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## Catalytic Cross-coupling Reactions in Biaryl Synthesis

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## 1. INTRODUCTION

### *1.1 General Aspects and Overview*

Biaryls ($Ar^1$-$Ar^2$) and their homologues such as teraryls, oligoaryls and polyaryls are an important class of organic compound; the biaryl unit is represented in several types of compounds of current interest including natural products, polymers, advanced materials, liquid crystals, ligands and molecules of medicinal interest. In view of the tremendous importance of biaryls, a number of catalytic methods for forming these molecules from two monoaryl precursors in a cross-coupling reaction have been developed over the last two decades.

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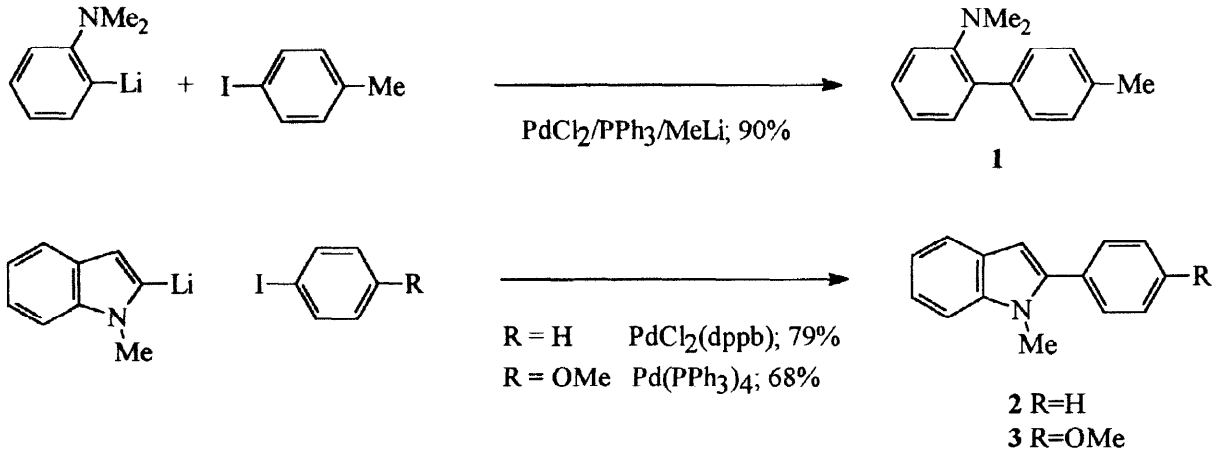
This Report will review the development of modern *catalytic* methods in biaryl synthesis and will provide a broad perspective of the more important methodologies as well as reporting methods which have not yet found widespread use. Methods which are not catalytic are not covered in this Report and neither are methods which can only give homo-coupled products.

The four most commonly used catalytic methods in biaryl synthesis are the Kharasch, Negishi, Stille and Suzuki reactions. These reactions enable the preparation of both symmetrical and unsymmetrical biaryls in a cross-coupling reaction and invariably proceed using either nickel or palladium catalysts.

The Kharasch reaction began to achieve importance as a method for biaryl synthesis in the mid to late 1970's. In this reaction an aryl Grignard reagent ($Ar^1MgX$, X = halogen) is generally reacted with an aryl halide ($Ar^2X$) in the presence of an appropriate catalyst to yield the biaryl ($Ar^1$-$Ar^2$). Other functionalised aryls can also partner the Grignard reagent in this reaction, for example, phenolic derivatives such as triflates, mesylates and ethers have been used as well as thiophenolic derivatives such as sulphides and sulphones. One disadvantage of the Kharasch reaction is that the polar nature of the Grignard reagent precludes the use of several types of functional groups in the coupling partner such as aldehydes, ketones, esters and nitro groups.

The Negishi reaction utilises arylzinc reagents ($Ar^1ZnX$, X = halogen) and aryl halides or triflates ($Ar^2X$, X = halogen or triflate) and began to assume importance in the mid 1970's. Unlike the Kharasch reaction, functional groups such as aldehydes, ketones, esters, amines and nitro groups *etc* are tolerated in the coupling partner of the arylzinc reagent. Although arylmagnesium and arylzinc reagents are precursors to biaryls in the Kharasch and Negishi reactions respectively, aryllithiums are not generally used due to their highly polar and basic nature. There are however, a few isolated examples where aryllithiums have been used successfully in biaryl synthesis as illustrated by the formation of compounds **1-3** (**Scheme 1**).[1-3]




**Scheme 1**

In the late 1970's the Stille reaction started to be used in biaryl synthesis and this reaction uses arylstannanes ($Ar^1SnR_3$, R = Me, Bu) and aryl halides or triflates ($Ar^2X$, X = halogen or triflate) as the coupling partners. This reaction is extremely versatile, proceeds under neutral conditions and can tolerate a wide range of substituents on both coupling partners. Thus, substituents which are not compatible with the Kharasch and Negishi reactions are often tolerated in the Stille reaction. The major disadvantage of the Stille reaction is the toxicity of the organotin reagents and byproducts.

The early 1980's saw the advent of the Suzuki reaction. The Suzuki reaction, like the Stille reaction, has proved extremely versitile and has found extensive use in natural product synthesis. Boronic acids [$Ar^1B(OH)_2$] are the usual substrates in this reaction together with aryl halides or triflates ($Ar^2X$, X = halogen or triflate) although esters of boronic acids and arylboranes are frequently used.

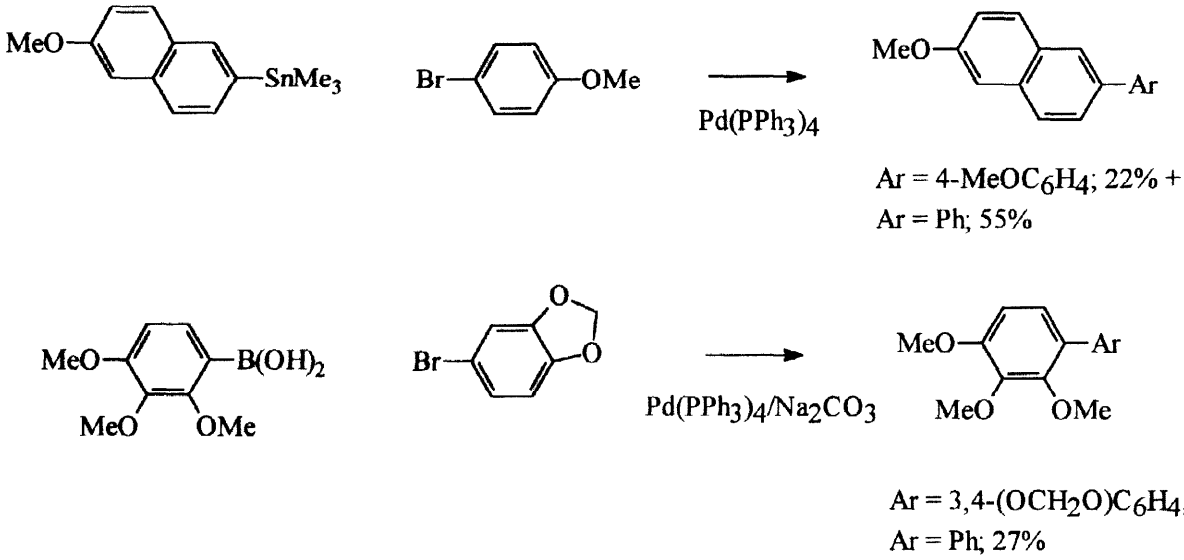
*1.2 Catalysts and Catalytic Cycles*

Numerous palladium and nickel catalysts have been employed in the Kharasch, Negishi, Stille and Suzuki reactions. The catalyst is frequently added as a metal(II) complex from which the catalytically active metal(0) species is generated *in situ*. The palladium(0) complex, $Pd(PPh_3)_4$ is one example of a preformed catalyst which has found widespread application in cross-coupling reactions. Palladium black has been successfully used as a catalyst on several occasions and water soluble catalysts have been developed for cross-coupling reactions in aqueous solution. Metals possessing chiral ligands have been used for the preparation of biaryls with axial chirality (atropisomers).

Most catalysts are associated with arylphosphine ligands and one of the consequences of using such ligands is the formation of 'scrambled' products in which the aryl group of the phosphine ligand has become incorporated into the product. In most cases this is not a major problem but two examples where considerable 'scrambling' has been observed in a Stille reaction[4] and a Suzuki reaction[5] are illustrated in **Scheme 2**. Arylphosphine ligands are often responsible for chain termination reactions in the synthesis of polyaryls and 'ligandless' catalysts have therefore been advocated for use in polymerisations.[6]

Other side reactions which are sometimes encounted to varying extents are homocoupling reactions and reductions and these reactions will be discussed at relevant points in the text.

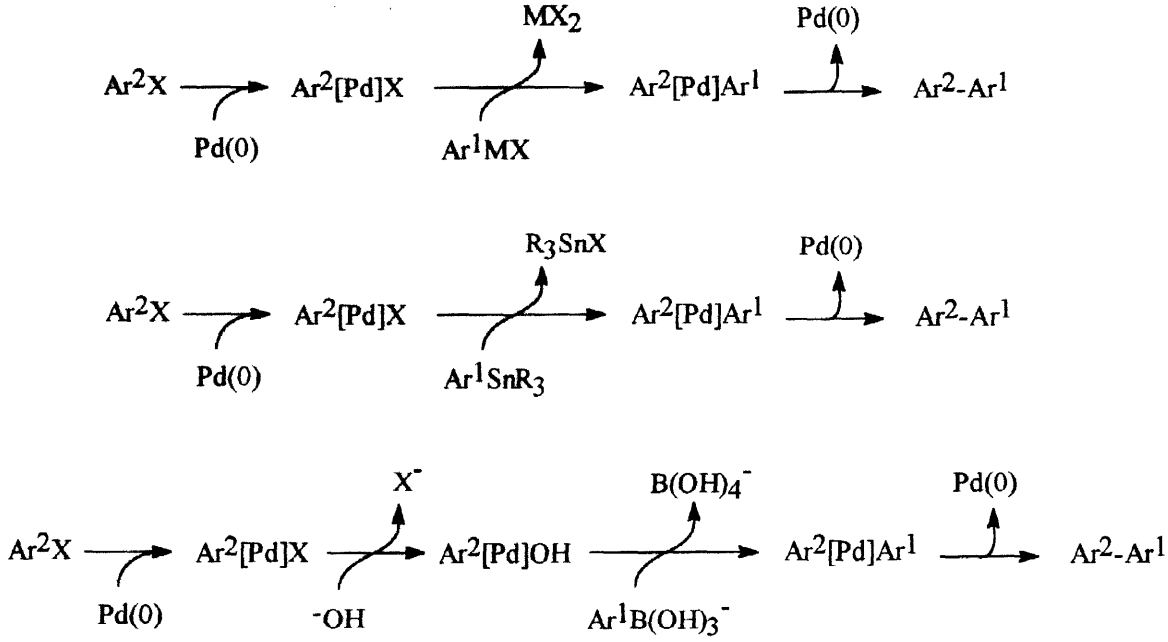
The structures of ligands contained in this Report are given in Section 8.




**Scheme 2**

The catalytic process associated with the Kharasch, Negishi, Stille and Suzuki reactions can be represented as shown in **Scheme 3** which illustrates these reactions with an aryl halide ($Ar^2X$, X = halogen) as one of the coupling partners in a palladium catalysed reaction. Potential ligands of the palladium(0) intermediates have been omitted for clarity and the processess depicted in **Scheme 3** can obviously be extended to nickel catalysed reactions and substrates other than aryl halides, for example aryl triflates. When aryl triflates are used, lithium chloride is an essential additive in the Stille reaction.

All the reactions shown in **Scheme 3** have three common steps; firstly an oxidative addition of the catalyst to the aryl halide giving an intermediate $Ar^2[Pd]X$; secondly a transmetallation step to yield a diarylated palladium moiety, $Ar^2[Pd]Ar^1$; and finally a reductive elimination from the diarylated palladium compound giving the biaryl product and the palladium(0) catalyst which re-enters the catalytic cycle.




**Scheme 3**

## 2. THE KHARASCH REACTION

*2.1 Chemoselectivity and Regioselectivity*

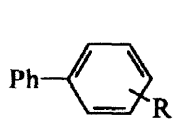
The reaction of 4-bromochlorobenzene with phenylmagnesium bromide catalysed by $PdPh(PPh_3)I$ gave 4-chlorobiphenyl **6** (73%) showing that the bromo substituent can be selectively coupled in the presence of a chloro substituent.[7] With these reagents and either $NiCl_2$ or $Ni(dppe)Cl_2$ as the catalyst the mono phenylated product **6** (18-71%) has been reported together with the diphenylated product, *para*-terphenyl **13** (3-37%) with the mono: diphenylated ratio depending upon the reaction conditions and the reagent stoichiometries.[8] 2-Tolylmagnesium bromide and 4-bromochlorobenzene gave higher yields (38-87%) of the biaryl **15** with various catalysts with very little of the corresponding teraryl product being formed (3-12%).[8] This Grignard reagent and 2-bromochlorobenzene afforded only 2-chloro-2'-methylbiphenyl **14** (32-49%).[8] The iodo substituent in 4-fluoroiodobenzene was also selectively replaced with phenylmagnesium bromide in a $PdPh(PPh_3)I$ catalysed reaction giving 4-fluorobiphenyl **8** (74%).[7]

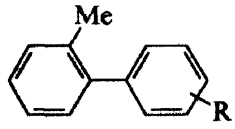
The preferential replacement of a methylthio group over an isopropylthio group has been reported as illustrated for the formation of biaryl **9** from phenylmagnesium bromide and the *ortho*-disulphide, 1,2-$(MeS)(Pr^iS)C_6H_4$ in the presence of $Ni(PPh_3)_2Cl_2$ as the catalyst.[9] A chloro substituent can also be selectively replaced in the presence of an isopropylthio group as exemplified by the formation of all three isomeric biaryls **9-11** (65-84%) from 1,n-$Cl(Pr^iS)C_6H_4$ using $Ni(PPh_3)_2Cl_2$ as the reaction catalyst.[10]

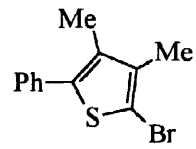
In dihaloaryls, where both halogen substituents are in identical chemical environments, it is often possible to replace only one halogen substituent in the Kharasch reaction. Thus, in a $[Ni(triphos)Cl]PF_6$ catalysed reaction, 1,2-dichlorobenzene and phenylmagnesium bromide gave 2-chlorobiphenyl **4** (53%) together with some of the diphenylated product, *ortho*-terphenyl **12** (17%).[11] Biaryl **4** (79%) has also been obtained from phenylmagnesium chloride and 1,2-dichlorobenzene with $Pd(dppf)Cl_2$ as the catalyst and this Grignard reagent and 1,3-dichlorobenzene gave 3-chlorobiphenyl **5** (85%) in an analogous reaction.[12] Similarly, 1,2-dibromobenzene and phenylmagnesium bromide gave biaryl **7** (75%) with very little (2-3%) of *ortho*-terphenyl **12** being formed in a $Pd(dppb)Cl_2$ catalysed reaction.[13]

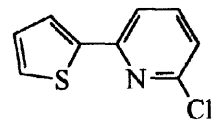
Examples of the selective replacement of one halogen in heterocyclic dihalo compounds are provided by formulae **16-18**.[13-15] Thus, phenylmagnesium bromide reacted with 2,5-dibromo-3,4-dimethylthiophene in the

presence of $Pd(PPh_3)_4$ giving product **16** (72%);[13,13a] 2-thienylmagnesium bromide and 2,5-dibromothiophene yielded the bithienyl **17** (53%) in a $Pd(dppf)Cl_2$ catalysed reaction[14] and 2,6-dichloropyridine and 2-thienylmagnesium bromide gave the heterobiaryl **18** (55%) with $Pd(dppb)Cl_2$ as catalyst.[15] Other substituents besides halogens can also be replaced with some selectively: 1,4-dimethoxybenzene and phenylmagnesium bromide gave a mixture of 4-methoxybiphenyl (33%) and *para*-terphenyl **13** (24%) in a $Ni(PPh_3)_2Cl_2$ catalysed reaction.[16]









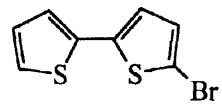
**4** R = 2-Cl
**5** R = 3-Cl
**6** R = 4-Cl
**7** R = 2-Br
**8** R = 4-F

**9** R = 2-SPr$^i$
**10** R = 3-SPr$^i$
**11** R = 4-SPr$^i$
**12** R = 2-Ph
**13** R = 4-Ph

**14** R = 2-Cl
**15** R = 4-Cl

**16**

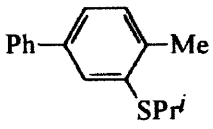
**18**



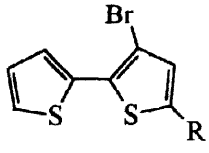
**17**

2,4-Bis(isopropylthio)toluene reacted regiospecifically with phenylmagnesium bromide in benzene at 50°C [$Ni(PPh_3)_2Cl_2$ catalyst] yielding biaryl **19** (55%) in which the less sterically crowded isopropylthio group had been replaced.[9] A 1:1 mixture of 2-thienylmagnesium bromide and 2,3-dibromothiophene afforded the bithienyl derivative **20** (82%) with $Pd(dppf)Cl_2$ as the catalyst whereas with a 2:1 mixture of these reagents the terthiophene **22** (85%) was produced.[14] A 3:1 mixture of this Grignard reagent and 2,3,5-tribromothiophene resulted in the displacement of only the 2- and 5- bromo substituents yielding the terthiophene **21** (89%).[14]

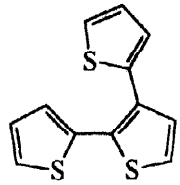
The 2-bromo substituent in 2,5-dibromopyridine can be selectively replaced as illustrated by the formation of the heterobiaryls **23** (95%) and **24** from 2,5-dibromopyridine and 2-thienylmagnesium bromide and 1-methyl-2-indolylmagnesium bromide respectively in $Pd(dppb)Cl_2$ catalysed reactions.[15]



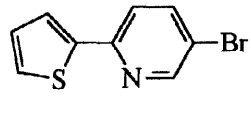
**19**



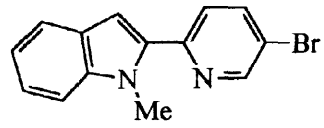
**20** R = H
**21** R = 2-thienyl



**22**



**23**



**24**

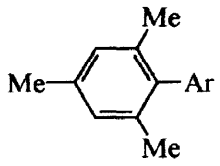
*2.2 Steric Considerations*

The palladium catalysed Kharasch reactions of mesitylmagnesium bromide and either bromobenzene or iodobenzene can give good yields of the biaryl **25**.[3,7,17] With chlorobenzene as the coupling partner, only low yields of this product are obtained.[17,18] Mesitylmagnesium bromide can also be coupled successfully with 2-bromonaphthalene in a $Ni(dppe)Cl_2$ catalysed reaction giving biaryl **26** in moderate (45%) yield.[18] Binaphthyl derivatives such as compounds **27-29** (55-79%) have been prepared from 2-methyl-1-naphthylmagnesium bromide and an appropriate bromonaphthalene coupling partner using $Ni(PPh_3)_2Cl_2$ as the catalyst.[19]

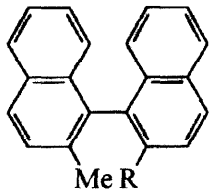
An excess of phenylmagnesium iodide reacted with 1,8-diiodonaphthalene giving 1,8-diphenylnaphthalene **30** in 70% yield. This reaction occurred in a mixture of ether and benzene at -10 to -15°C with $Ni(acac)_2$ as the catalyst.[20]

In cases where both coupling partners possess *ortho* substituents the yields of biaryls are generally not good. Thus, 2-methoxyphenylmagnesium bromide and 2-bromotoluene gave a low yield (8%) of biaryl **31** with 0.02 equivalents of $Pd(PPh_3)_4$ as the catalyst but the yield could be increased to 39% when a stoichiometric

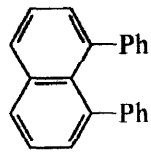
quantity of this catalyst was used.[3] The biaryl **32** was formed (42%) from the reaction between 2-tolylmagnesium bromide and sulphone **33** in a $Ni(acac)_2$ catalysed reaction in THF at 20°C.[21]



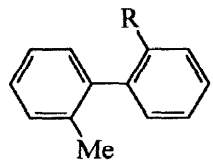
**25** Ar = Ph
**26** Ar = 1-naphthyl



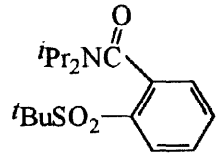
**27** R = H
**28** R = Me
**29** R = OMe



**30**



**31** R = OMe
**32** R = $CON^iPr_2$

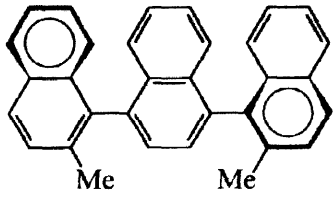


**33**

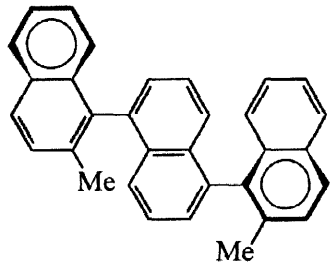
Several groups have reported the synthesis of the chiral binaphthyl **28** with a range of enantiomeric excesses (ee's). Early examples used chiral nickel catalysts and gave poor ee's as well as low yields[17,22] whereas later examples gave good ee's (95%) and yields (69-77%).[23,24,24a] With a chiral palladium catalyst, only low yields and poor ee's were obtained.[25]

Chiral ternaphthyls have been prepared from 2-methyl-1-naphthylmagnesium bromide and dibromonaphthalenes using a mixture of $NiBr_2$ and the chiral ligand, (*S*)-(*R*)-PPFOMe, as the catalyst.[26] Thus, this Grignard reagent with 1,4-dibromonaphthalene afforded an 86:14 mixture (74%) of the ternaphthyl **34** (95% ee) and its corresponding meso isomer, and 1,5-dibromonaphthalene gave an 84:16 mixture (89%) of compound **35** (99% ee) and its meso isomer.

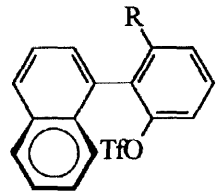
In an enantio position-selective cross-coupling reaction, the pro-*R* triflate group in biaryl **36** was replaced by phenylmagnesium bromide yielding the teraryl **37** (87%, 93% ee) in a Pd[(*S*)-phephos]$Cl_2$ catalysed reaction at -30°C.[27]



**34**



**35**



**36** R = OTf
**37** R = Ph

*2.3 General Survey of the Kharasch Reaction*

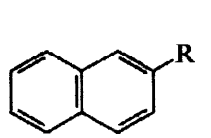
The normal coupling partner for a Grignard reagent in the Kharasch reaction is an arylhalide but a number of other partners have been used. Thus, 2-phenylnaphthalene **38** has been prepared from phenylmagnesium bromide and the following compounds: 2-methoxynaphthalene **39** [77% yield, $Pd(PPh_3)_2Cl_2$[28] or $Ni(PPh_3)_2Cl_2$[16] as the catalyst]; tosylate **40** [60% yield, $Ni(PPh_3)_2Cl_2$[16] as the catalyst]; phosphate **41** [75% yield, $Ni(acac)_2$[29] as the catalyst] and the tetrazoyl ether **42** [55% yield, $Ni(PPh_3)_2Cl_2$[30] as the catalyst]. 1-Phenylnaphthalene **43** has been prepared from phenylmagnesium bromide and either 1-bromonaphthalene [91% yield, $Ni(dppe)Cl_2$[18] as the catalyst] or 1-methoxynaphthalene [70% yield, $Pd(PPh_3)_2Cl_2$[28] or $Ni(PPh_3)_2Cl_2$[16] as the catalyst]. 1-Naphthylmagnesium bromide and bromobenzene also gave compound **43** in excellent yield (98%) using $Ni(dppe)Cl_2$ as the catalyst.[18] 3,4-Dimethoxynaphthalene and phenylmagnesium bromide afforded 3,4-diphenylnaphthalene **44** (45%) in either nickel or palladium catalysed reactions.[16,28]

Carbamates have also been used as coupling partners with Grignard reagents as exemplified by the formation of biphenyls **45** (80%) and **47** (73%) from the reaction of carbamates **46** and **48** respectively with phenylmagnesium bromide/chloride in $Ni(acac)_2$ catalysed reactions.[31]

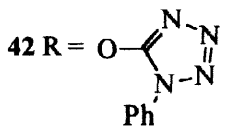
The synthesis of 4-methylbiphenyl provides several examples of arylthiol coupling partners. Thus, 4-tolylmagnesium bromide reacted with both thiophenol and thioanisole in $Ni(PPh_3)_2Cl_2$ catalysed reactions giving 4-methylbiphenyl in 62% and 74% yields respectively,[32] and with phenyl *tert*-butylsulfone giving this product (80%) in a $Ni(acac)_2$ catalysed reaction.[21,21a] Diphenylsulfide, diphenylsulfoxide and diphenylsulfone also gave this product (53-74%).[32] Homocoupled and reduced byproducts are sometimes formed in significant quantities when aryl *tert*-butylsulfones are used as coupling partners with aryl-Grignard reagents.[21,21a] The quaternary salt **49** and phenylmagnesium bromide also afforded 4-methylbiphenyl (31%) in a Kharasch reaction catalysed by $Ni(dppp)Cl_2$[33] and this Grignard reagent and the tetrazoyl ether **50** gave 4-methoxybiphenyl in moderate yield (49%) with $Ni(PPh_3)_2$ as the catalyst.[30]

*Para*-terphenyl **13** has been prepared from phenylmagnesium bromide and 1,4-disubstituted benzene derivatives such as 1,4-dibromobenzene (>80%),[34] 1,4-dimethoxybenzene (24%),[16,28] the bissulphides **51** (89%),[9] and **52** (84%)[9] and the 1,4-bisphosphate **53** (80%).[29] The corresponding 1,2- and 1,3-bissulfide derivatives of compound **52** also yielded *meta*-terphenyl (77%) and *ortho*-terphenyl **12** (67%).[9] Compound **12** has also been obtained from 2-iodobiphenyl and phenylmagnesium bromide (70-90%) with various nickel catalysts.[16]

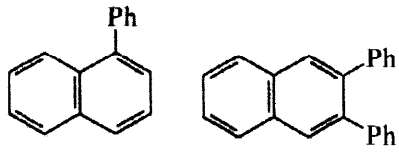
Biphenyl has been prepared in high yield from iodobenzene and phenylmagnesium bromide using various palladium catalysts, including palladium black.[35] Phenylmagnesium bromide also coupled with 4-fluoroiodobenzene giving 4-fluorobiphenyl **8** (92%, $PdCl_2$ catalyst) and 3-fluoroiodobenzene similarly gave 3-fluorobiphenyl (85%). However, 2-fluoroiodobenzene decomposed *via* benzyne formation when treated with this Grignard reagent.[35]



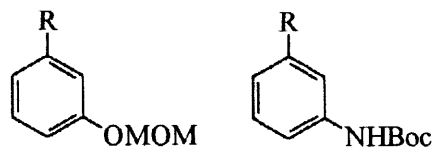
**38** R = Ph
**39** R = OMe
**40** R = $OSO_2(4\text{-}MeC_6H_4)$
**41** R = $OP(O)OEt_2$



**42** R =



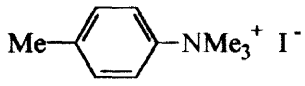
**43** **44**



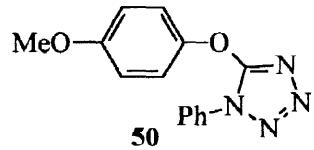
**45** R = Ph
**46** R = $OCONEt_2$



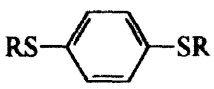
**47** R = Ph
**48** R = $OCONEt_2$



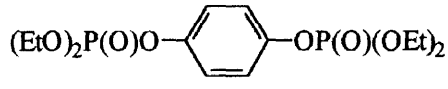
**49**



**50**



**51** R = $Bu^t$
**52** R = $Pr^i$

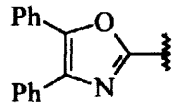
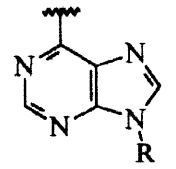
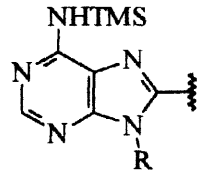


**53**

**Table 1** illustrates some representative examples of the phenylation of heterocyclic compounds with phenylmagnesium bromide/chloride and other substituted Grignard reagents similarly gave arylated heterobiaryls. 2-Phenylthiophene has also been prepared from 2-thienylmagnesium bromide and bromobenzene [$Ni(dppp)Cl_2$ catalyst, 56% yield] but with chlorobenzene the yield is poor (17%).[36] 1-Methyl-2-phenylpyrrole has been prepared (87%) from bromobenzene and 1-methyl-2-pyrrolylmagnesium bromide in the presence of $Pd(dppb)Cl_2$ as the catalyst.[2]

**Table 1**. Phenylation of Heterocycles using the Kharasch Reaction

Het-X + PhMgBr/Cl → Het-Ph

| Het | X | Catalyst | Yield (%) | Reference |
|---|---|---|---|---|
| 2-thienyl | Br | $Ni(dppp)Cl_2$ | 98 | 36 |
| 3-thienyl | Br | $Ni(dppe)Cl_2$ | 80 | 37 |
| 2-furyl | Br | $Ni(dppe)Cl_2$ | 82 | 38 |
| 3-furyl | Br | $Ni(dppe)Cl_2$ | 93 | 38 |
|  | SMe | $Ni(dppe)Cl_2$ | 90 | 39 |
| 2-benzothiazoyl | SH, SMe | $Ni(dppp)Cl_2$ | 79-98 | 40 |
| " | Cl | $Ni(PPh_3)_2Cl_2$ | 70 | 41 |
| 2-pyridyl | SH, SMe | $Ni(dppp)Cl_2$ | 79-88 | 40 |
| " | $OCONEt_2$ | $Ni(acac)_2$ | 30-80 | 31 |
| 3-pyridyl | Br | $Ni(PPh_3)_2Cl_2$ | 54 | 42 |
| " | OTf | $Ni(acac)_2$ | 65 | 31 |
| " | $OCONEt_2$ | $Ni(acac)_2$ | 72 | 31 |
| 4-pyridyl | $OCONEt_2$ | $Ni(acac)_2$ | 81 | 31 |
| 2,6-diphenyl-4-pyridyl | SMe | $Ni(PPh_3)_2Cl_2$ | 87 | 43 |
| 5/6/7/8-isoquinolyl | Br,Cl | $Ni(dppp)Cl_2$ | 69-85 | 44 |
| 4,6-dimethylpyrimid-2-yl | SH, SMe | $Ni(dppp)Cl_2$ | 43-94 | 40 |
|  | | | | |
| R = H | SMe | $Ni(dppp)Cl_2$ | 68 | 45 |
| R = protected sugar | Cl | $Ni(dppp)Cl_2$ | 40 | 46 |
|  | Br | $Ni(PPh_3)_2Cl_2$ | 15 | 47 |
| R = protected suga | | | | |

Numerous bithienyl and terthienyl derivatives have been prepared using the Kharasch reaction. These compounds are often precursors of oligo and polythiophenes which have been used extensively as conducting polymers. Terthiophenes also exhibit phototoxic properties and have thus received attention because of their biological activities. Thus, 2,2'-bithienyl **54** has been prepared in high yield (81-90%) from 2-thienylmagnesium bromide and bromothiophene in a $Ni(dppp)Cl_2$ catalysed reaction[36,48] and the dimethyl derivative **55** (83%) has similarly been prepared.[48] 2,3'-Bithienyl (77-100%)[36,49] and 3,3'-bithienyl (88%)[49] have also been prepared in nickel catalysed cross-coupling reactions.

Terthiophenes are often prepared from a dibromothiophene and a thiophene derived Grignard reagent and yields are generally excellent.[14,49,49a] For example, the parent compound, 2,2':5',2"-terthiophene **56** (α-terthienyl) has been prepared (80-86%) in a $Ni(dppp)Cl_2$ catalysed reaction.[36,48] The alkylated derivative **57**

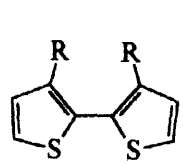
of α-terthiophene **56** has been prepared in excellent yield (92%) as a precursor to soluble sexithiophenes[50] and other alkylated bi- and terthienyls have been synthesised.[51]

The symmetrical selenium containing biaryl **60** has been prepared (85%) from the bromoaryl precursor **58** and the Grignard reagent **59** in a $Pd(PPh_3)_4$ catalysed reaction.[52] Related sulfur containing heterocycles also underwent similar nickel catalysed cross-coupling reactions.[52]

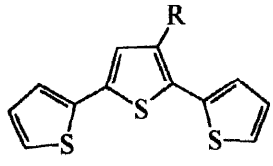
2,2'-Bipyridyl has been prepared in low yield (13%) from 2-bromopyridine and 2-pyridylmagnesium bromide with $Ni(dppp)Cl_2$ as the catalyst.[36]

A number of heterobiaryls possessing two different types of heterocyclic ring have been prepared using the Kharasch reaction. Examples include the thienylpyridines **61** (78%)[36] and **62** (70%),[53] the thienylquinoline **63** (49%)[36] and the thienylisoquinoline **64** (69%),[54] all of which were synthesised from 2-thienylmagnesium bromide and the appropriate bromoaryl coupling partner in nickel catalysed reactions.

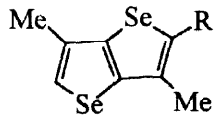
Numerous teraryls possessing three different types of heterocyclic ring have been prepared using two sequential Kharasch reactions.[15] The bisthienylpyridines **65** and **66** have been prepared in a nickel catalysed reaction in good yield from 2,6-dibromopyridine and 2-thienylmagnesium bromide or 3-methyl-2-thienylmagnesium bromide as appropriate. These teraryls have been prepared as intermediates in the synthesis of 'donor-acceptor' polymers **67**.[55]



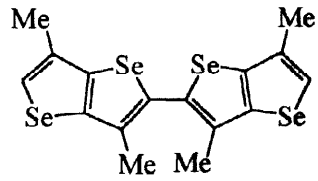
**54** R = H
**55** R = Me



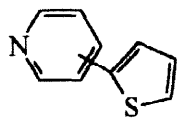
**56** R = H
**57** R = $C_{10}H_{21}$

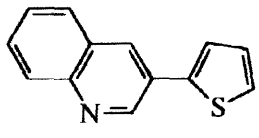


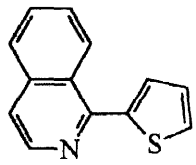
**58** R = Br
**59** R = MgBr

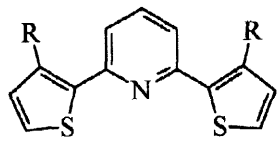


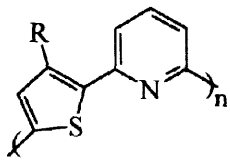
**60**











**61** 2-substituted
**62** 4-substituted

**63**

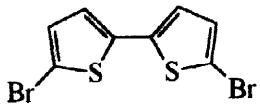
**64**

**65** R = H
**66** R = Me

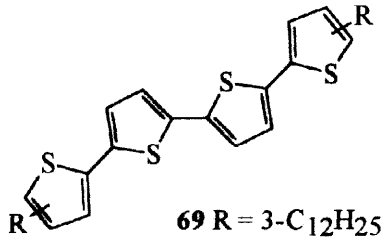
**67**

The quaterthiophenes **69** (75%)[56] and **70**,[51] which possess alkyl substituents to enhance solubility, have both been prepared in a $Ni(dppp)Cl_2$ catalysed reaction from the dibromo precursor **68** and the appropriate 3- or 5-alkylthienylmagnesium bromide. The quinquethiophene **72** (83%) has been synthesised from the terthiophene **71** and thienylmagnesium bromide in a $Ni(dppe)Cl_2$ catalysed reaction.[57] A number of 'capped' oligothiophenes have also been prepared.[53,58]

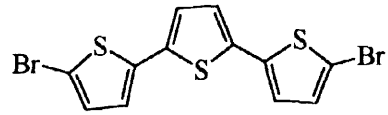
The Kharasch reaction has been used in polymer synthesis. Poly(*para*-phenylene) has been prepared from 1,4-dibromobenzene and magnesium metal *via* 4-bromophenylmagnesium bromide using $Ni(bpy)Cl_2$ as the reaction catalyst in THF at reflux.[59] Alkylated poly(*para*-phenylene) derivatives have also been prepared.[59a] 1,3-Dichlorobenzene and 4,4'-dibromodiphenylether were similarly polymerised and α-linked polythiophene has been prepared from 2,5-dibromothiophene using this methodology.[60] The bis-Grignard reagent, 1,4-$C_6H_4(MgBr)_2$, gave polymer **73** with 2,5-dibromothiophene and polymer **74** with 2,6-dibromopyridine.[61,62]



**68**



**69** R = 3-$C_{12}H_{25}$
**70** R = 5-$C_{12}H_{25}$



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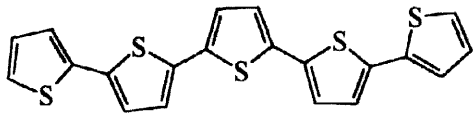
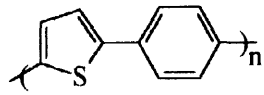
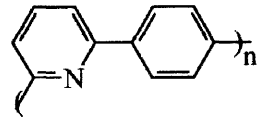


**72**



**73**



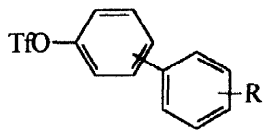
**74**

## 3. THE NEGISHI REACTION

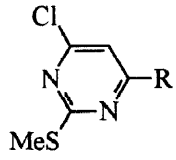
*3.1 Chemoselectivity and Regioselectivity*

All three isomers of the iodotriflate **75** reacted with a number of arylzinc compounds **76** at the iodo substituent in a palladium catalysed reaction yielding biaryls **77** (72-88%).[63] The pyrimidine derivative **78** gave biaryl **79** (79%) when reacted with 3-methoxyphenylzinc chloride in a $Pd(PPh_3)_4$ catalysed reaction.[64] In a regioselective reaction, 3,4-dimethoxyphenylzinc chloride reacted at the 4-bromo substituent of methyl 3,4-dibromobenzoate giving biaryl **80** (53%) in a palladium catalysed reaction.[65]

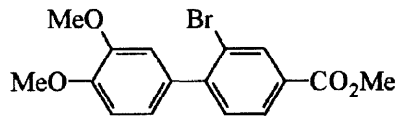
**75** **76**



**77**



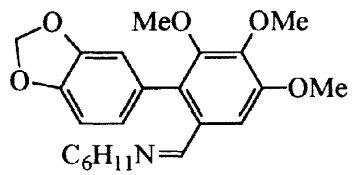
**78** R = I
**79** R = 3-$MeOC_6H_4$



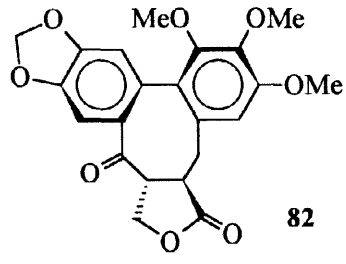
**80**

*3.2 Steric Considerations*

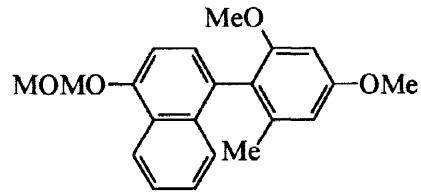
The tolerence of the Negishii reaction to steric effects is illustrated by the formation of the biaryls **81** (80%)[66,67] and **83** (50%)[68] in $Ni(PPh_3)_4$ and $Pd(PPh_3)_4$ catalysed reactions respectively. In these two biaryls, the left-hand fragment is derived from the corresponding arylzinc chloride and the right-hand fragment from the appropriate aryl iodide. Thus, *ortho* disubstituted aryl iodides undergo the Negishi reaction in useful yields. In the former reaction, the imine **81** is not isolated but is hydrolysed to the corresponding aldehyde which was then used in the synthesis of (-)-Steganone **82**. If the corresponding aryl bromide replaced the aryl iodide in the latter reaction, the yield of product **83** was low (16%).



**81**



**82**

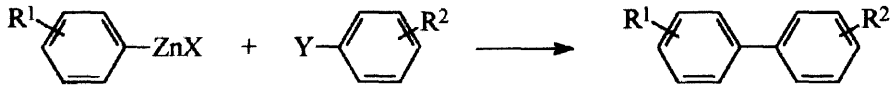


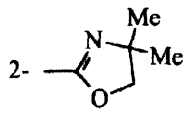
**83**

*3.3 General Survey of the Negishi Reaction*

**Table 2** illustrates some representative examples of the formation of simple biaryls using the Negishi reaction. The reactions generally proceed in good yield and substituents such as nitrile, ester and cyano groups, which are not tolerated in the Kharasch reaction, couple smoothly in the Negishi reaction. In addition to aryl halides as the usual coupling partner of the arylzinc reagent, other partners such as aryl triflates and fluorosulfonates have been used.

**Table 2**. Synthesis of Biphenyls using the Negishi Reaction




| $R^1$ | $R^2$ | X | Y | Catalyst | Yield (%) | Reference |
|---|---|---|---|---|---|---|
| H | H | Cl | $OSO_2F$ | $Pd(PPh_3)_4$ | 95 | 69 |
| H | 4-OMe | Cl | $OSO_2F$ | $Pd(PPh_3)_4$ | 56 | 69 |
| H | 4-OMe | Cl | I | $Ni(PPh_3)_4$ | 85 | 70 |
| H | 4-CHO | Cl | Br | $Pd(PPh_3)_2Cl_2$ | 92 | 71 |
| H | 4-CN | Cl | Br | $Ni(PPh_3)_4$ | 90 | 70 |
| H | 4-$CO_2$Me | Cl | Br | $Ni(PPh_3)_4$ | 70 | 70 |
| H | 4-$NO_2$ | Cl | I | a | 90 | 70 |
| 4-Cl | 3-$NO_2$ | Br | OTf | $Pd(dba)_2$/dppf | 84 | 63 |
| 2-Me | 4-$NO_2$ | Cl | Br | $Pd(PPh_3)_4$ | 78 | 72 |
| 3-Me | 3-Me | Cl | I | $Ni(PPh_3)_4$ | 95 | 70 |
| 2-CN | 3-$CO_2$Et | Br | Br | $Pd(PPh_3)_4$ | 93 | 73 |
| 4-CN | 4-CN | Br | Br | $Pd(PPh_3)_4$ | 95 | 73 |
| 4-CN | 2-$CO_2$Me | Br | I | b | 84 | 63 |
| 4-CN | 4-$CO_2$Et | Br | I | $Pd(PPh_3)_4$ | 82 | 73 |
| 3-$CO_2$Me | 4-CN | Br | Br | $Pd(PPh_3)_4$ | 82 | 73 |
| 4-$CO_2$Et | 4-CN | I | Br | $Pd(PPh_3)_4$ | 80 | 73 |
| 4-$CO_2$Et | 4-$CO_2$Et | I | I | $Pd(PPh_3)_4$ | 94 | 73 |
| 2-$CONMe_2$ | 3-$CO_2$Me | Cl | OTf | $Pd(PPh_3)_4$ | 81 | 74 |
| 2-$CONMe_2$ | 3-$NO_2$ | Cl | OTf | $Pd(PPh_3)_4$ | 80 | 74 |
|  | H | Cl | I | $Pd(PPh_3)_4$ | 75 | 74 |
| " | 2-Me | Cl | I | $Pd(PPh_3)_4$ | 66 | 74 |
| " | 4-$CO_2$Me | Cl | I | $Pd(PPh_3)_4$ | 70 | 74 |
| " | 3-$NO_2$ | Cl | I | $Pd(PPh_3)_4$ | 54 | 74 |

a $Pd(PPh)_3Cl_2$ + DIBAL, b $Pd(dba)_2$/ tris(2-furyl)phosphine

Simple biaryls possessing an amine substituent can also be prepared using Negishi methodology as exemplified by the preparation of 2-amino-4'-methyl-3-cyanobiphenyl [72% yield, $Pd(dppf)Cl_2$ catalyst] from 6-iodoanthranilonitrile and 4-tolylzinc bromide.[75]

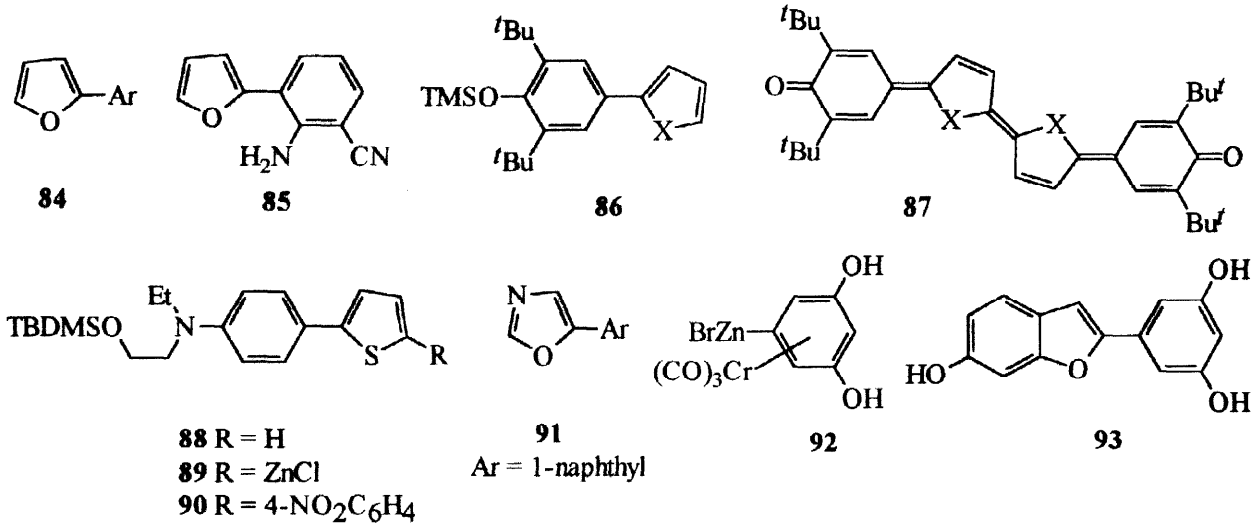
The Negishi reaction has been used to prepare a diverse variety of heterobiaryls. In furan chemistry, 2-furylzinc chloride has been coupled with aryl bromides,[76,77] aryl triflates[78] and aryl fluorosulfonates[69] yielding products of general structure **84** in which the aryl group is a substituted benzene or naphthalene moiety. These reactions are usually catalysed by $Pd(PPh_3)_4$ and give good yields of products. Additionally, 2-phenylfuran has

been prepared from both 2-iodofuran and phenylzinc chloride (91%) and from iodobenzene and 2-furylzinc chloride (89%) in $Pd(PPh_3)_4$ catalysed reactions.[79] 2-Furylzinc bromide and 6-iodoanthranilonitrile gave the amine **85** (98%) in a $Pd(dppf)Cl_2$ catalysed reaction.[75]

A number of heteroquaterphenoquinones **87** have been prepared from biaryls **86** (X= O,S,Se,NR).[80] Biaryls **86** (75-79%) were synthesised from the appropriate iodophenol and heteroarylzinc chloride precursors in $Pd(PPh_3)_4$ catalysed reactions. The arylated thiophene **88** [63%, $Pd(PPh_3)_4$ catalyst] has been prepared from 2-thienylzinc bromide and the appropriate 4-bromoaniline derivative. Compound **88** was subsequently used in the synthesis of the teraryl **90** in a second Negishi reaction of the arylzinc derivative **89** and 4-bromonitrobenzene. This teraryl **90** was then used for the synthesis of non-linear optical (NLO) polyimides.[81]

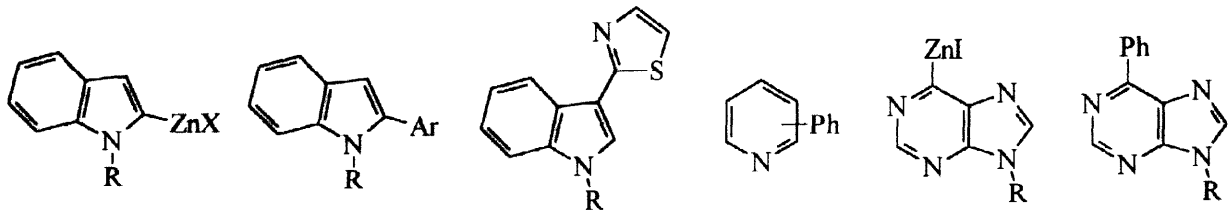
A number of 1,3-oxazoylzinc chloride derivatives have been coupled with aryl iodides or triflates in palladium catalysed reactions.[82] For example, 1,3-oxazo-5-ylzinc chloride with either 1-iodonaphthalene or its corresponding triflate afforded biaryl **91** in 78% and 83% yields respectively.

The organozinc reagent **92** was coupled in good yield [82%, $Pd(PPh_3)_4$ catalyst] with 5-hydroxy-2-iodobenzo[*b*]furan giving the chromium tricarbonyl complex of Moracin M **93**.[83]



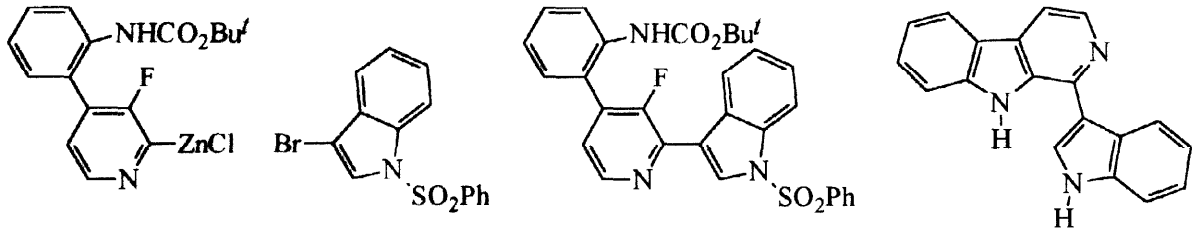

The phenylation of indolylzinc halides with aryl iodides has attracted considerable attention. Thus, the indolylzinc halides of general structure **94** (R = $CH_2OMe$, $CO_2Bu^t$, $SO_2Ph$ and $CO_2Li$) reacted with iodobenzene in a series of $Pd(PPh_3)_4$ catalysed reactions yielding the 2-phenylindole derivatives **95** generally in moderate to good yields. When R = $CO_2Li$, this group is lost on work-up giving the product **95** (R = H).[84-86] Organozinc reagents **94** (R = $SO_2Ph$) have also been reacted with a wide range of substituted 2-pyridyl halides yielding products **96** in palladium catalysed reactions.[87,88] 3-Aryl-1-phenylsulfonylindole derivatives have also been prepared using similar methodology,[86] including the thiazole derivative **97** which was the precursor to the natural product, Camalexin **98**.[84]

Phenylpyridine derivatives **99** and substituted phenylpyridines have been successfully prepared using the Negishi reaction usually in good yield[74,89,90,90a] and 3-phenylquinoline was synthesised (96%) from 3-quinoloylzinc iodide and iodobenzene with $Pd(PPh_3)_4$ as the catalyst.[90] The purine derived zinc compounds **100** (R = $CH_2Ph$ or protected sugar) have been phenylated with iodobenzene (52-80%) giving products **101** using $Pd(dba)_2$ as the catalyst in the presence of tris(2-furyl)phosphine.[91] Substituted iodobenzenes similarly coupled with compound **100**.[91]



**94** **95** Ar = Ph; **96** Ar = substituted 2-pyridyl **97** R = $SO_2Ph$; **98** R = H **99** **100** **101**

A diverse range of biaryls in which both aryl fragments are heteroaryl groups have been prepared using the Negishi reaction. The synthesis of heteroaryl substituted indoles has already been discussed above and a further example is compound **104** which was obtained from precursors **102** and **103** in 47% yield in a $Pd(PPh_3)_4$ catalysed reaction.[92] Biaryl **104** was subsequently used in the synthesis of Eudistomin U **105**.



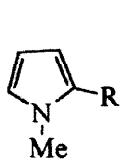
**102** **103** **104** **105**

The two heteroaryl pyrrole derivatives **107** (71%) and **108** (73%) have been prepared from the zinc reagent **106** and the appropriate heteroaryl bromide using $Pd(dppb)Cl_2$ as the catalyst.[2] 2-Furylzinc chloride and the appropriate pyridyl triflate afforded biaryl **109** (81%)[78] in a $Pd(PPh_3)_4$ catalysed reaction and the furylzinc chloride **110** and 4-chloropyridine gave the fluorescent heterocycle **111** (64%)[76] with $Pd(dppb)Cl_2$ as the catalyst. The imidazole derivatives **113** [60-93%, $Pd(PPh_3)_4$ catalyst] were prepared from zinc reagents **112** (R = Me, $CH_2OEt$, $SO_2NMe_2$) and 2-bromopyridine.[93]

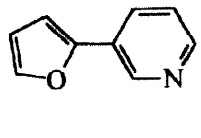
Teraryl analogues of the selenium containing heterocycle **60** have been prepared in low yield by the Negishi reaction[52] and the teraryl **65** has been synthesised in good yield (76%) from 2-thienylzinc chloride and 2,6-dibromopyridine in a $Pd(PPh_3)_4$ catalysed reaction.[94] 2-Thienylzinc bromide also reacted with the bromopyrimidine derivative **114** yielding the biaryl **115** [35%, $Ni(PPh_3)_4$ catalyst] which, after removal of the TMS groups, gave uracil analogues.[95]

2,3'-Bipyridyl (81%) was synthesised from 3-pyridylzinc iodide and 2-bromopyridine in a $Pd(PPh_3)_4$ catalysed reaction.[89] Pyridylzinc halides have also been coupled with a number of halo quinolines. Thus, 2-pyridylzinc bromide and 3-iodoquinoline afforded 3-(2-pyridyl)quinoline in moderate yield (53%) in a $Pd(PPh_3)_4$ catalysed reaction and 3-pyridylzinc iodide and 2-iodoquinoline gave 2-(3-pyridyl)quinoline (73%) with this catalyst.[90] Several substituted pyridylzinc halides were reacted with 6-haloquinol-2-one derivatives in $Pd(PPh_3)_4$ catalysed reactions giving a series of substituted 6-pyridylquinol-2-ones (36-96%).[96]

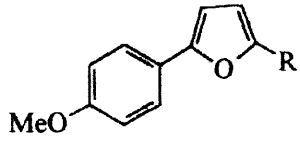
The bis-organozinc chloride **116** reacted with bromobenzene in a palladium catalysed reaction giving the oligomer **117** (87%) and with 1,4-dibromobenzene yielding the polymer **118** (94%). The thiophene analogue **73** of this polymer was also synthesised using a Negishi reaction.[97] Substituted α-linked polythiophenes[98-100] and poly(*para*-phenylene)[100] have been prepared using the Negishi reaction. Pyridyl-capped thiophene oligomers have also been prepared in moderate yield.[53]



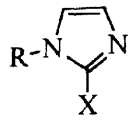
**106** R = ZnCl
**107** R = 2-pyridyl
**108** R = 3-thienyl



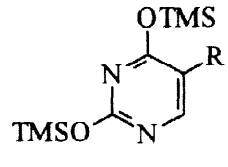
**109**



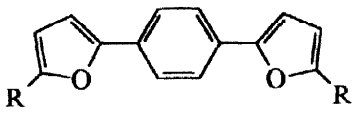
**110** R = ZnCl
**111** R = 4-pyridyl



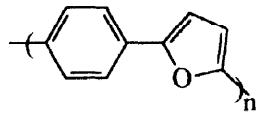
**112** X = ZnCl
**113** X = 2-pyridyl



**114** R = Br
**115** R = 2-thienyl



**116** R = ZnCl
**117** R = Ph



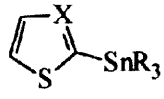
**118**

## 4. THE STILLE REACTION

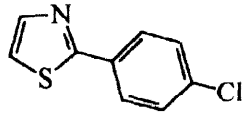
*4.1 Chemoselectivity and Regioselectivity*

The thiazole derivative **120** (R = Me) reacted with 4-bromochlorobenzene selectively at the bromo substituent yielding biaryl **121** (80%) in a $Pd(PPh_3)_2Cl_2$ catalysed reaction[101] and the pyrimidine derivative **122** gave product **123** (60%) with stannane **119** (R = Bu) with this catalyst.[102] The stannane **124** couples [$Pd(PPh_3)_4$ catalyst] selectively with halogenated pyrimidine and purine derivatives in good yield selectively at the stannyl group in a Stille reaction, and not at the boron moiety in a Suzuki reaction.[103,104] The boron-containing biaryl products of these reactions are of potential use in $^{10}B$ neutron capture therapy.

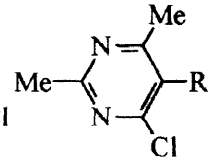
The dibromoimidazole **125** reacted at the 2-bromo substituent with $PhSnMe_3$ giving heterocycle **126** (58%) in a $Pd(PPh_3)_2Cl_2$ catalysed reaction.[105]



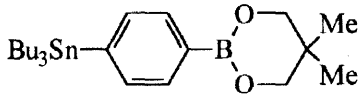
**119** X = CH
**120** X = N



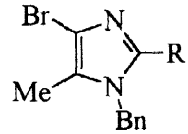
**121**



**122** R = I
**123** R = 2-thienyl



**124**

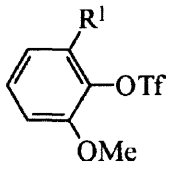


**125** R = Br
**126** R = Ph

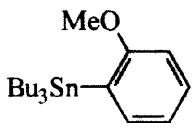
*4.2 Steric Considerations*

A number of *ortho* substituted biphenyls of general structure **129** have been successfully prepared in $Pd(PPh_3)_2Cl_2$ catalysed Stille reactions of the triflates **127** and $PhSnBu_3$ or stannane **128**.[106,107] For example, triflates **127** ($R^1$ = OMe) and **127** ($R^1$ = $CO_2Me$) gave biphenyls **129** ($R^1$ = OMe, $R^2$ = H) (74%) and **129** ($R^1$ = $CO_2Me$, $R^2$ = H) (87%) respectively with $PhSnBu_3$. However, when the more sterically demanding stannane **128** was reacted with these triflates, only the former triflate gave a product **129** ($R^1$ = $R^2$ = OMe) which was isolated either in low yield (33%) or in moderate yield (49%)[108] when CuBr was present as a co-catalyst. 4-Methyl-2,2',6,6'-tetramethoxybiphenyl-4'-carbaldehyde **130** has also been obtained (25%) in a related Stille reaction.[108] Mesityl bromide has been successfully arylated in a Stille reaction[109] and the phenylation of both 2,4-dinitroiodobenzene and 2,4,6-trinitroiodobenzene has been achieved.[110]

It is of particular interest to note that compound **83** could not be synthesised using a Stille reaction whereas a Negishi reaction gave a moderate yield of this compound and a Suzuki reaction afforded a good yield.[68]




127

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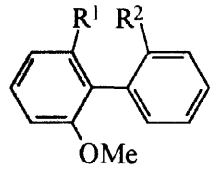
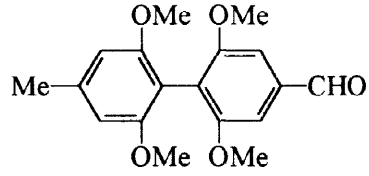



129




130

*4.3 General Survey of the Stille Reaction*

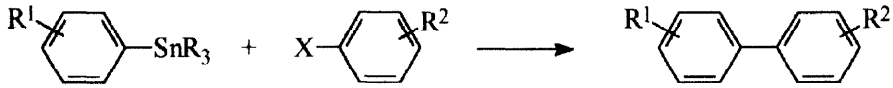
Arylstannanes possessing a tributyltin or trimethyltin moiety are the most commonly used biaryl precursors in the Stille reaction. Arylstannanes with fluorinated alkyl substituents have recently been developed for biaryl synthesis.[111] Arylstannoates, prepared from potassium hydroxide and $ArSnCl_3$ have been used to prepare biphenyl derivatives in good yield in an aqueous Stille reaction.[112,113] The Stille reaction is often improved by the addition of copper salts[114-116] and one explanation for this observation is that transmetallation of the arylstannane by the copper salt occurs yielding a more reactive organocopper reagent.

The coupling partner of the arylstannane is usually an aryl halide or an aryl triflate. When triflates are used, lithium chloride is almost always necessary as a co-reagent. Other coupling partners have also been used less frequently; for example diazonium salts[117] and hypervalent iodine reagents.[118]

Of particular current interest is the fact that the Stille reaction is also amenable to solid phase synthesis and the synthesis of biphenyl derivatives in solid phase reactions has been reported in several recent publications.[119-121]

**Table 3** illustrates a selection of Stille reactions which have yielded biphenyls as products. A number of

**Table 3**. Synthesis of Biphenyls using the Stille Reaction




| $R^1$ | $R^2$ | R | X | Catalyst | Yield (%) | Reference |
|---|---|---|---|---|---|---|
| H | H | Ph | Br | $BnPd(PPh_3)_2Cl$ | 78 | 122 |
| H | H | Bu | $IPh^+ BF_4^-$ | Pd/C | 95 | 118 |
| H | 4-Me | Bu | $N_2^+ BF_4^-$ | a | 59-66 | 117 |
| H | 4-$NO_2$ | Me | I | $ArPd(PPh_3)_2I$ | 83 | 110 |
| H | 4-COMe | Me | OTf | $Pd(PPh_3)_4$ | 85 | 123 |
| H | 4-COMe | Me/Bu | OTf | $Pd_2(dba)_3/AsPh_3$ | 74-82 | 124 |
| H | 4-COMe | Bu | b | c | 72 | 125 |
| 4-Cl | 4-CHO | Bu | Br | $Pd(PPh_3)_4$ | 75 | 109 |
| 4-Cl | 4-COMe | Bu | Br | $Pd(PPh_3)_4$ | 89 | 109 |
| 4-Me | 4-CN | Bu | Br | $Pd(PPh_3)_4$ | 92 | 109 |
| 4-Me | 4-$NO_2$ | Bu | Br | $Pd(PPh_3)_4$ | 68 | 109 |
| 4-Me | 4-COMe | Bu | Br | $Pd(PPh_3)_4$ | 90 | 109 |
| 2-OMe | 4-COMe | Bu | Tf | $Pd_2(dba)_3/AsPh_3$ | 88 | 124 |
| 4-OMe | 4-$NO_2$ | Bu | OMs | $Pd(PPh_3)_4$ | 48 | 126 |
| 4-OMe | 4-$NO_2$ | Bu | OTf | $Pd(PPh_3)_4$ | 74 | 123 |
| 2-CHO | 4-COMe | Bu | OTf | $Pd_2(dba)_3/AsPh_3$ | 25 | 124 |

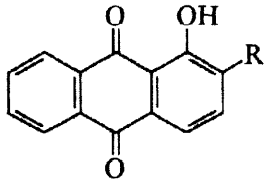
a $Pd(OAc)_2$ or $Pd(dba)_2$, b $OSO_2(4\text{-}FC_6H_4)$, c $Pd(OAc)_2$/ $Ph_2PMe$

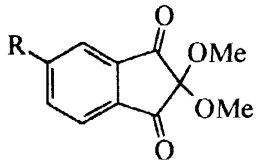
different palladium catalysts have been used and yields are generally good to excellent. Both 1-phenylnaphthalene **43** and 2-phenylnaphthalene **38** have been prepared in good yield [$Pd(dba)_2/PPh_3$ catalyst] from the appropriate naphthyl triflate and $PhSnBu_3$[127] and the triflates derived from salicylaldehyde[128] and substituted ethyl salicylates[129] have also been coupled with stannanes.

Byproducts resulting from the transfer of methyl or butyl groups from the stannanes $ArSnMe_3$ or $ArSnBu_3$ respectively to the coupling partner are frequently observed in the Stille reaction. One illustrative example[130] is the reaction of the anthraquinone triflate **131** with $PhSnMe_3$ in a $Pd(dppf)Cl_2$ catalysed reaction which gave a 2:1 mixture (85%) of phenylated product **134** and methylated product **132**. With $PhSnBu_3$ the reaction was more selective affording a 4:1 mixture (71%) of phenylated product **134** and butylated compound **133**. Other anthraquinone triflate derivatives were successfully phenylated.

5-Arylninhydrin derivatives with improved chromogenic and luminescent properties have been prepared using Stille and Suzuki methodologies. In one Stille reaction, bromide **135** reacted with 2-tributylstannylbenzo[*b*]thiophene [$Pd(PPh_3)_4$ catalyst] yielding product **136** (73%).[131]

**131** R = OTf
**132** R = Me
**133** R = Bu
**134** R = Ph



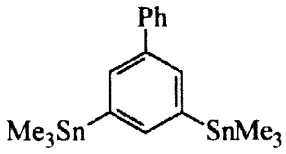


**135** R = Br
**136** R = 2-benzo[*b*]thienyl

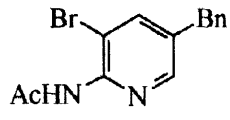
Numerous heterobiaryls possessing one heterocyclic and one carbocyclic moiety have been successfully prepared using the Stille reaction as indicated in **Table 4** (following page). The entries listed in **Table 4** have been grouped into two types depending upon whether a heteroaromatic (method A) or carbocyclic aromatic (method B) stannane precursor was used and generally either synthetic method gave good yields.

The arylstannane, $PhSnMe_3$, has also be generated *in situ* from bromobenzene and $Me_3SnSnMe_3$. In the presence of 2-pyridyl triflate and $Pd(PPh_3)_4$ as the catalyst, 2-phenylpyridine (55%) is produced. Other bromobenzene derivatives also gave moderate yields (35-50%) of substituted 2-phenylpyridines and 3-bromopyridine and 2-bromothiophene similarly yielded 2,3'-bipyridyl (53%) and 2-(2-thienyl)pyridine **61** (63%) respectively.[138]

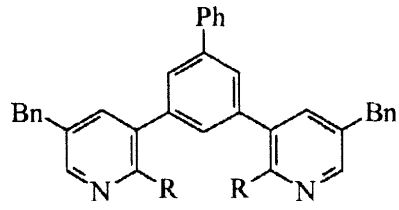
The Stille reaction has been used to synthesise reaction templates. Thus, the bis-stannane **137** and pyridine derivative **138** yielded the teraryl **139** [(60%), $Pd(PPh_3)_2Cl_2$ catalyst] which was then converted in three steps into the template **140**. This template was designed to hydrogen bond the substrates **141** and **142** prior to nucleophilic substitution of compound **141** with compound **142**.[139]



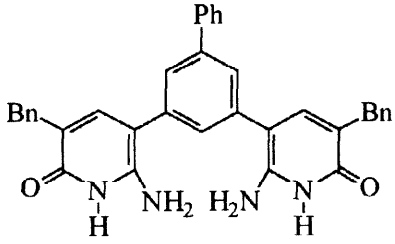
**137**



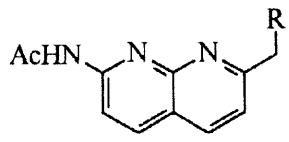
**138**



**139** R = NHAc

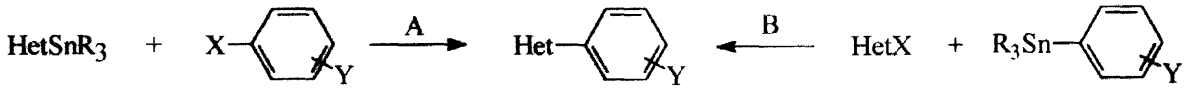


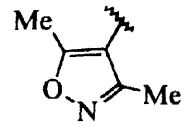
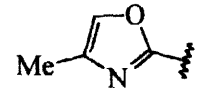
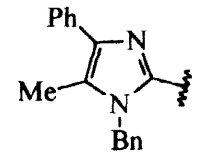
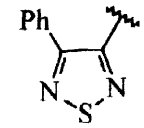
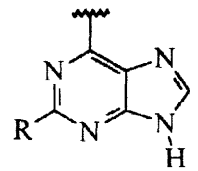
**140**



**141** R = $NH_2$
**142** R = Br

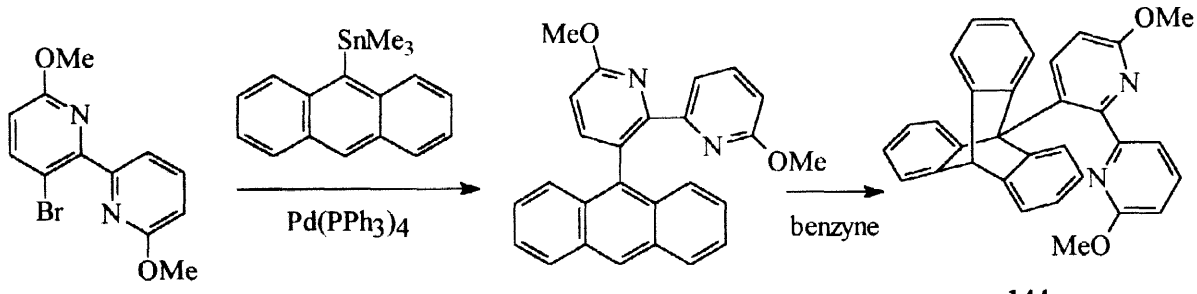
**Table 4**. Synthesis of Heterobiaryls using the Stille Reaction




| A/B | Het | Y | R | X | Catalyst | Yield (%) | Ref. |
|---|---|---|---|---|---|---|---|
| A | 2-thienyl | H | Bu | $IPh^+ BF_4^-$ | $PdCl_2$ | 87 | 118 |
| B | 2-thienyl | H | Bu | I | Pd/C | 77 | 114 |
| A | 2-thienyl | 2-$CO_2$Me | Bu | I | $Pd(PPh_3)_2Cl_2$ | 81 | 101 |
| A | 2-furyl | 4-$CO_2$Me | Me | I | $Pd(PPh_3)_2Cl_2$ | 73 | 101 |
| A | 1-methyl-2-pyrrolyl | H | Me | I | $Pd(PPh_3)_2Cl_2$ | 54 | 101 |
| B |  | H | Bu | I | $Pd(PPh_3)_2Cl_2$ | 58 | 132 |
| A |  | H | Me | I | $Pd(PPh_3)_4$ | 80 | 133 |
| A | " | 4-COMe | Me | I | $Pd(PPh_3)_4$ | 100 | 133 |
| A | 1-methylimidazol-2-yl | H | Bu | Br | $Pd(PPh_3)_2Cl_2$ | 89 | 134 |
| A | " | 2/3/4-$CH_2R^a$ | Bu | Br | $Pd(PPh_3)_2Cl_2$ | 24-69 | 134a |
| B |  | H | Me | Br | $Pd(PPh_3)_2Cl_2$ | 60 | 105 |
| B |  | 4-Cl | Bu | Cl/Br/OTf | $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ | 7-90 | 135 |
| A | 2-benzo[*b*]thienyl | 4-COPh | Bu | I | Pd/C | 60 | 114 |
| A | 2-benzothiazoyl | H | Bu | Br | $Pd(PPh_3)_2Cl_2$ | 75 | 134 |
| B | 2-benzothiazoyl | H | Bu | Cl | $Pd(PPh_3)_2Cl_2$ | 86 | 134 |
| A | 2-benzoxazoyl | H | Bu | Br | $Pd(PPh_3)_2Cl_2$ | 75 | 134 |
| A | 2-pyridyl | 4-$CO_2$Me | Me | I | $Pd(PPh_3)_2Cl_2$ | 95 | 101 |
| B | 2-quinolyl | H | Bu | OTf | $Pd(PPh_3)_2Cl_2$ | 88 | 136 |
| B | 8-quinolyl | H | Bu | b | c | 68 | 125 |
| B | 2-isoquinolyl | H | Bu | OTf | $Pd(PPh_3)_2Cl_2$ | 53 | 136 |
| B |  R = H, $NH_2$ | H | Bu | Cl | $Pd(PPh_3)_2Cl_2$ | 73-81 | 137 |

a R = $P(O)OEt_2$, b $OSO_2(4\text{-}FC_6H_4)$, c $Pd(OAc)_2$/ $Ph_2PMe$

Materials for use in the nanotechnology field have been prepared using Stille methodology. The 'molecular brake' **144** has been synthesised from the bipyridyl precursor **143** as shown in **Scheme 4**. The bipyridyl moiety of heterocycle **144** can coordinate to a suitable metal and thus activate the 'brake'.[140]



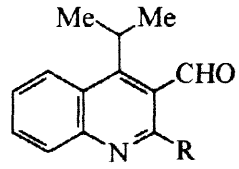

**143** **144**

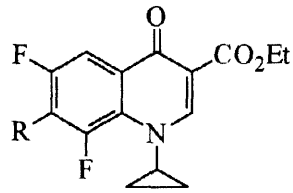
**Scheme 4**

The Stille reaction has been used to prepare a number of arylated quinoline derivatives of medicinal interest and two relevant examples include the preparation of compound **146** [95%, $Pd(PPh_3)_4$ catalyst], an intermediate in the synthesis of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR) inhibitors, from triflate **145** and 4-$FC_6H_4SnBu_3$[141] and the preparation of the anti-bacterial quinolones **148** [5-74%, $Pd(PPh_3)_2Cl_2$ catalyst] from bromides **147** and appropriate pyridylstannanes.[142]

Several groups have reported the synthesis of 2-arylated indole derivatives in excellent yields from a 2-stannylated indole and an aryl halide.[143-145] Numerous arylated pyrimidines,[102,146,147,147a] pyrazines and pyrazine *N*-oxides[148,149] have been prepared using a Stille reaction.

**145** R = OTf
**146** R = 4-fluorophenyl



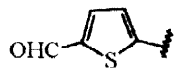
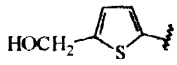
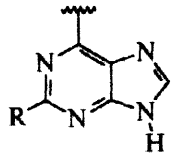
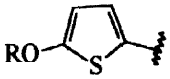
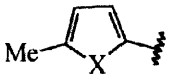
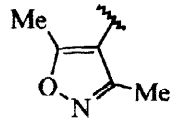
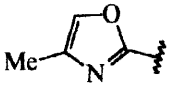
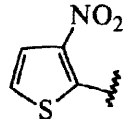

**147** R = Br
**148** R = substituted pyridyl

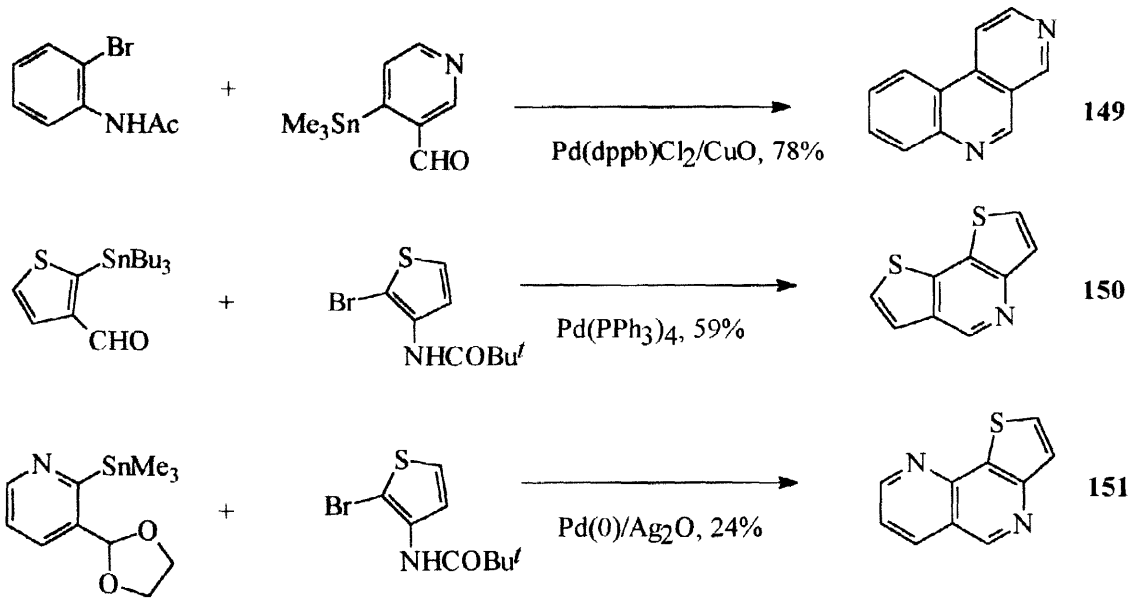
A diverse variety of biaryls in which both aryl fragments are heterocyclic moieties have been prepared using the Stille reaction and some representative examples are shown in Table 5 (following page). The yields of products are generally good to excellent and $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ are usually employed as the reaction catalysts.

The fused tricyclic heteroaromatic compounds **149**[155], **150**[156] and **151**[153] have been prepared using the Stille reaction as shown in **Scheme 5**. The initially formed biaryls were not isolated but the adjacent aldehyde or protected aldehyde and substituted amine substituents underwent cyclisation giving the products. Other isomers of the heterocycles shown in **Scheme 5** have also been prepared in a similar fashion.[157,158] In the synthesis of compound **149**, it was noted that the yield was increased from 43% to 78% by the addition of CuO and the formation of compound **151** was promoted by the addition of $Ag_2O$.

**Table 5.** Synthesis of Heterobiaryls using the Stille Reaction

$$Het^1SnR_3 + Het^2X \rightarrow Het^1\text{-}Het^2$$

| $Het^1$ | $Het^2$ | R | X | Catalyst | Yield (%) | Reference |
|---|---|---|---|---|---|---|
| 2-thienyl | 2-thienyl | Bu | I | $Pd(PPh_3)_2Cl_2$ | 80 | 150 |
| 2-thienyl | 2-thienyl | Bu | $IPh^+ BF_4^-$ | $PdCl_2$ | 94 | 118 |
| 2-thienyl | 2-quinolyl | Bu | OTf | $Pd(PPh_3)_4$ | 71 | 136 |
| 2-thienyl |  | Bu | I | $Pd(PPh_3)_2Cl_2$ | 71 | 150 |
| 2-thienyl |  | Bu | I | $Pd(PPh_3)_2Cl_2$ | 79 | 150 |
| 2-thienyl |  R = H, $NH_2$ | Bu | Cl | $Pd(PPh_3)_2Cl_2$ | 76-81 | 137 |
|  R = Me, Bu | 2/3/4-pyridyl | Me | Br | $Pd(PPh_3)_4$ | 77-82 | 151 |
|  X = O,S |  | Bu | I | $Pd(PPh_3)_2Cl_2$ | 84-85 | 132 |
| 2/4/5-thiazoyl | 2/4/5-thiazoyl | Me | Br | $Pd(PPh_3)_4$ | 59-77 | 152 |
|  | 3-pyridyl | Me | Br | $Pd(PPh_3)_4$ | 100 | 133 |
| " | 2-quinoloyl | Me | Br | $Pd(PPh_3)_4$ | 92 | 133 |
| 2-pyridyl |  | Bu | Br | $Pd(PPh_3)_4$ | 51 | 153 |
| 2-pyridyl | 2-thiazoyl | Bu | Br | $Pd(PPh_3)_4$ | 60 | 153 |
| 2-pyridyl | 4-pyridyl | Bu | Br | $Pd(PPh_3)_4$ | 70 | 153 |
| 2/3/4-pyridyl | 2/3/4-pyridyl | Me | Br | $Pd(PPh_3)_4$ | 59-77 | 154 |
| 3-quinolyl | 2-pyridyl | Me | Br | $Pd(PPh_3)_4$ | 79 | 154 |

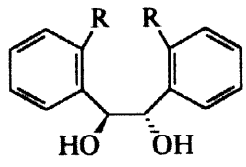



**Scheme 5**

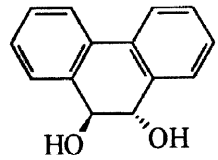
The Stille reaction has also been successfully used in the preparation of teraryls, oligoaryls and polyaryls. In the thiophene field, α-terthiophene **56** (61%)[150] has been synthesised from 2,5-diiodothiophene and 2-tributylstannylthiophene; methoxy-substituted ter-, quater- and quinquethiophenes have been prepared;[159] thiophene tetramers and seximers possessing 2-hydroxyethyl substituents have been synthesised as potential precursors of water soluble thiophene oligomers[160,161] and trimethylsilyl-capped oligothiophenes have been reported.[162] Long-chain alkyl and alkoxy derivatives of polymer **73**[163,164] have been reported and thiophene-containing photorefractive polymers have been prepared.[165] Several types of 'donor-acceptor' polymers have also been synthesised using the Stille reaction.[166]

Dihalo- thiophenes, thiazoles and pyridines have been coupled to stannanes derived from furan, thiophene, selenophene and thiazole yielding a plethora of teraryls.[167] Terthiazoles,[152] terpyridines,[168] quaterpyridines[169,170] and oligopyridines[170] are also available using the Stille reaction.

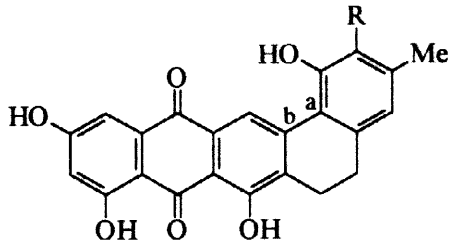
The Stille reaction has enjoyed considerable success in the synthesis of a large number of natural products which possess a biaryl moiety. In the formulae which follow, the letters 'a' and 'b' have been used to denote the origin of the aryl-aryl bond in each of the natural product synthesis and the yields refer to the biaryl formation step. The chiral 9,10-dihydrophenanthrenediol unit **153** of pradimicins and benanomicins has been prepared (48-88%) from the precursors **152** (R = Br, I, OTf) in a $Pd(PPh_3)_4$ catalysed reaction in the presence of either $(Me_3Sn)_2$ or $(Bu_3Sn)_2$.[170a] One of the R substituents in compounds **152** is converted into the appropriate stannyl group by the tin reagent and a subsequent Stille reaction then occurs. The pentacyclic benzo[*a*]naphthacenequinone natural products G-2N **154** (R = H) and G-2A **154** (R = $CO_2H$) have both been prepared from a common precursor, ester **154** (R = $CO_2Me$), which was synthesised in 44% yield using an intramolecular Stille reaction.[171] In this reaction, the arylstannane coupling partner was generated *in situ* from the corresponding aryl bromide with $(Me_3Sn)_2$. The naphthylisoquinoline alkaloid, Pindikamine A **156** has been prepared in several steps from the precursor **155** which was synthesised using a Stille reaction.[172] A stannyl analogue of compound **92** has been used in the synthesis of Moracin M **93**.[83]



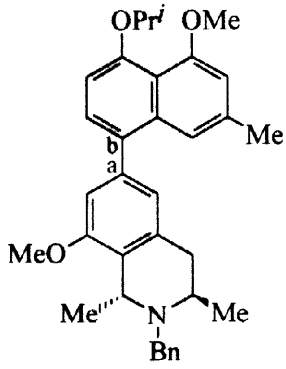
152



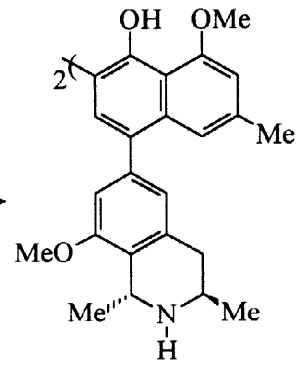
153



154
a=OTf, b=Br (see text)
$(Me_3Sn)_2$/ $Pd(PPh_3)_4$, 44%

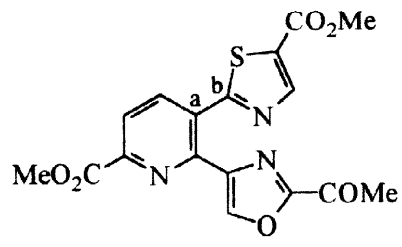


155
a=OTf, b=$SnBu_3$
$Pd(PPh_3)_2Cl_2$/ $PPh_3$ / CuBr, 63%

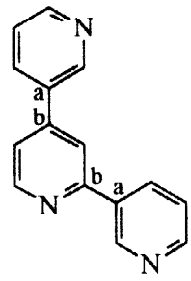


156

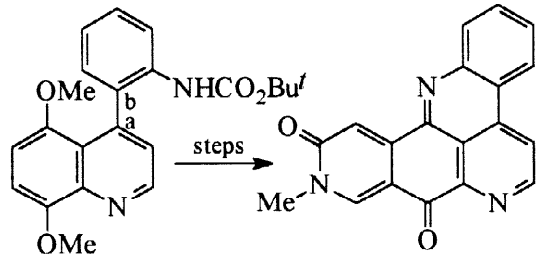
In the area of pyridine natural products, Dimethyl Sulfomycinamate **157**, the methanolysis product of the antibiotic Sulfomycin I has been prepared.[173,174] The 2-stannylthiazole coupling partner of the pyridine triflate was prepared *in situ* from the corresponding bromothiazole in this coupling reaction. Several model coupling reactions were also investigated. The terpyridyl, Nicotelline **158** has been prepared from 3-bromopyridine and 2,4-bis(trimethylstannyl)pyridine.[154] The quinoline derivatives **159** and **161** have both been converted into the cytotoxic alkaloid Amphimedine **160**[175] and the non-natural isomer, Isoasididemin **163**,[176] of the pentacyclic alkaloid Ascididemin **162** respectively. The synthesis of compound **161** also provides another example of chemoselectivity in the Stille reaction; the quinolyl precursor to compound **161** reacted at the triflate group and not at the 6-bromo substituent. Continuing the theme of quinoline chemistry, the alkaloid Dubamine **164**[123] and the pyridylquinoline **165**[177] have also been prepared using Stille methodology. Compound **165** and related derivatives were prepared as analogues of the anti-tumor antibiotic Streptonigrin.



157
a=OTf, b=Br (see text)
$(Bu_3Sn)_2$/ $Pd(PPh_3)_4$/ $Pd(PPh_3)_2Cl_2$, 35%

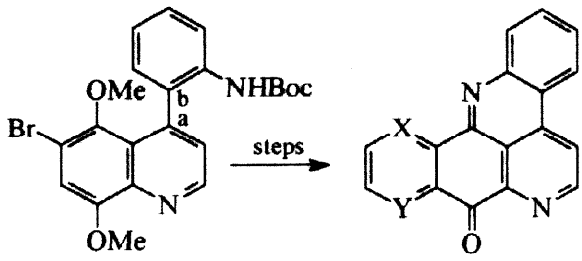


158
a=Br, b=$SnMe_3$
$Pd(PPh_3)_4$, 48%



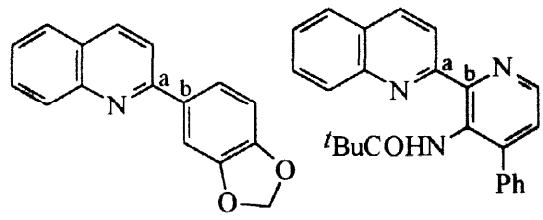
159
a=OTf, b=$SnMe_3$
$Pd(PPh_3)_4$, 87%

160



**161**
a=OTf, b=$SnMe_3$
$Pd(PPh_3)_4$/ CuBr, 60-64%

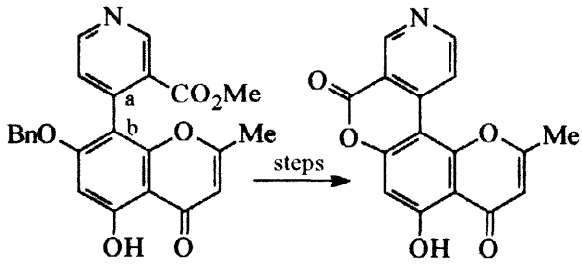
**162** X=CH, Y=N
**163** X=N, Y=CH



**164**
a=OTf, b=$SnMe_3$
$Pd(PPh_3)_4$, 79%

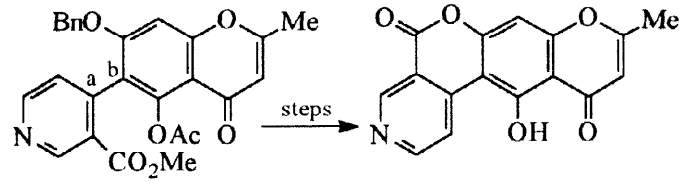
**165**
a=$SnMe_3$, b=OTf
$Pd(PPh_3)_4$, 67%

The lactones, Schumanniophytine **167** and Isoschumanniophytine **169** have both been prepared from the pyridylchromones **166** and **168** respectively.[178] The indole alkaloid, Hippadine **172** has been prepared by two methods. In one method,[179] the biaryl **170** was prepared using a Stille reaction and was subsequently converted into Hippadine **172** and in another method an intramolecular cyclisation (68% yield) of a dibromo precursor in the presence of $(Bu_3Sn)_2$ (which transforms one bromo substituent into a tributylstannyl group) was used.[180] Pratosine **173** was also prepared from biaryl **170**.[179] Phenylation of the carbazole triflate precursor of compound **175** with $PhSnMe_3$ resulted in the loss of the $CO_2Bu^t$ group giving Hyellazole **174** directly.[181] Micrococcinic acid **176** has been prepared using Stille methodology to form all of the aryl-aryl bonds.[182]



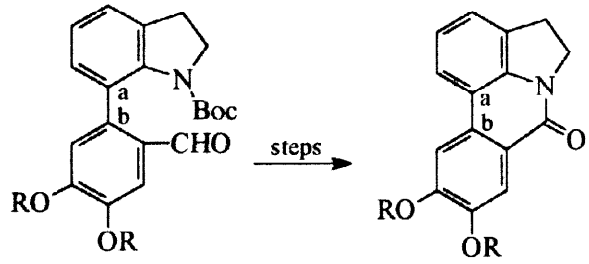
**166**
a=$SnMe_3$, b=Br
$Pd(PPh_3)_2Cl_2$, 25%

**167**



**168**
a=$SnMe_3$, b=Br
$Pd(PPh_3)_2Cl_2$, 36%

**169**

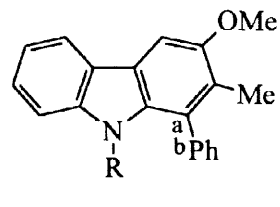


**170** R = $-CH_2-$
a=$SnBu_3$, b=Br
$Pd(OAc)_2$/ P(*o*-tolyl)$_3$/ $Et_3N$, 63%

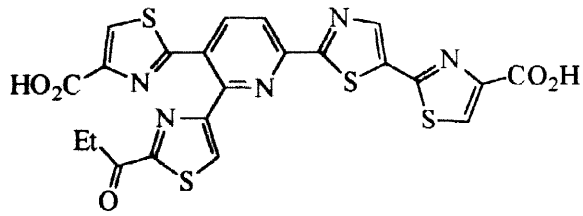
**171** R = Me
a=$SnBu_3$, b=Br
$Pd(OAc)_2$/ P(*o*-tolyl)$_3$/ $Et_3N$, 65%

**172** R = $-CH_2-$
a=b=Br (see text)
$(Bu_3Sn)_2$/ $Pd(PPh_3)_2Cl_2$, 68%

**173** R = Me



**174** R = H, 63%
**175** R = $CO_2Bu^t$
a=$OSO_2CF_3$, b=$SnMe_3$
$Pd(PPh_3)_4$

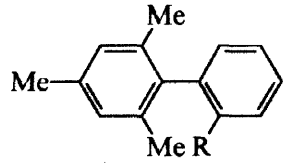


**176** Micrococcinic acid

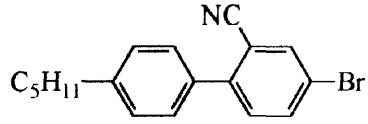
## 5. THE SUZUKI REACTION

*5.1 Chemoselectivity and Regioselectivity*

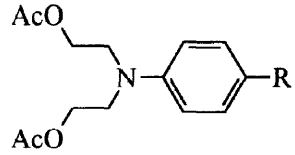
Phenylboronic acid reacted with 4-bromochlorobenzene exclusively at the bromo substituent giving 4-chlorobiphenyl **6** (74%) in a $Pd(PPh_3)_4$ catalysed reaction.[183] Mesitylboronic acid coupled with 2-chloroiodobenzene (94%) and 2-bromoiodobenzene (56%) [$Pd(PPh_3)_4$ catalyst, $Ba(OH)_2$ base] giving the biphenyl derivatives **177** and **178** respectively.[184] Both 3-bromoiodobenzene and 4-bromoiodobenzene have been coupled sequentially with *meta*-tolylboronic acid and then phenylboronic acid yielding methylated *meta*- and *para*-terphenyl derivatives respectively in good yield.[185] 3-Bromo-5-iodobenzonitrile reacted with 4-(*n*-pentyl)phenylboronic acid at the iodo substituent [$Pd(PPh_3)_4$ catalyst] affording the biphenyl derivative **179** in 74% yield.[186] Other boronic acids similarly coupled with 3-bromo-5-iodobenzonitrile.[186,187] Only a low selectivity was observed when boronic acids were reacted with 2,5-dibromobenzonitrile in a 1:1 ratio but with a 2:1 ratio of reactants coupling occurred at both bromo substituents giving terphenyls in moderate yield.[186] Although alkyl substituted derivatives of 4-bromophenylboronic acid polymerise yielding alkylated poly(*para*-phenylenes),[188] 4-bromophenylboronic acid and the iodoaniline **180** gave the biphenyl product **181** in a Suzuki reaction.[189] One bromo substituent in 1,3,5-tribromobenzene can be selectively replaced by phenylboronic acid giving 3,5-dibromobiphenyl in 67% yield.[139]



**177** R = Cl
**178** R = Br



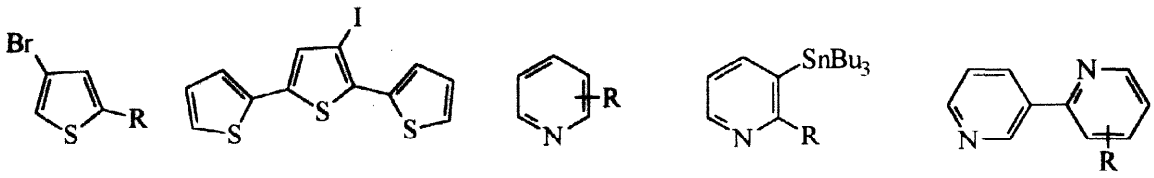
**179**



**180** R = I
**181** R = 4-Br$C_6H_4$

2,4-Dibromothiophene reacted regiospecifically with both 2- and 3-thienylboronic acids giving the bithienyls **182** (35%) and **183** (65%) respectively in a $Pd(PPh_3)_4$ catalysed reaction.[190] 2,3,5-Triiodothiophene and 2-thienylboronic acid afforded the terthiophene derivative **184** (60%) in which two of the iodo substituents have been replaced.[190]

The pyridylborane **185** reacted selectively [$Pd(PPh_3)_4$ catalyst] at the bromo substituent of pyridine derivative **187** in a Suzuki reaction rather than at the stannyl group in a Stille reaction giving the bipyridyl **188** in 86% yield.[191] With 2,3-dichloropyridine and 2,4-dichloropyridine this borane **185** reacted selectively at the 2-positions affording bipyridyls **189** (92%) and **190** (57%) respectively.[191] 2,6-Dichloropyridine can be mono-arylated with borane **185** giving bipyridyl **191**[192] and 2,6-dibromopyridine gave bipyridyl **192** (67%) and 6-bromo-2,4'-bipyridyl (57%) with boranes **185** and **186** respectively.[193] 2,5-Dichloropyridine was selectively phenylated (71%) at the 2-position by phenylboronic acid yielding 2-chloro-6-phenylpyridine in a $Pd(dppb)Cl_2$ catalysed reaction.[194,195] In pyrimidine chemistry, the iodo substituent of compound **78** has been replaced in preference to the chloro substituent in a Suzuki reaction using phenylboronic acid.[64]



**182** R = 2-thienyl
**183** R = 3-thienyl

**184**

**185** R = 3-$BEt_2$
**186** R = 4-$BEt_2$

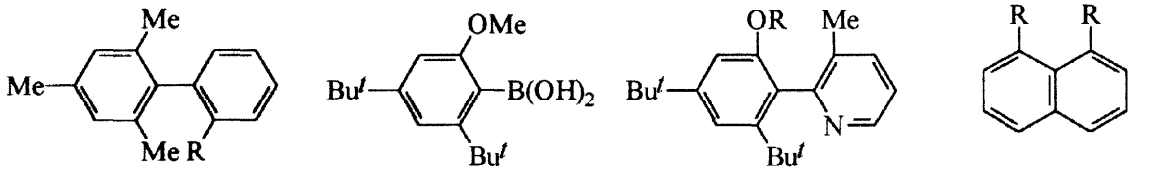
**187** R = Br
**188** R = 3-pyridyl

**189** R = 3-Cl
**190** R = 4-Cl
**191** R = 6-Cl
**192** R = 6-Br

*5.2 Steric Considerations*

The synthesis of compounds **177** and **178** in a Suzuki reaction illustrates that biphenyl derivatives possessing three *ortho* substituents are readily available. The related biphenyl derivatives **193**,[184] **194**[184,196] and **195**[197] have also been prepared using Suzuki methodology and further examples of the preparation of biphenyls possessing three *ortho* substituents in natural product chemistry are given below in Section 5.3. The most commonly used base in the Suzuki reaction is $Na_2CO_3$ and this base is often ineffective with sterically demanding coupling reactions. If $Ba(OH)_2$ or $K_3PO_4$ is used in sterically demanding reactions, good yields of products are usually obtained.[196]

The boronic acid **196** and 2-bromo-3-methylpyridine gave the biaryl **198** [$Pd(PPh_3)_4$ catalyst, $KOBu^t$ base] in 83% yield. This compound was subsequently demethylated affording the phenolic derivative **197** which, after resolution, was used as a chiral ligand for the enantioselective addition of $Et_2Zn$ to arylaldehydes.[198] The bis-borane **199** and 3-bromopyridine gave product **200** in high yield in a $Pd(PPh_3)_4$ catalysed reaction.[199]



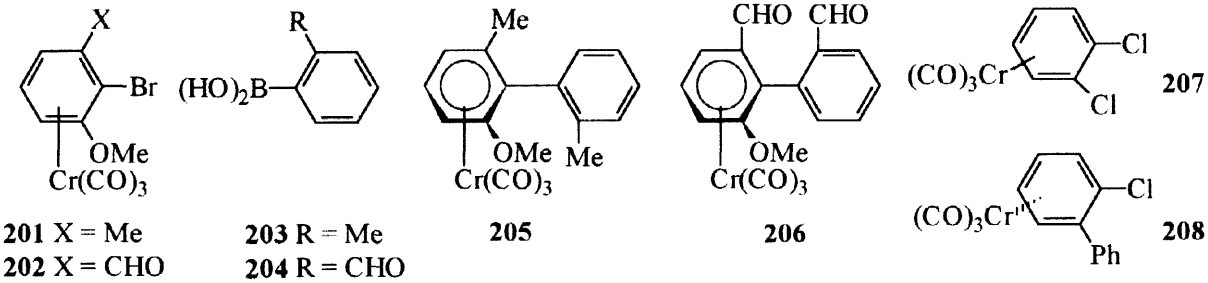
**193** R = OMe
**194** R = CHO
**195** R = $NO_2$

**196**

**197** R = H
**198** R = OMe

**199** R = $BEt_2$
**200** R = 3-pyridyl

Chromium tricarbonyl complexes of bromobenzene derivatives have been coupled with boronic acids yielding biaryls with axial chirality in $Pd(PPh_3)_4$ catalysed reactions in the presence of $Na_2CO_3$.[200] Thus, compound **201** and boronic acid **203** afforded product **205** (96%) whereas compound **202** and boronic acid **204** gave biaryl **206** (43%). Other chromium tricarbonyl complexes and boronic acids similarly gave related biaryl products. Complex **207** reacted with phenylboronic acid in the presence of the chiral ligand, (*S*)-(*R*)-PPFA, yielding a 73:27 mixture (55%) of compound **208** (69% ee) and the corresponding achiral diphenylation product.[201] Similar results were obtained with 2-tolylboronic acid although the ee was lower.



**201** X = Me
**202** X = CHO

**203** R = Me
**204** R = CHO

**205**

**206**

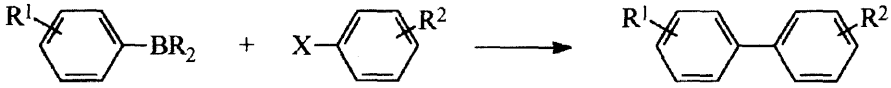
**207**

**208**

*5.3 General Survey of the Suzuki Reaction*

The preparation of biphenyls using Suzuki methodology is well documented in the literature and some representative examples are given in **Table 6**. The yield of biphenyl products are invariably good to excellent.

**Table 6.** Synthesis of Biphenyls using the Suzuki Reaction



| $R^1$ | $R^2$ | R | X | Catalyst | Base | Yield (%) | Reference |
|---|---|---|---|---|---|---|---|
| H | H | OH | OTf | $Pd(PPh_3)_4$ | $K_3PO_4$ | 83 | 202 |
| H | 4-OH | OH | I | $Pd(OAc)_2$ | $Na_2CO_3$ | 80 | 203 |
| H | 4-OMe | $O(CH_2)_3O$ | I | $Pd(dppe)Cl_2$ | TlOH | 82 | 204 |
| H | 4-CHO | OH | Br | $Pd/C+PPh_3$ | $Na_2CO_3$ | 96 | 205 |
| H | 2/3/4-$CO_2H$ | OH | I | $Pd(OAc)_2$ | $Na_2CO_3$ | 60-95 | 202, 206 |
| H | 4-$CO_2Me$ | OH | Br | $Pd(PPh_3)_4$ | $Na_2CO_3$ | 94 | 183 |
| H | 2-$NO_2$ | OH | Br | $Pd(PPh_3)_4$ | $Na_2CO_3$ | 98 | 197 |
| 4-F | H | OH | I | $Pd(OAc)_2$ | $Na_2CO_3$ | >95 | 207 |
| 4-F | 4-CHO | OH | Br | $Pd/C+PPh_3$ | $Na_2CO_3$ | 84 | 205 |
| 4-Me | 4-OMe | OH | OTf | $Pd(PPh_3)_4$ | $K_3PO_4$ | 85 | 208 |
| 4-Me | 4-$SO_3Na$ | OH | Br | a | $Na_2CO_3$ | 78 | 209 |
| 4-Me | 4-$NO_2$ | OH | OTf | $Pd(PPh_3)_4$ | $K_3PO_4$ | 82 | 202, 208 |
| 2-CHO | 4-Me | OH | I | $Pd(PPh_3)_4$ | $Na_2CO_3$ | 54[b] | 196 |
| 2-CHO | 4-Me | $O(CH_2)_3O$ | I | $Pd(PPh_3)_4$ | $K_3PO_4$ | 89 | 196 |
| 2-CHO | 2-$NO_2$ | OH | Br | $Pd(PPh_3)_4$ | $Et_3N$ | 82 | 210 |
| 2-$CONPr^i_2$ | H | OH | Br | $Pd(PPh_3)_4$ | $Na_2CO_3$ | 82 | 211 |
| 2-$CONPr^i_2$ | 2-$CONEt_2$ | OH | Br | $Pd(PPh_3)_4$ | $Na_2CO_3$ | 44 | 211 |
| 3-$NO_2$ | H | OH | Br | $Pd(PPh_3)_4$ | $Na_2CO_3$ | 95 | 197 |
| 4-$NO_2$ | 4-COMe | OBu | Br | $Pd(PPh_3)_4$ | $Tl_2CO_3$ | 90 | 204 |

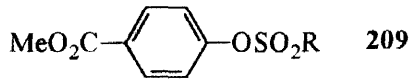
a $Pd[Ph_2P(3\text{-}SO_3H.C_6H_4)]_3$, b deboronylation also occurs giving benzaldehyde (39%)

In addition to the biphenyls listed in **Table 6**, other more highly substituted biphenyls,[212-218,218a] related compounds such as arylated naphthalenes,[207,219] arylated binaphthyls[220] and phenanthrenes[219] have also been prepared using the Suzuki reaction. Appropriately *ortho* substituted biphenyls have been synthesised as precursors to phenanthrols[214] and nitrofluorenones.[215] Biphenyl derivatives can also be prepared using solid phase synthesis.[121,221,222]

Other applications of the Suzuki reaction in biphenyl chemistry include the preparation of butylated hydroxybiphenyls as anti-oxidants,[223] 5-arylninhydrin derivatives from compound **135** and arylboronic acids,[131] and liquid crystals.[186,187,224,225] Biphenyl derivatives have also been synthesised for the medicinal chemistry field; examples include amino acid analogues[226-228] and *N*-methyl-D-aspartate (NMDA) antagonists.[229]

Borates such as $Ph_4BNa$ are frequently used as coupling partners of arylhalides in the Suzuki reaction and several biphenyl derivatives have been prepared using this methodology.[203,230] Borates of general structure $Ar^1XB(OR)_2^-$ $Li^+$ (X = Me, Bu) gave biphenyls ($Ar^1$-$Ar^2$) with mesylates ($Ar^2OMs$) in $Ni(PPh_3)_2Cl_2$ catalysed reactions.[231]

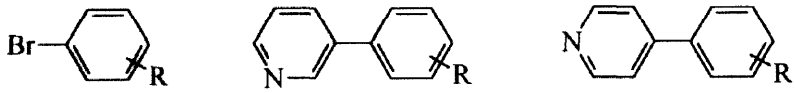
The reaction of phenylboronic acid with esters of general structure **209** (R = Me, $CF_3$, Ph, 4-$FC_6H_4$, 4-$MeC_6H_4$) has been studied. The best yield of methyl biphenyl-4-carboxylate was obtained with the triflate **209** (R = $CF_3$).[232]



**209**

The fluoride anion can also be used as a base in the Suzuki reaction. Thus, phenylboronic acid has been reacted with a range of bromobenzene derivatives [$Pd(PPh_3)_4$ catalyst] in the presence of a variety of fluoride sources ($Et_4NF$, $Bu_4NF$, CsF or KF) and biphenyls were produced generally in good yield.[233]

There are many examples of the synthesis of heterobiaryls possessing one heterocyclic and one carbocyclic ring. In pyridine chemistry for example, borane **185** has been coupled [$Pd(PPh_3)_4$ catalyst] with bromoaryls **210** (R = 2- or 4-Cl, Me, OMe, COMe, $CO_2Me$, $NO_2$) affording heterobiaryls **211** in 53-87% yield[234] and borane **186** also gave heterobiaryls **212** (R = 2- or 4-Me, $CO_2Me$, $NO_2$) in 47-77% yield.[193] Other arylated pyridines,[185,202,204,208,209,211,235,236] pyrazines,[185,194,236,237,238] pyrimidines,[185,194] quinolines,[194,239-241] imidazoles,[105] furans,[241a] thiophenes,[210,211] indoles,[242-244,244a] and porphyrins[245-247] have similarly been prepared using the Suzuki reaction.



**210** **211** **212**

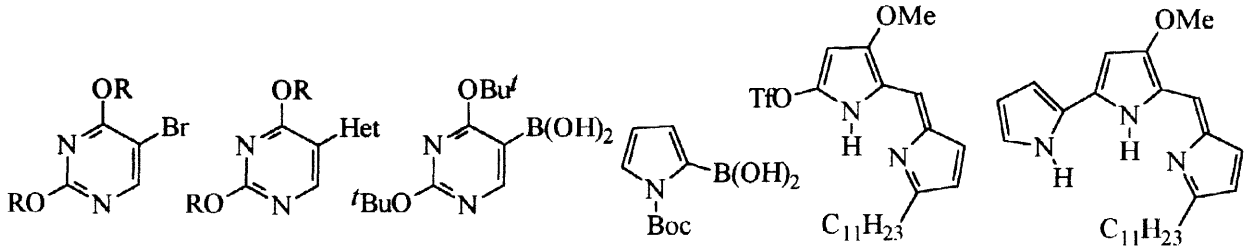
The preparation of heterobiaryls using the Suzuki reaction in which both aryl moieties are heterocycles has attracted considerable attention and some illustrative examples of the synthesis of parent heterobiaryls are shown in **Table 7**. The catalyst in all of the reactions cited in **Table 7** was $Pd(PPh_3)_4$ and the yields of products are generally good to excellent. Numerous substituted derivatives of the heterocycles listed in **Table 7** have also been prepared.

**Table 7.** Synthesis of Heterobiaryls using the Suzuki Reaction

$$Het^1BR_2 + Het^2X \rightarrow Het^1\text{-}Het^2$$

| $Het^1$ | $Het^2$ | R | X | Base | Yield (%) | Reference |
|---|---|---|---|---|---|---|
| 2-thienyl | 3-thienyl | OH | Br | $Na_2CO_3$ | 40-70 | 248 |
| 3-thienyl | 2-thienyl | OH | Br | $Na_2CO_3$ | 72 | 249 |
| 3-thienyl | 3-thienyl | OH | Br | $Na_2CO_3$ | 70 | 248,249 |
| 2-thienyl | 2/3/4-pyridyl | OH | Br | $Na_2CO_3$ | 57-68 | 250 |
| 3-thienyl | 2/3/4-pyridyl | OH | Br | $Na_2CO_3$ | 69-74 | 250 |
| 5-indolyl | 2/3-furyl | OH | Br | $NaHCO_3$ | 65-82 | 242 |
| 5-indolyl | 2/3-thienyl | OH | Br | $NaHCO_3$ | 78-86 | 242 |
| 5-indolyl | 2/3/4-pyridyl | OH | Br | $NaHCO_3$ | 65-90 | 242 |
| 3-pyridyl | 2-pyridyl | Et | Cl/Br | KOH | 82-85 | 192 |
| 4-pyridyl | 2/3-thienyl | Et | Br | $Na_2CO_3$ | 66-67 | 193 |
| 4-pyridyl | 3-pyridyl | Et | Br | $Na_2CO_3$ | 64 | 193 |
| 4-pyridyl | 2/3-quinoloyl | Et | Br | $Na_2CO_3$ | 70-74 | 193 |

A number of uracil analogues have been synthesised as potential anti-viral agents using the Suzuki reaction.[95,251,252] For example, pyrimidine derivatives **213** and **214** have been coupled with heteroaryl boronic acids, $HetB(OH)_2$ (Het = 2/3-thienyl, 2/3-selenyl *etc*) giving biaryls **215** and **216** respectively which, after removal of the *O*-protecting group, give uracil analogues. Heteroaryl bromides can also be coupled with boronic acid **217** giving products **216**.[95] The pyrrole-containing immunosuppressive-agent undecylprodigiosine **220** has been synthesised using a Suzuki reaction of boronic acid **218** and triflate **219**.[253] The Boc group of boronic acid **218** is lost during the coupling process.



**213** R = Bn
**214** R = Bu$^t$

**215** R = Bn
**216** R = Bu$^t$

**217**

**218**

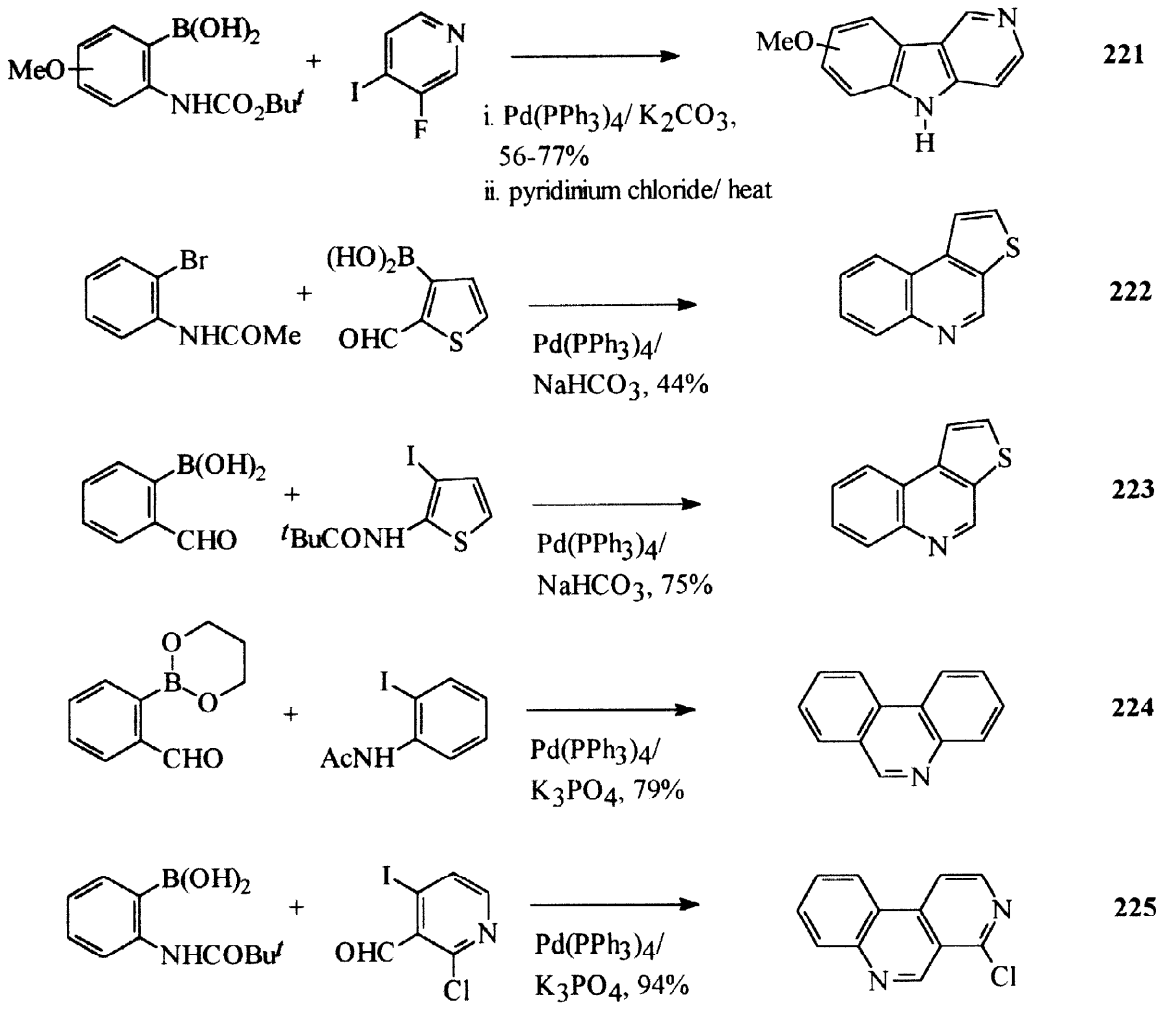
**219**

**220**

**Scheme 5** illustrated how the Stille reaction could be applied to the synthesis of tricyclic heterocycles. The Suzuki reaction has also been employed in the synthesis of tricyclic heterocycles by cyclistion of biaryl precursors and heterocyles **221**,[254] **222**,[255] **223**,[255] **224**[184] and **225**[256,257] provide representative examples (**Scheme 6**). Substituted phenanthridines and phenanthridinones have also been prepared using similar methodologies.[258]

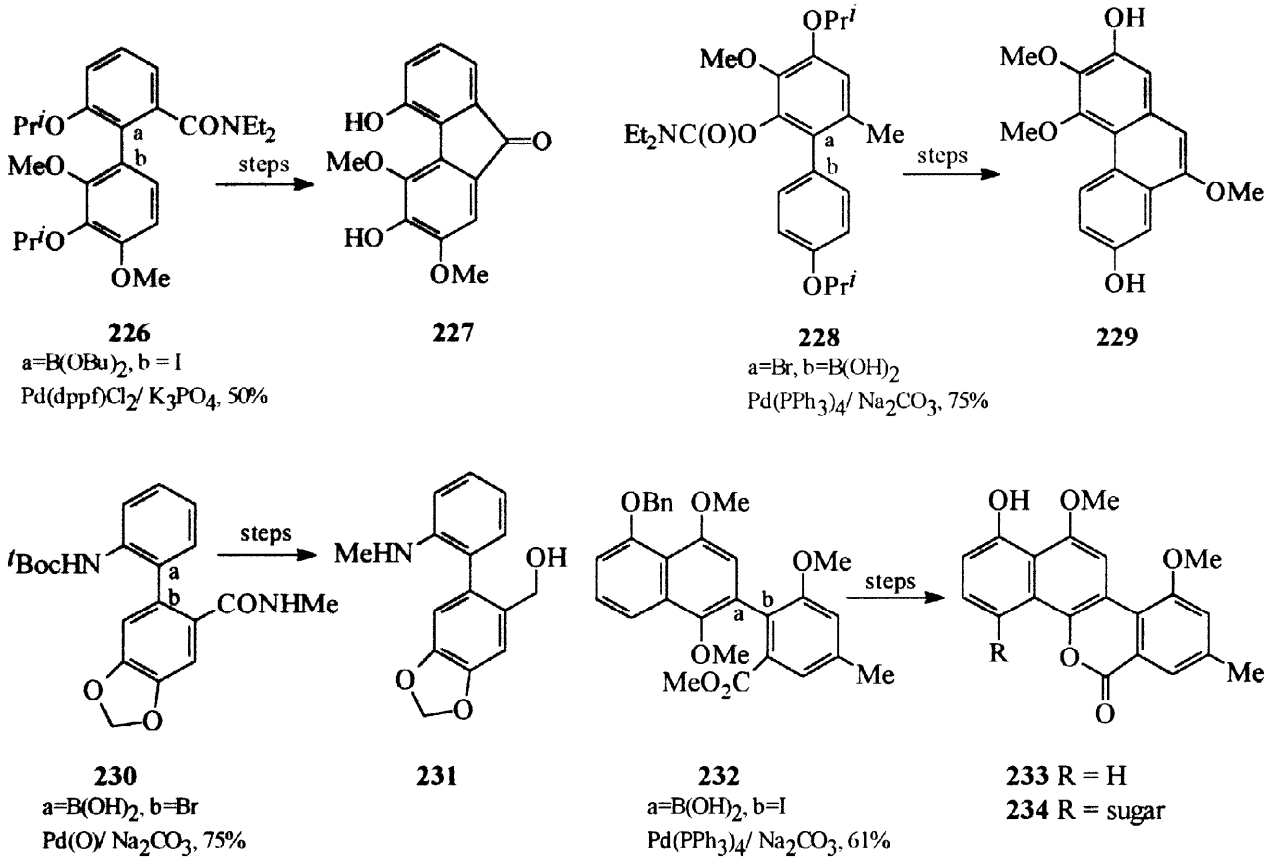
Terpyridyls,[193] quateropyridyls[169] and a plethora of teraryls[167] with three heterocyclic rings have been prepared using the Suzuki reaction.

The Suzuki reaction has found widespread application in polymer chemistry. Poly(*para*-phenylene) derivatives,[259] alkyl substituted poly(*para*-phenylenes),[188,260-262] water soluble poly(*para*-phenylenes)[263] and polyphenylene dendrimers[264,265] have all been prepared. Polymers possessing alternating substituted biphenyl and binaphthyl moieties have also been prepared[266] and the preparation of 'graphite ribbons' from alkynyl substituted poly(*para*-phenylenes) has been reported.[267] A series of butylated oligonaphthalenes have been synthesised[268] and chiral polynaphthols have been reported.[269] In heterocyclic chemistry, alkylated polymers of 2-phenylpyrrole[270] and trimethylsilyl-capped oligothiophenes have been prepared.[162]




**Scheme 6**

The Suzuki reaction has found extensive application in natural product chemistry and some illustrative examples are now described. The fluorenone derived natural product, Dengibsinin **227** has been prepared from the biphenyl precursor **226** which was prepared using a Suzuki reaction.[271] The synthesis of biphenyl **226**, which possess three *ortho* substituents provides a further example of the tolerance of the Suzuki reaction to steric effects. The phenanthrene derived compound, Gymnopusin **229** has been prepared from biphenyl **228**[272] and Ismine **231** was synthesised from biphenyl **230**.[258] The aglycone **233** of the benzonaphthopyrone antibiotics **234** has been synthesised from biaryl **232**[273] and other lactones such as Autumnariol have similarly been prepared.[274]




**226**
a=B(OBu)$_2$, b = I
Pd(dppf)Cl$_2$/ K$_3$PO$_4$, 50%

**227**

**228**
a=Br, b=B(OH)$_2$
Pd(PPh$_3$)$_4$/ Na$_2$CO$_3$, 75%

**229**

**230**
a=B(OH)$_2$, b=Br
Pd(O)/ Na$_2$CO$_3$, 75%

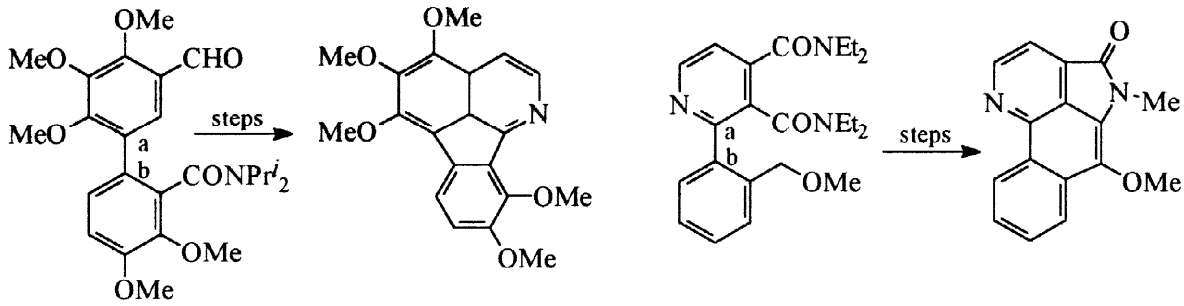
**231**

**232**
a=B(OH)$_2$, b=I
Pd(PPh$_3$)$_4$/ Na$_2$CO$_3$, 61%

**233** R = H
**234** R = sugar

Examples of the synthesis of alkaloids using the Suzuki reaction include the preparation of Imeluteine **236** from biphenyl **235**,[271,271a] Eupolauramine **238** from biaryl **237**,[275] Ellipticine **240** from heterocycle **239**,[276] the quaterpyridine **242**, an isomer of Nemertelline **241**[277] and the teraryl, Nortopsentin A **243**.[278] Nemertelline **241** has been prepared (68%) using Stille methodology from bipyridyls **188** and **190**.[191] The quaterpyridine structure **242** had originally been assigned to Nemertelline **241** and its synthesis was undertaken for this reason. The alkaloids Dubamine **164** and Hippadine **172** have both been prepared using the Stille reaction as outline in Section 4.3 and the Suzuki reaction has also been applied to the synthesis of these two heterocycles[194,240,279] as well as related alkaloids such as Ungerimine.[279]

The synthesis of Michellamines such as the atropisomers Michellamine A **244** and Michellamine B **245** has attracted considerable interest.[68,280,281] In one synthesis of compounds **244** and **245**, a bis-Suzuki reaction was employed to form the quateraryl skeleton from tetrahydroisoquinolyl and binaphthyl precursors.[280] Analogues of Michellamine B **245** have also been prepared.[282]

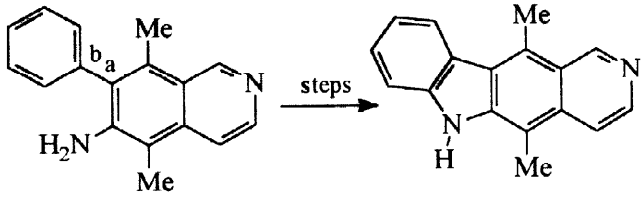



**235**
a=Br, b=B(OH)$_2$
Pd(PPh$_3$)$_4$/ Na$_2$CO$_3$, 93%

**236**

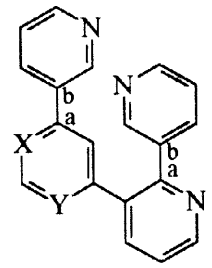
**237**
a=Br, b=B(OH)$_2$
Pd(PPh$_3$)$_4$/ Na$_2$CO$_3$

**238**

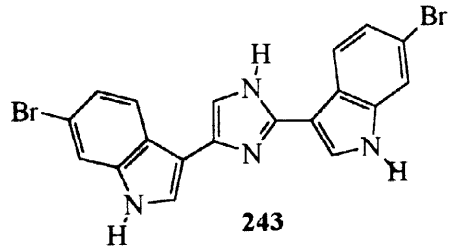



**239**
a=Br, b=$B(OH)_2$
$Pd(PPh_3)_4$/ $Na_2CO_3$, 99%

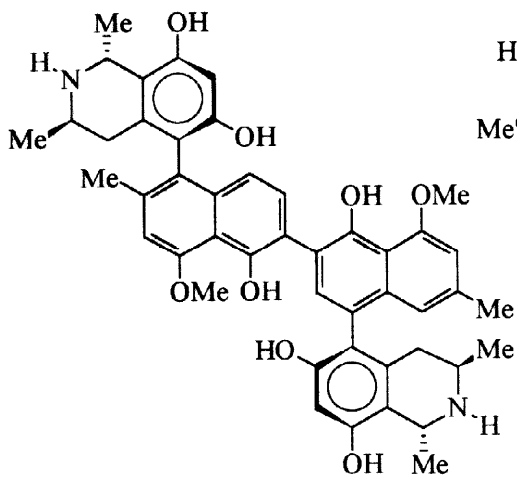
**240**

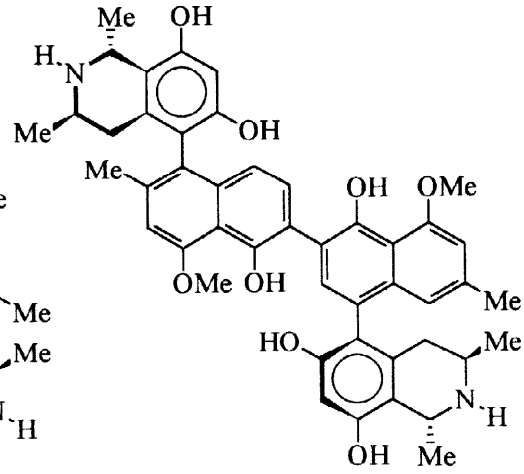



**241** X = N, Y = CH
**242** X = CH, Y = N
a=Cl, b=$BEt_2$
$Pd(PPh_3)_4$, 64%




**243**



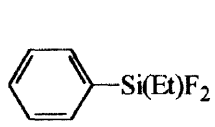

**244** **245**

## 6. OTHER CROSS-COUPLING REACTIONS

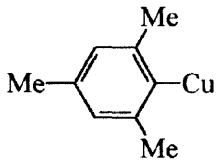
Aryl silanes such as compound **246**[283] and related compounds[284,285] underwent a fluoride promoted cross-coupling reaction with aryl halides or triflates in the presence of a palladium catalyst yielding biaryls. For example, compound **246** and 2-iodoanisole afforded 2-methoxybiphenyl (45%) and 3-methoxybiphenyl (83%) was obtained from 3-iodoanisole and silane **246**.

Organomercury compounds ($^1Ar_2Hg$) have been coupled with aryl iodides ($Ar^2I$) in the presence of a palladium catalyst giving biphenyl derivatives in good yield. 4-Nitrobiphenyl (98%) and 4'-X-4-nitrobiphenyls (X= Cl, Me, OMe) (97-99%) have been synthesised using this chemistry[286] and heterobiaryls have similarly been prepared.[287]

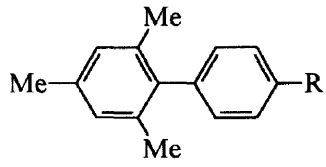
In copper chemistry, compound **247** reacted with a number of 4-substituted aryl iodides yielding products **248** (R = Cl, OMe, COMe, CN, $NO_2$) in good yield (70-90%).[288] The catalyst was $PdPh(PPh_3)_2I$ and both the yield rate of reaction was accelerated by the presence of $Bu_4NI$. The role of the $Bu_4NI$ was to form a more reactive organocopper intermediate, [mesitylCuI]$^-$ $Bu_4N^+$.




**246**




**247**




**248**

## 7. REVIEW ARTICLES

There are a substantial number of review articles of various lengths and detail in the literature which have Sections describing catalytic cross-coupling reactions in biaryl synthesis.[187,289-311] Many of these reviews consider cross-coupling reactions in a broader sense, for example the cross-coupling of aryl and vinyl moieties and of two different vinyl moieties but these reactions are usually mechanistically closely related to the reactions covered in this Review. Several of these reviews also give historical developments of catalytic cross-coupling reactions.

## 8. LIGAND ABBREVIATIONS AND STRUCTURES

The structure of ligands considered in this review are given in **Table 8** (following page). It should however be appreciated that an extensive number of other ligands have been used in catalytic cross-coupling reactions.

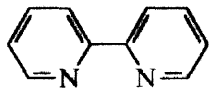
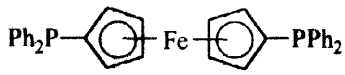
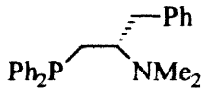
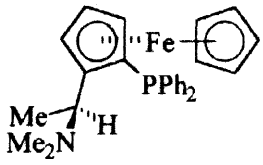
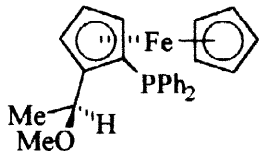
## 9. CONCLUDING REMARKS

It is clear that the transition metal mediated coupling route to biaryls and heterobiaryls has come of age and is routinely employed in laboratories throughout the world. It is however appropriate within the context of this Review to broadly summarize the relative advantages and disadvantages of the Kharasch, Negishi, Stille and Suzuki reactions so that a judicious choice from these reactions can be made by the practitioner when contemplating the preparation of a biaryl molecule.

In terms of overall functional group compatibility, the Stille and Suzuki reactions tolerate a wide range of functional groups and biaryls possessing electronically different aryl fragments are amenable to synthesis using these methodologies. The Suzuki reaction is especially suited to sterically crowded biaryls. Both the Stille and Suzuki reactions can tolerate water and both arylstannanes and arylboronic acids are relatively easy to prepare.

For structurally uncomplicated biaryls possessing functional groups which can tolerate Grignard reagents, the Kharasch reaction is often a useful preliminary method to try if the Grignard reagent and its coupling partner are readily available.

**Table 8.** Ligand Abbreviations and Structures

| Abbreviation | Structure | Name |
|---|---|---|
| acac | MeCOCH=C(O-)Me | acetylacetonate |
| dba | PhCH=CHCOCH=CHPh | dibenzylideneacetone |
| bpy |  | 2,2'-bipyridyl |
| dppe | $Ph_2PCH_2CH_2PPh_2$ | 1,2-bis(diphenylphosphino)ethane |
| dppp | $Ph_2PCH_2CH_2CH_2PPh_2$ | 1,3-bis(diphenylphosphino)propane |
| dppb | $Ph_2PCH_2CH_2CH_2CH_2PPh_2$ | 1,4-bis(diphenylphosphino)butane |
| dppf |  | 1,1'-bis(diphenylphosphino)ferrocene |
| (*S*)-phephos |  | (*S*)-2-(dimethylamino)-1-(diphenylphosphino)-3-phenylpropane |
| (*S*)-(*R*)-PPFA |  | (*S*)-*N*,*N*-dimethyl-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine |
| (*S*)-(*R*)-PPFOMe |  | (*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether |
| triphos | $(Ph_2PCH_2CH_2)PPh$ | bis[2-(diphenylphosphino)ethyl]phenylphosphine |

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