoates by cross-coupling. The method is applicable to cyclic analogues, such as 4-alkenylcoumarins:[91]

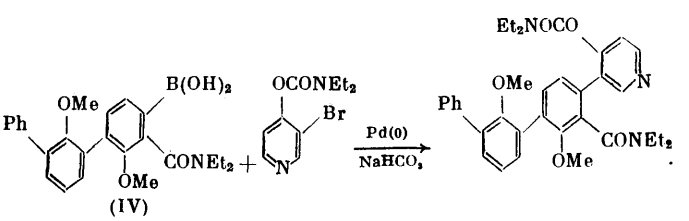


Reference has been given to an original method of preparing *m*-terphenyls containing heteroarene residues.[92] Aromatic compounds with substituents which faciliate *o*-metallation may be used for the preparation of *o*-substituted boronic acids. The latter couple effectively with hererocyclic halides, e. g. 3-bromopyridine:



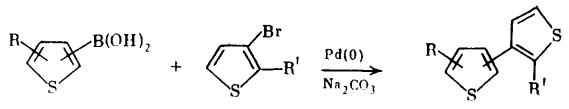
R = $CO_2N(Pr\text{-}i)_2$, $OCONEt_2$, OCH_2OMe, $NHCO_2Bu\text{-}t$.

To illustrate the possibility of preparing polyfunctionalised heteroarenes, we show below the synthesis of pyridotetraphenyl by cross-coupling of (IV) with a 4-pyridyl carbamate:[93]



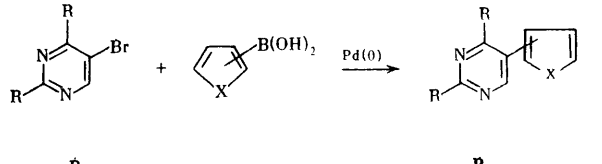
Palladium(0)-catalysed cross-coupling of 2- and 3-thienylboronic acids with mono- and poly-halogenothiophenes provides the basis of a method of preparing bi- and poly-thienyls.[94–96] It has been adapted to the synthesis of compounds with a variety of

substitutents in the thiophene rings, e. g.



R = H, 2-CHO, 4-CHO; R′ = H, 2-CHO, 2-NO_2, 2-SMe.

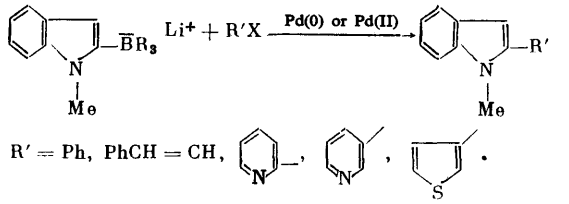
The method has been adapted to the synthesis of other linearly condensed polyheterocycles — thienopyridines,[97,98] thieno- and selenopheno-pyrimidines,[73] benzo- and thieno-condensed quinolines and naphthyridines,[99,100] e. g.



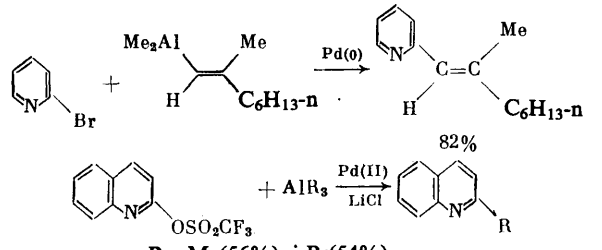
48 – 84%

X = S, Se

Palladium-catalysed coupling of indolylborates with vinyl, aryl and heterocyclic halides has proved of value for the synthesis of 2-substituted indoles:[101]

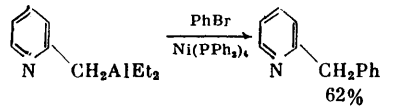


Cross-coupling can also be performed in many instances with organoaluminium compounds. Thus, chloropyrazines,[102] chloropyrazine *N*-oxides,[103] 2-bromopyridine,[19] and 2-quinolinyl triflate[104] react smoothly with organoaluminium compounds in the presence of a palladium catalyst.



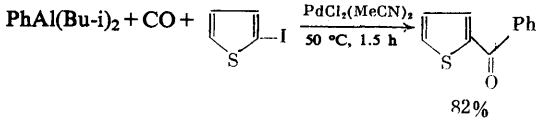
R = Me(56%), i-Pr(54%).

In addition to this, 2- and 4-picolinyl-aluminium and -zinc reagents readily react with aryl and heterocyclic halides in the presence of a Ni(0) catalyst,[105] e. g.



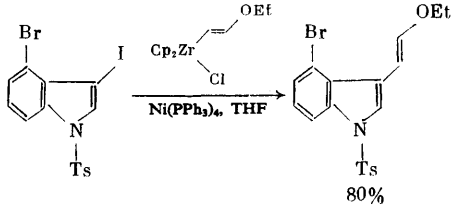
62%

2-Benzoylthiophene is formed smoothly on carbonylation of 2-iodothiophene in the presene of phenyldiisobutylalane:[106]



82%

The 2-ethoxyvinyl group may be effectively transferred from zirconium to the 3-position of indole via Ni(0)-catalysed oxidative addition-transacetalation:[107]

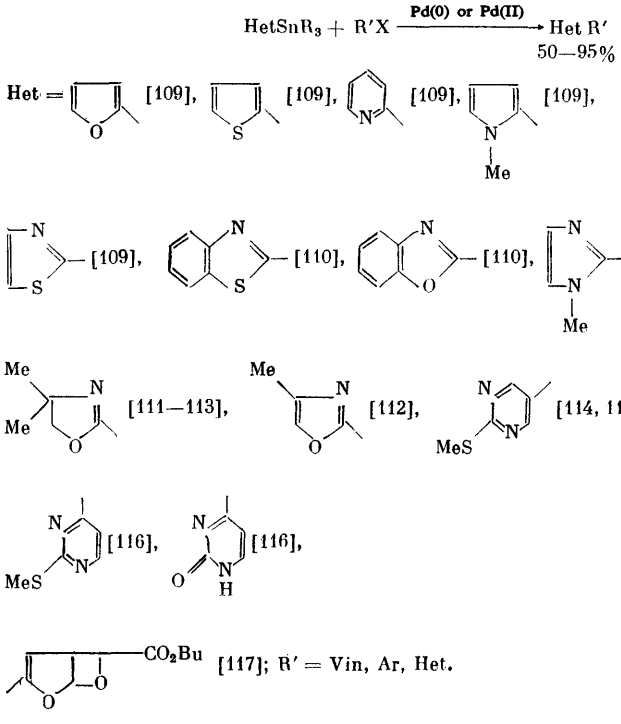


80%

5-Alkenyldeoxyuridines have been prepared by Pd-catalysed coupling of vinylzirconium compounds with deoxyuridine.[108]

4. Organotin compounds

Organotin compounds have been widely used in cross-coupling in view of their chemical stability, the simplicity of their purification, and the possibility of incorporating a variety of functionalised residues. Five- and six-membered heterocyclics with a F_3Sn group have been coupled with aryl, heterocyclic, and vinyl halides:

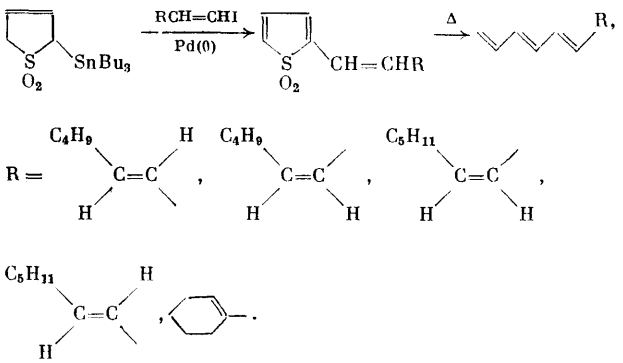


[117]; R′ = Vin, Ar, Het.

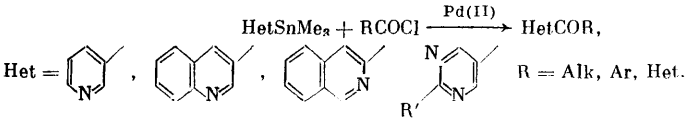
Cross-coupling with oxazolines is particularly interesting since such compounds serve as synthons for preparing carboxylic acids, aldehydes, nitriles and other functionalised derivatives.[118]

The cross-coupling of 2-tributylstannyl-2,5-dihydrothiophene *S,S*-dioxide with vinyl iodides is the key step in the preparation of conjugated trienes, which are generated in desulfonylation of the

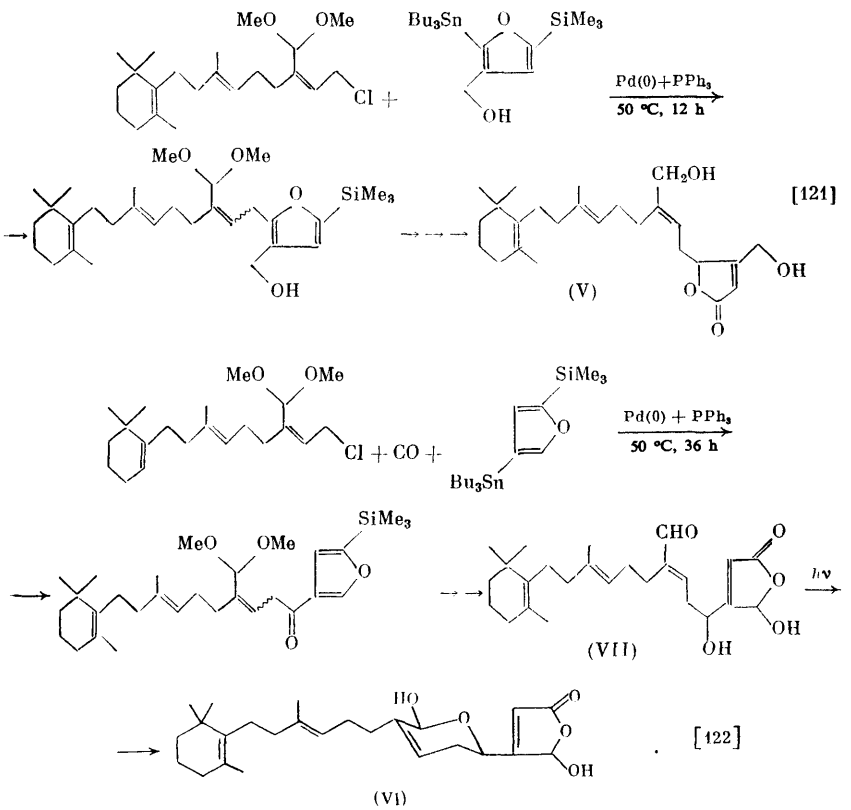
intermediate 2-vinyl derivatives.:[119]



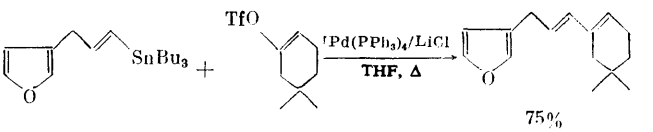
Ketones have been prepared by treatment of trimethylstannyl derivatives of pyridine, quinoline, isoquinoline and pyrimidine with acyl halides in the presence of a Pd catalyst:[114,120]



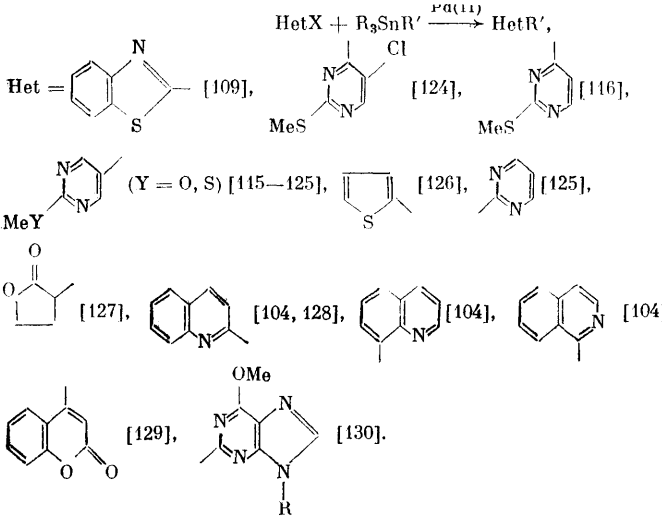
Cross-coupling with stannylfurans has been applied to the synthesis of the biologically active terpenoids, (*E*)-neomanoalide (V), manoalide (VI), and secomanoalide (VII). These compounds possess antiinflammatory and antifungal activity and have an effect on phospholipid metabolism.[121,122]



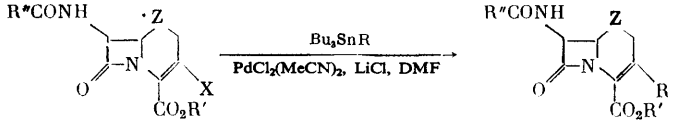
Pd-catalysed coupling of vinyl triflates (TfOR) with organostannanes has been adapted in an elegant synthesis of pleraplysillin:[123]



Various heterocyclic halides and triflates participate in catalysed coupling with organostannanes:

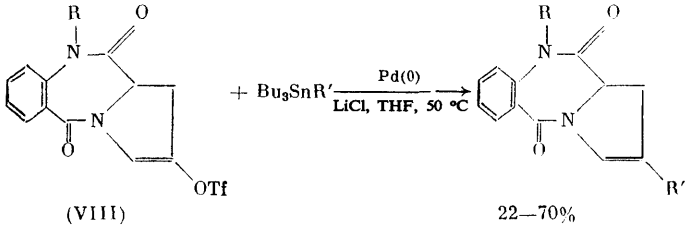


Substituents may be introduced into the 3-position of the caphalosporin and 1-carbacephalosporin nuclei by Pd-catalysed cross-coupling:[131–133]



$Z = CH_2$, S; X = OTf, Br.

Anthramycin analogues have been synthesised by cross-coupling of triflate (VIII) with various unsaturated compounds having a Bu_3Sn residue:[134]



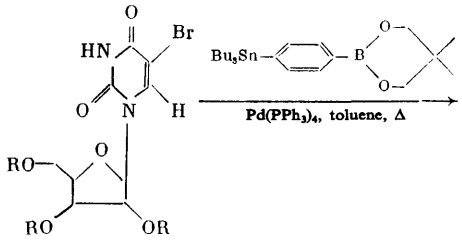
(VIII) 22—70%

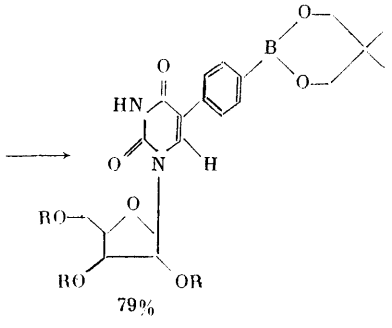
R = Me, CH_2OMe; R′ = CH_2=CH, EtO_2CCH=CH,

MeO_2CCH=CH, H_2NCCH=CH.

The same products have been obtained independently by interaction of triflate (VIII) with acrylic acid amides and esters in the presence of a Pd catalyst.

Cross-coupling of halogenonucleosides with boron-substituted arylstannanes has been extended to the synthesis of ^{10}B-containing nucleosides which are of value in neutron-capture therapy:[135]

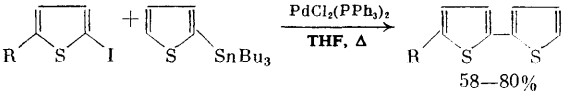




79%

R = $SiMe_2$(Bu-t).

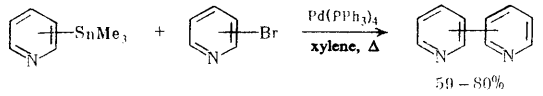
Bi- and poly-nuclear heterocyclics have been synthesised by reaction of heterocyclic halides with trialkylstannylheterocyclics. 2,2′-Bithienyls have thus been prepared in high yield by cross-coupling of 2-iodothiophenes with 2-stannylthiophenes:[136]



58—80%

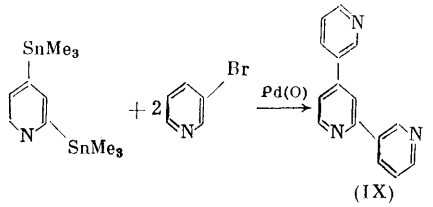
R = H, CH_2OAc, CH_2OH, CHO, CH_2OCOCH_2Pr-i, $C{\equiv}CCH_2CH_2OCOCH_2Pr$-i.

Isomeric bipyridyls are formed by interaction of trimethylstannylpyridines with bromopyridines:[137]



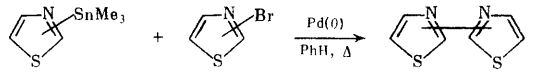
50—80%

The reaction has been extended to the preparation of substituted quinolines. The synthesis of nicotelline(IX) is of particular interest:

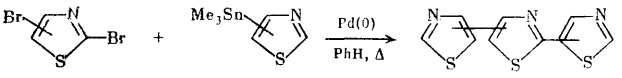


(IX)

Bi- and ter-thiazolyls have been obtained by cross-coupling of stannyl- and halogeno-thiazoles:[138]

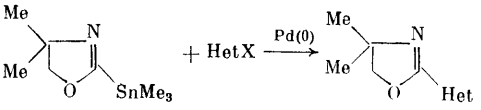


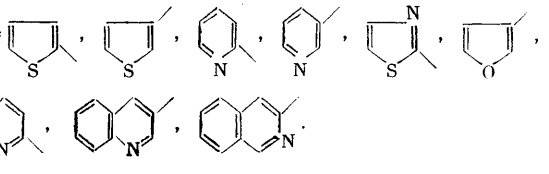
Double cross-coupling takes place readily with dibromothiazoles.



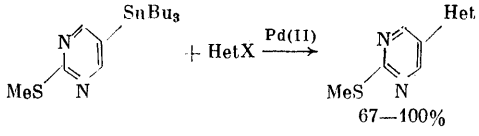
75—92%

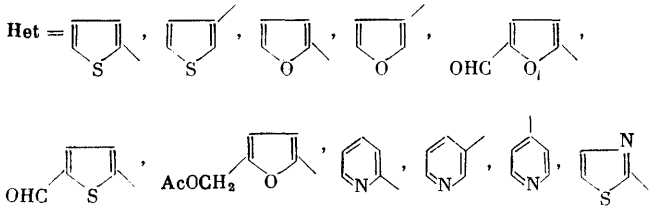
Catalytic cross-coupling of stannyl-oxazoles or -oxazolines with a variety of heterocyclic halides has been applied to the synthesis of oxazol-2-yl- and oxazolin-2-yl-heterocyclics which are intermediates *en route* to carboxylic acid derivatives,[112] e. .g.



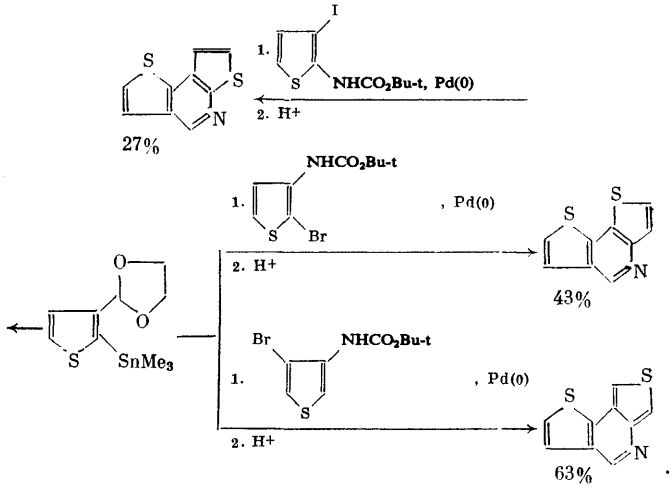
Het = 

5-(Tributylstannyl)pyrimidines couple effectively with various heterocyclic halides to give the corresponding unsymmetrical biheterocyclics:[139]





Isomeric dithienopyridines have been prepared by a novel route involving Pd-catalysed coupling of 2-(2′-trimethylstannyl-3′-thienyl)-1,3-dioxolane with tert-butyl *N*-(*o*-halogenothienyl)carbamates followed by acidic hydrolysis. The ultimate cyclisation takes place instantaneously under the conditions of the hydrolytic step.[140,141]

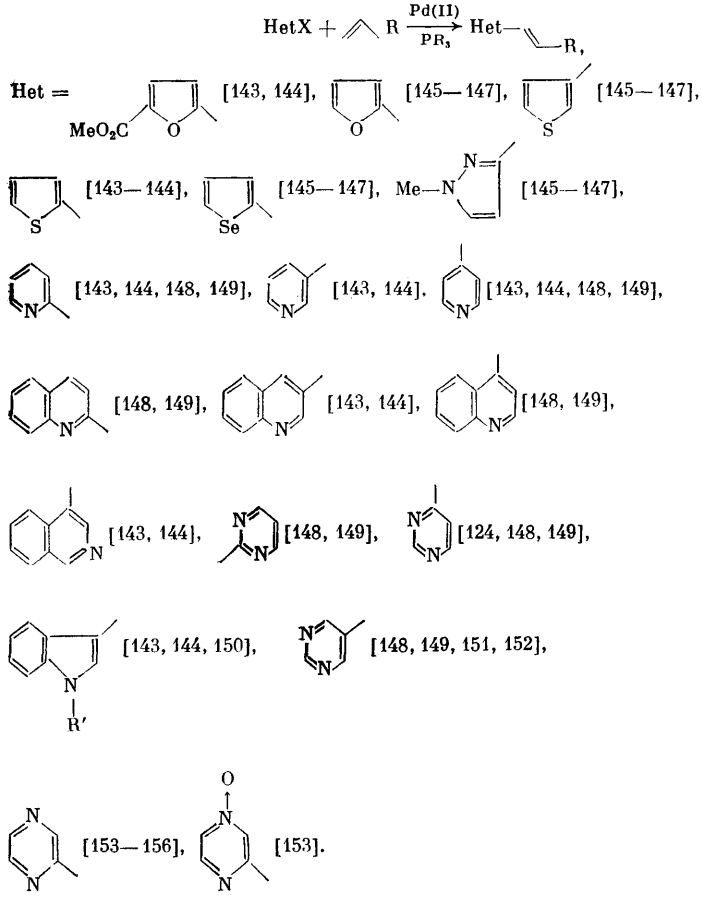


III. Reactions of heterocyclic halides with alkenes and alkynes

1. Reactions of heterocyclic halides with alkenes

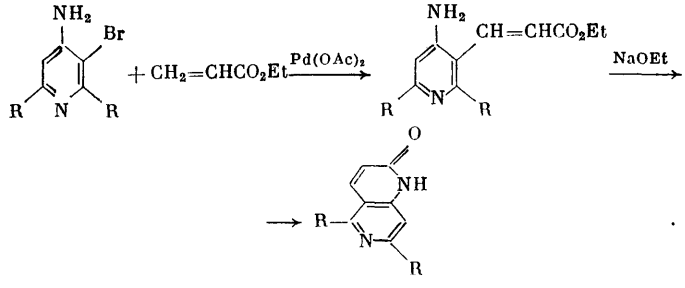
Palladium-catalysed vinylation of organic halides provides a route to substituted heterocyclics by carbon–carbon bond formation.[5,142] This method has been widely used with organic halides which do not possess a β-hydrogen atom, such as aryl, benzyl, vinyl and heterocyclic halides. In the previous sections of this review we have examined cross-coupling of heterocyclic halides with metal alkenyls as a route to vinylheterocyclics. Clearly, palladium-catalysed reaction of heterocyclic halides with alkenes themselves is more preferable. This is the basis of the Heck reaction.

Vinylheterocyclics can thus be prepared by Pd-catalysed condensation with a wide spectrum of alkenes—alkyl acrylates, acrylonitrile, styrene, vinylpyridines, butenylphthalimide, vinyltrimethylsilane, α-acetamidoacrylates, indole, etc.



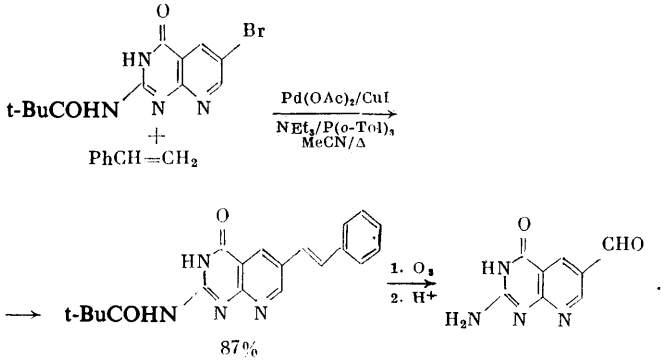
Heterocyclic triflates also participate in the Heck reaction with activated olefins.[104] Palladium catalysis is effective in the functionalisation of the pyrimidine ring of nucleosides.[130]

Isomeric naphthyridines have been prepared by a novel two-step conversion involving Pd-catalysed cross-coupling of *o*-amino-substituted 2-, 3- and 4-halogenopyridines with ethyl acrylate followed by cyclisation,[157–161] e. g.

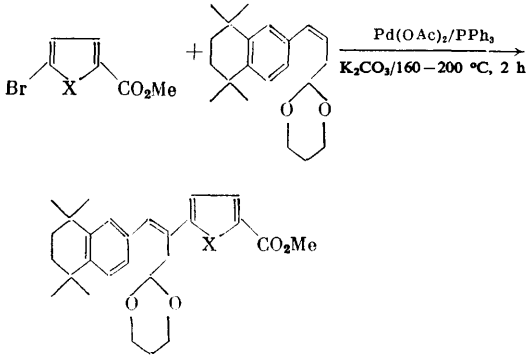


6-Formyl-5-deazapterin, a key intermediate in the synthesis of various 5-deaza-analogues of folic acid, has been readily prepared by Pd-catalysed cross-coupling of 2-pivaloyl-6-bromo-5-deazapterin with

styrene, followed by ozonolysis and hydrolysis

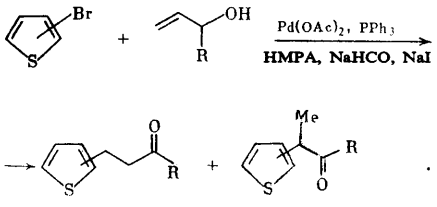


The Heck reaction is particularly useful for the preparation of synthons *en route* to retinoids.[163] Thus, bromo-furans and -thiophenes readily couple with ω-substituted styrenes to give the corresponding (*E*)-stilbenes:



X = O, S.

Treatment of 2- and 3-bromo-thiophenes with allyl alcohols affords aldehydes and ketones with a thienyl residue.[164–166] β-Thienylcarbonyl compounds are formed as the major products:

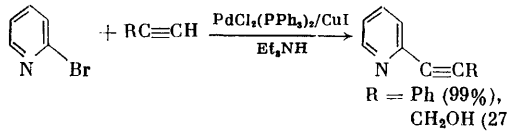


3-Bromopyridine reacts with allyl alcohols similarly.[167]

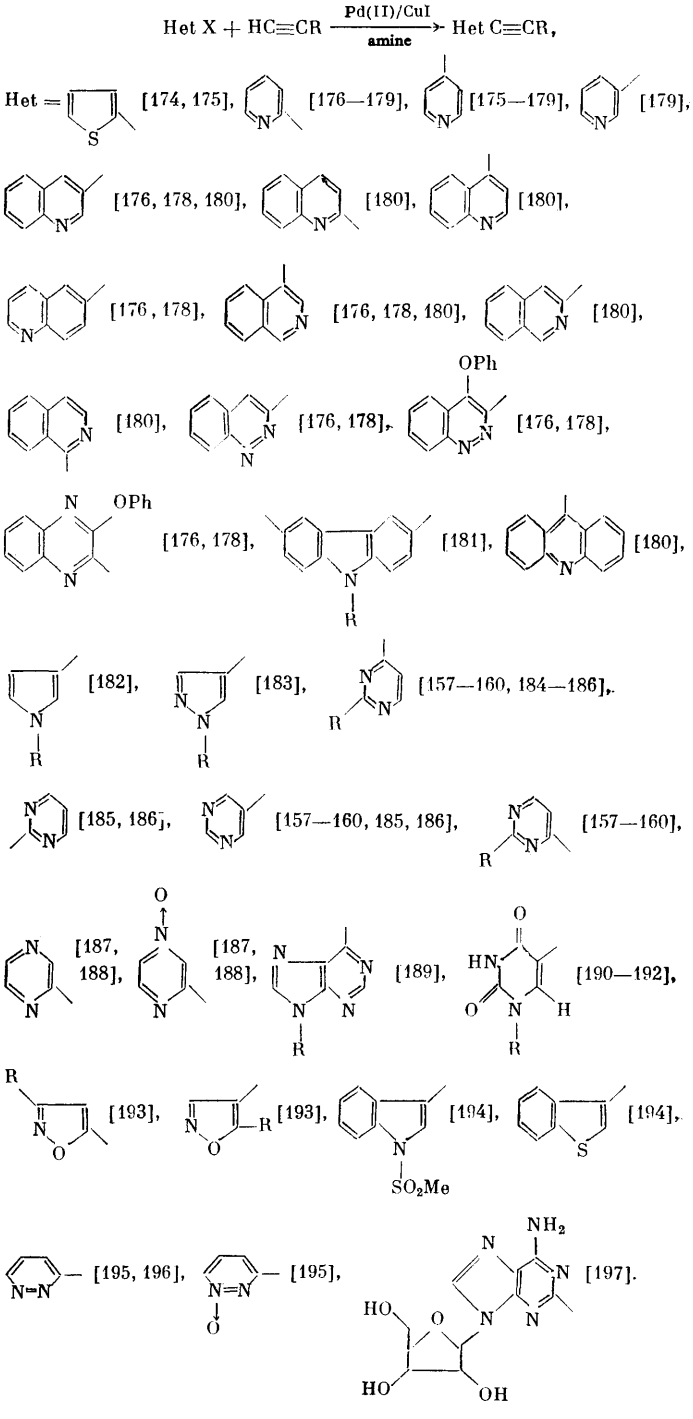
Heterocyclic mercurials react with alkenes in the same way as heterocyclic halides. Thus, 5-alkenyluracil nucleosides and nucleotides have been synthesised by Pd-catalysed cross-coupling of the appropriate mercuriuracil derivatives with a variety of alkenes.[168–170]

2. Reactions of heterocyclic halides with alkynes

The preparation of alkynylarenes by Pd-catalysed reaction of aryl halides with terminal alkynes was pioneered in 1975.[171–173] Sonogashira et al.[171] showed that reaction was most efficient with CuI as co-catalyst. In this way, 2-alkynylpyridines were prepared by reaction of 2-bromopyridine with acetylene derivatives:

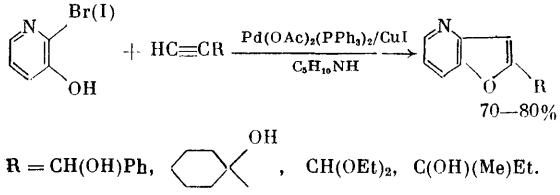


Subsequently, the method was extended to the preparation of a variety of alkynylheterocyclics. As a rule, the yield of the latter is high and the method is preparatively useful.

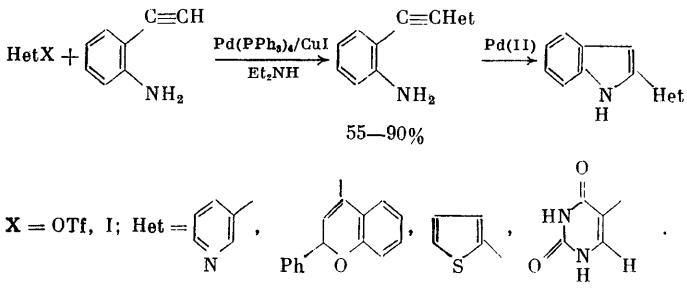


Bis(alkynyl)heterocyclics are formed by reaction of heterocyclic dihalides, e.g. diiodopyrimidines[185,186] and dibromopyridines[198], with terminal acetylenes. Mono-alkynyl derivatives may be isolated by mixing the appropriate proportion of the two reactants. Pyridyl triflates react with terminal acetylenes in the same way as pyridyl bromides.[198]

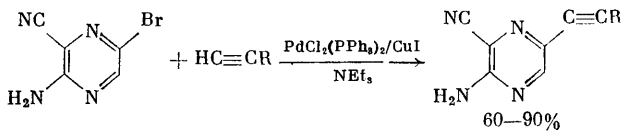
Palladium-catalysed reaction of 3-hydroxy-2-halogenopyridines with terminal acetylenes leads directly to furo[3,2-*b*]pyridines:[199]



2-Substituted indoles have been prepared by coupling heterocyclic triflates or halides with 2-ethynylaniline, followed by Pd(II)-catalysed ring closure of the product:[200]

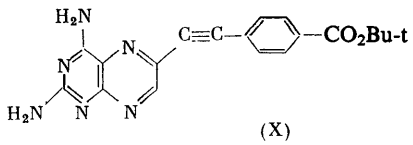


2-Amino-3-cyano-5-bromopyrazine couples with acetylenes as follows:[201,202]



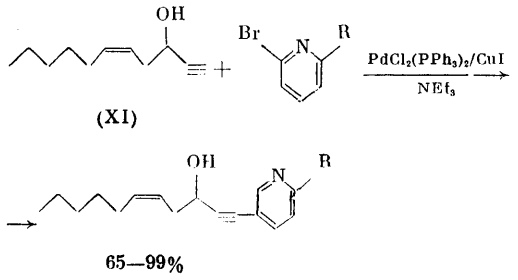
R = Ar, Bu, t-Bu, $MeOCH_2$.

This method is effective for the synthesis of pteridine (X), an intermediate *en route* to the anticancer drug, methotrexate.

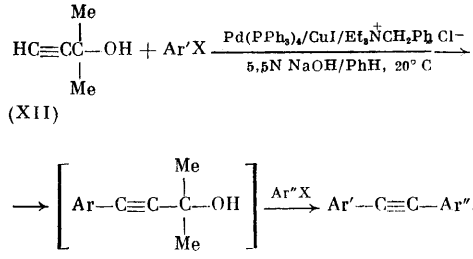


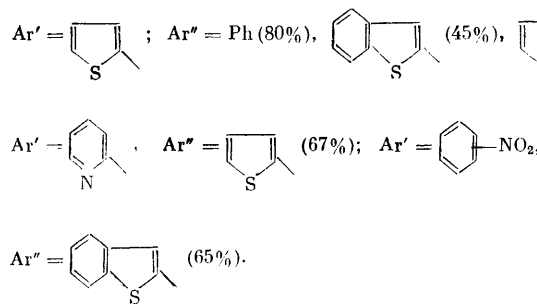
(X)

Synthons for the preparation of leukotriene B_4 antagonists have been synthesised by reaction of 6-substituted 2-bromopyridines with acetylene (XI):[203]

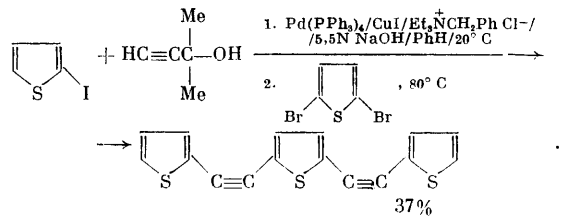


The readily available dimethylethynylcarbinol (XII) couples effectively in the presence of a Pd-catalyst to yield symmetrically and unsymmetrically disubstituted diarylacetylenes in one step.[204] The reaction of (XII) with heterocyclic halides affords the corresponding arylalkynols quantitatively under phase transfer catalysis. The addition of a second molecule of aryl or heterocyclic halide during the reaction leads to the corresponding disubstituted acetylene on raising the temperature to 70–80 °C:

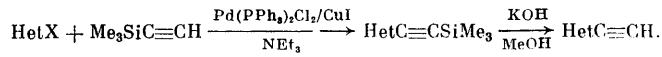




Bisacetylenic compounds, such as 2,5-bis(2′-thienylethynyl)-thiophene, may also be prepared by this route.



Cross-coupling of azinyl and diazinyl halides with trimethylsilylacetylene, followed by desilylation, provides a preparative route to the corresponding ethynylheteroarenes:[205]



IV. Other reactions

Homo-coupling of heterocyclics can be effected by complex metal catalysis. Thus, reductive dimerisation of heterocyclic halides takes place in the presence of both Ni and Pd catalysts. The following systems have been used for homocoupling: $Zn/NiCl_2/PPh_3$ [206–210], $Zn/NiCl_2(PEt_3)_2$ [211], $Ni(COD)_2$ [212],

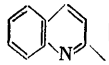
Pd–C/NaOH/HCOONa/H_2O/$Et_3\overset{+}{N}CH_2PhCl^-$ [213], Raney nickel [214], $Ni(OAc)_2$/NaH/PPh_3/*t*-BuOK [215], and $NiBr_2(PPh_3)_2$/Zn/Et_4NI [216]:

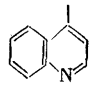
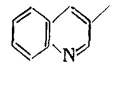
HetX $\xrightarrow{\text{catalyst}}$ Het—Het,

Het =  [206, 210—212],  [211],

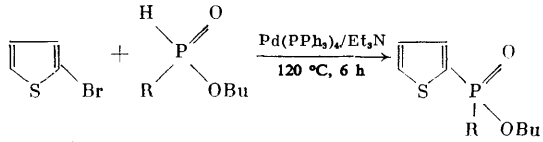
 [207—210, 213—216],

 [200—202, 208, 209],  [200—202, 206, 208],

 [200—202, 209],  [208—210, 216],  [211],

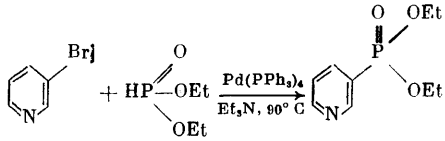
 [211],  [216]  [216],  [216].

Heterocyclic halides also participate in Pd-catalysed cross-coupling with phosphorus compounds possessing a P–H bond. Thus, 2-thienyl bromide reacts with monobutyl alkyl- or aryl-phosphonites in the presence of a Pd(0) catalyst:



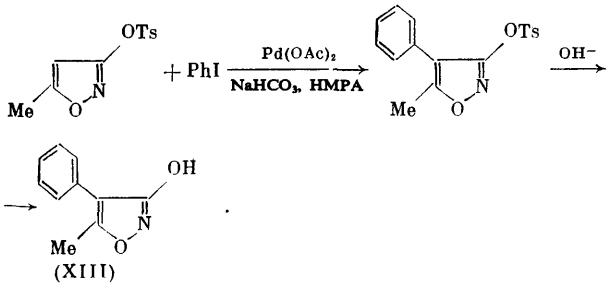
R = Me (70%) [217], Ph (53%) [218].

Diethyl 3-pyridylphosphonate is obtained by coupling of 3-bromopyridine with diethyl phosphite:[219]



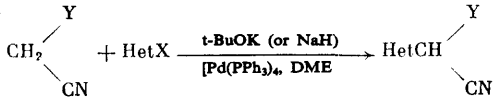
77%

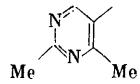
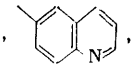
Isoxazole derivatives couple with aryl iodides in the presence of a Pd catalyst to give 4-arylisoxazoles.[220] 4-Phenylmuscimol (XIII), an important neuro-pharmacological drug, has been obtained by this route.

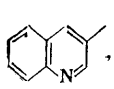
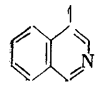


(XIII)

The incorporation of active methylene groups into "unreactive" positions of *N*-heteroarene ring can be conveniently achieved under Pd catalysis. Thus, heterocyclic halides react with the carbanions derived from malononitrile and ethyl cyanoacetate to give the corresponding heteroarylmalonitriles and ethyl α-cyano(heteroaryl)-acetates. Reaction is of a general nature:[221]

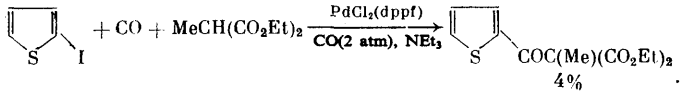


X = Br, I; Y = CO_2Et, CN; Het =  ,  ,  ,

 ,  .

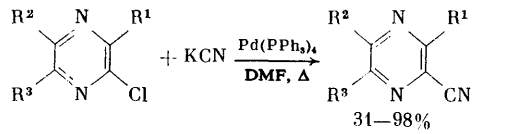
Although $Pd(PPh_3)_2Cl_2$ may be used as catalyst for such coupling with aryl halides[222,223], it is unsuitable for the reactions with heterocyclic halides shown above.

It should be noted that 2-iodiothiophene, like iodobenzene, couples with active methylene groups on carbonylation to give a low yield of the corresponding ketone:[224]



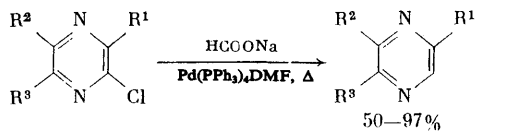
4%

A general synthesis of 2-cyanopyrazines by Pd(0)-catalysed replacement of chlorine by cyano group has been reported:[225]



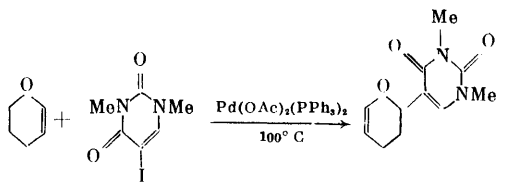
31—98%

Dicyanopyrazines are obtained similarly from the corresponding dichloropyrazines. However, 2-chloropyrazine, as well as its 1- and 4-oxides, are readily dechlorinated on heating with sodium formate in the presence of a Pd(0) catalyst:[226]



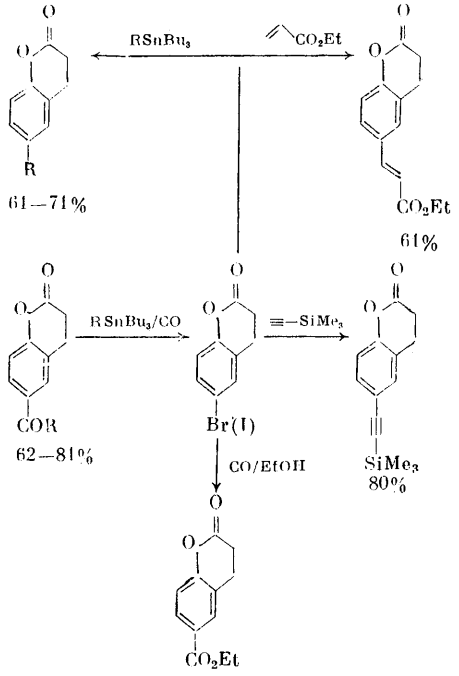
50—97%

Dihydropyran couples with 1,3-dimethyl-5-iodouracil in the presence of a Pd(II) catalyst:[227]



Functional groups may be introduced into the 6-position of the dihydrocoumarin ring by Pd-catalysed coupling (Scheme 2).[228]

Scheme 2



R = Vin, Ph, PhC≡C.

The catalytic formation of a carbon—carbon bond in heterocyclic systems, as described in this review, is potentially very useful in the synthesis of physiologically active compounds and natural products.

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