

# Aryl–Aryl Bond Formation One Century after the Discovery of the Ullmann Reaction

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## 1. Introduction

Aryl–aryl bond formation is one of the most important tools of modern organic synthesis. These bonds are very often found in natural products such as alkaloids as well as in numerous biologically active parts of pharmaceutical and agrochemical specialties. Many commercial dyes contain several aromatic rings bound together. Polyaromatics also possess original physical properties which could lead to applications as organic conductors or semiconductors. Last but not least, di- or triaromatic rings are the backbone of some of the most efficient and selective ligands for asymmetric catalysis, especially when atropisomerism is possible. As a consequence, over the last 10 years more than 700 articles have dealt with new results in the area of aryl–aryl bond formation.

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Marc Sévignon was born in Rennes, France, in 1974. He entered the Chemistry program at the Ecole Supérieure de Chimie-Physique-Electronique de Lyon (CPE Lyon) in 1994. He performed two six-month internships in organic synthesis at the Rhône-Poulenc Rorer Research Center of Dagenham (England) in the laboratory of Dr. D. Lythgoe and in heterogeneous catalysis at the Rhône-Poulenc Industrialization Research Center (Saint-Fons, France) in the team of Dr. P. Métivier. He graduated from CPE Lyon in 1998. Interested in the preparation of "organic materials", he joined the group of Professor M. Lemaire at Lyon and first worked on the synthesis of organic conducting polymers of asymmetric electrocatalysis. He is currently pursuing doctoral studies in the area of synthesis of specific molecules and resins for deep desulfurization of gasoil.

On the other hand, few reviews are devoted to aryl–aryl bond formation, and to our knowledge, none of them deals with all types of methodology. Indeed, the palladium-catalyzed Stille and Suzuki reactions have been the most studied over the past few years, but many specific synthetic problems of aryl–aryl bond formation could be (and are) solved by using other metals as the catalyst or as the reagent. In addition, oxidative methods appear to be competitive in some cases as do reactions with radicals as chemical intermediates. The present article aims to propose a larger scope than the last few reviews by including both older methods that are still competitively efficient and less common new concepts in the field of



Christel Gozzi was born in 1969 in Valence (France). She graduated from Ecole Supérieure de Chimie Industrielle de Lyon in 1991. She received her Ph.D. degree from the University of Lyon in 1994 for studies concerning new potential Thromboxane antagonists bearing a 7-azanorbornane skeleton under the direction of Professor J. Goré. Since 1995, she has worked in the group of Professor M. Lemaire, especially on contract work for various companies. Apart from industrial studies, her research interests lie in palladium-catalyzed aryl cross couplings with application in the syntheses of biologically active molecules and conducting polymers.



Emmanuelle Schulz was born in Cayenne. She graduated from Ecole Supérieure de Chimie Industrielle de Lyon in 1989 and received her Ph.D. degree from the University of Lyon in 1992 for studies concerning the total synthesis of Strigol, under the direction of Professor P. Welzel at the Ruhr-Universität Bochum, RFA. After an industrial postdoctoral position at the Research Center La Dargoire (Rhône-Poulenc Agrochimie), she joined the group of Marc Lemaire in 1993. In 1997, she obtained a permanent position at the "Centre National de la Recherche Scientifique" (CNRS). Since September 2000 she has worked at the "Institut de Chimie Moléculaire d'Orsay" in the "Laboratoire de Catalyse Moléculaire" of Professor J.-C. Fiaud. Her research topics include the preparation of "organic materials" for various applications: chiral ligands for the homogeneous and heterogeneous asymmetric catalysis, organic conducting polymers for asymmetric electrocatalysis, and specific resins for depollution (especially useful for the petroleum industry).

aryl–aryl bond formation. The diversity of the approaches also shows that none of them is self-sufficient in practical organic synthesis. Aryl–aryl bond formation has been known for more than a century and was one of the first reactions using a transition metal (copper in its higher oxidation states should be considered a transition metal). The evolution of this field is also a good illustration of the development of modern organic chemistry, particularly the increasing importance of transition-metal catalysis. Indeed, during the first 70 years of the 20th century, copper was almost the only metal usable for aryl–aryl bond formation, initially as copper metal



Professor Marc Lemaire was born in 1949 in Paris. He was employed several years in the pharmaceutical industry as a technician, and then he obtained the engineer level (CNAM Paris 1979) and his Ph.D. degree at the Paris VI University (Professor J.P. Guetté; "New chlorinating reagent"). In 1983 he obtained a postdoctoral position in the University of Groningen (The Netherlands; Professor F.M. Kellogg; "Thiamacrocycles as ligand for asymmetric catalysis"). He returned to Paris and obtained an assistant position at CNAM, and then he became a professor at the University of Lyon. His group is working in five main areas: (1) heterogeneous catalysis in fine chemistry, (2) asymmetric catalysis, (3) separation science, including new ligands for liquid–liquid extraction, new ionoselective materials, new complexing agents of nanofiltration–complexation systems, (4) organic conductors, including poly(thiophenes) and poly(pyrroles), and (5) deep desulfurization of gasoil.

in the reductive symmetrical coupling of aryl halides (the Ullmann reaction). Several modifications and improvements of this reaction still justify today the use of copper derivatives in several synthetic cases. The most important case may be the association of copper salts with aryl anions in an oxidative process. This last modification allows cross coupling and, in many cases, the use of substoichiometric (if not truly catalytic) amounts of metal. With some specific substrates, oxidative methods using copper(II) in the presence of chiral nitrogen-containing ligands give rise to the formation of biaryl with good diastereoselectivities. Historically, the major technological breakthrough could be the use of nickel instead of copper, first in stoichiometric amounts in an Ullmann-like procedure and then under catalytic conditions with diphosphine complexes and Grignard reagent. The latter method launched a number of changes allowing the use of more and more efficient catalysts, including palladium complexes and simultaneously less reactive, more selective nucleophilic reagents. Many organometallic reagents were tested with success using this general methodology. The most fruitful among them are zinc, tin, and boron derivatives. Zinc derivatives compared with magnesium are much more compatible with various functional groups and strongly increase the scope of application of organometallic cross couplings of aryl substrates and reagents. The last two heteroelements (tin and boron) possess an electronegativity close to that of carbon, and their derivatives can tolerate the presence of almost any functional group. Over the last 10 years, interesting and useful results have been published using all these types of methodologies. Interestingly, the most recently used transition metals have generated the greatest number of publications. Nowadays, many more syntheses use pal-



ladium catalysts than their nickel and copper counterparts. The Suzuki reaction is the most exemplified, even using modern technologies (polymer-supported reagent, biphasic catalysis, supercritical conditions, etc.). Increasing the scope of the Suzuki reaction (and, to a lesser extent, the Stille reaction) has probably been one of the most popular aims of research in academic institutions over the past few years.

One of the noteworthy applications of the methods for aryl–aryl bond formation lies in the synthesis of oligomers and polymers with long conjugated chains. Originally, such materials were formed by using electrochemical or chemical oxidative coupling with relatively low regularities in the case of substituted monomers (head-to-head or head-to-tail junctions, for example). The application of new methods of catalytic aryl–aryl bond formation has given rise to longer, more regular, less dispersed materials and will be described with examples in this review.

We have collected the results obtained in the field of aryl–aryl bond formation using all types of technologies and reactions. We believe that this enormous diversity has few equivalents with any other type of chemical transformation. Although this article cannot be exhaustive, we have attempted to draw a complete picture of the current efforts of organic chemists in this area. We hope that this analysis will be useful in encouraging further studies in less popular types of reactions. We have chosen to organize the article by the type of transition-metal used (copper, nickel, palladium). It is noteworthy that this classification is also historically consistent.

## II. Aryl–Aryl Bond Formation Using Copper as Reagent or Catalyst

Copper is the most ancient transition metal used for the synthesis of biaryls and it is still employed nowadays. This part will deal with recent developments in aryl–aryl bond formation using copper derivatives as reagents or catalysts. Reactions involving cuprates and other metals (nickel, palladium) as catalysts will be discussed later.

The use of copper in order to obtain the coupling of aromatic species can involve several types of mechanisms. Due to the numerous possibilities of intermediates and to the different oxidation and coordination states of copper, it is not always easy to ascertain an accurate mechanism of this reaction. Nevertheless, we propose to distinguish four types of couplings of aromatic rings, using copper derivatives, which may overlap.

The first type implies the use of aromatic halides, generally iodides or bromides, as substrates and copper metal as the reagent. The reaction, which involves the formation of a cuprate as the intermediate and copper halide as a byproduct, is the reductive coupling known as “the Ullmann reaction”. Although a few results have been obtained using catalytic amounts of copper, these reactions are still studied due to the fact that in several cases unsymmetrical and asymmetrical couplings are achieved.

The second type is closely related to the first but involves the formation of an aryl carbanion as the intermediate. As oxidative addition to the copper is

the limiting step in the “classical” Ullmann reaction, preparation of the carbanion provides milder conditions with a higher rate. With this methodology catalytic amounts of copper (generally Cu(I)) can be used, but conversely a stoichiometric (or greater) amount of base or organometallic is required. The reaction requires the reduction of the substrate (formation of the carbanion) and a transmetalation followed by a reductive elimination of the copper intermediate complex.

The third type is clearly an oxidation of two C–H aromatic bonds to form a C–C bond. These reactions are performed thanks to the oxidative properties of copper(II), and the use of substrates with a low oxidation potential is required. Both catalytic and stoichiometric amounts of Cu(II) have been used.

The fourth type and last one is the Pschorr reaction which involves the decomposition of diazonium in the presence of copper (generally Cu(I)) into radicals. This reaction, discovered before the Ullmann reaction, is limited by the access to the required diazonium salt.

### 1. Reductive Coupling of Aromatic Halides (The Ullmann Reaction)

#### A. Aromatic Coupling Using Stoichiometric Amount of Copper

The Ullmann reaction, initially reported in 1901,<sup>1</sup> has long been employed by chemists to generate a C–C bond between two aromatic nuclei. Typically two molecular equivalents of aryl halide are reacted with one equivalent of finely divided copper at high temperature (above 200 °C) to form a biaryl and a copper halide. This procedure and variants were comprehensively reviewed several decades ago.<sup>2,3,4</sup> Considerable improvements have been made through the last century. Dimethylformamide is a solvent which permits the use of lower temperatures and a lower proportion of copper. Besides, the use of an activated form of Cu powder, made by the reduction of copper(I) iodide with potassium, allows the reaction to be carried out at even lower temperatures (about 85 °C) with improved yields. As the reaction is heterogeneous, it can be accelerated considerably using ultrasound.<sup>5</sup>

Regarding the relationship between the structure of an aryl halide and its reactivity, electron-withdrawing groups such as nitro and carboxymethyl, especially in the ortho-position to the halogen atom, provide an activating effect. On the other hand, the presence of substituents which provide alternative reaction sites, such as amino, hydroxyl, and free carboxyl groups, greatly limit or prevent the reaction. Furthermore, bulky groups in the ortho-position exert an inhibitive influence.

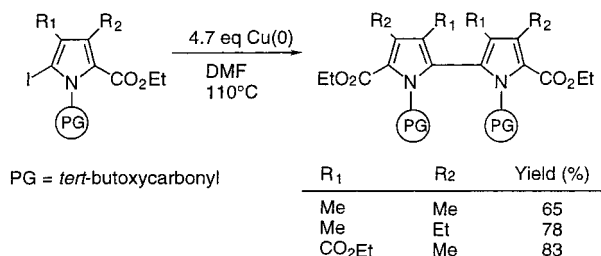
Obviously the major limitation of the original Ullmann reaction was the obtention of only symmetrical biaryls. Several attempts to synthesize unsymmetrical biaryls have been made, and some success has been achieved by associating aryl halides of different reactivities. These extensions of the original Ullmann reaction to unsymmetrical biaryls formation did however require the use of a significant excess of the “activated” aryl.

We will present recent uses of stoichiometric amounts of copper to perform first symmetrical and then unsymmetrical couplings.

**a. Symmetrical Couplings.** Symmetrical coupling of substituted benzene rings and aromatic heterocycles using copper as the reducing and coupling agent can be performed in both inter- and intramolecular reactions. There are many more examples of the former than the latter.

Sessler et al.<sup>6</sup> developed an efficient procedure for the preparation of alkyl-substituted 2,2'-bipyrrroles. It involved first the protection of the nitrogen atom (with di-*tert*-butyl-dicarbonate), then an Ullmann-type coupling, followed by the deprotection of the resulting 2,2'-bipyrrroles (Scheme 1).

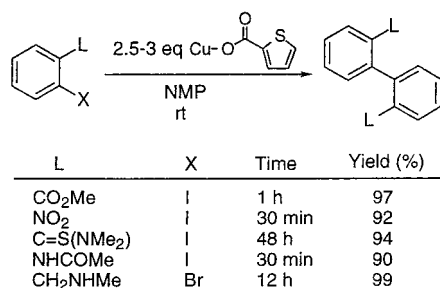
#### Scheme 1



The only byproduct was the substituted 2-pyrrole due to the reduction of the C–I bond of the starting material. The key step was the protection of the pyrrolic nitrogen. Since it has been shown that higher yields of substituted 2,2'-bipyrrroles are typically obtained when one or more electron-withdrawing group is present in the pyrrolic system, the authors have protected the pyrrolic nitrogen with a labile electron-withdrawing group (*tert*-butoxycarbonyl) in order to avoid any coupling between the nitrogen and the 2-position of a second pyrrole. Using appropriate N-protection, the yields of 2,2'-bipyrrrole were enhanced by 20–30%.

Using copper(I)-thiophene-2-carboxylate (CuTC, see below) as a promoter, Liebeskind et al.<sup>7</sup> reported a CuTC-mediated Ullmann-reductive coupling of substituted aromatic iodides and bromides, 2-iodoheteroaromatics, at room temperature. As depicted in Schemes 2 and 3, the CuTC-mediated reaction was

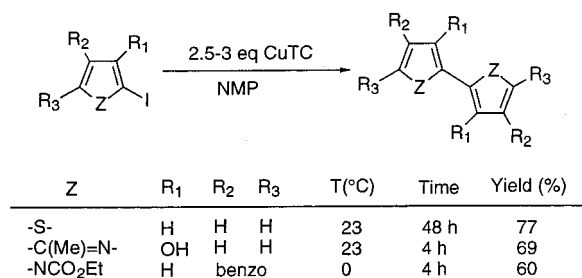
#### Scheme 2



quite general and tolerant of various functional groups.

Efficient reductive coupling of the aromatic substrates required the presence of an *ortho*-ligating, electron-withdrawing or electron-donating, substituent while 2-iodoheteroaromatics did not. The reduc-

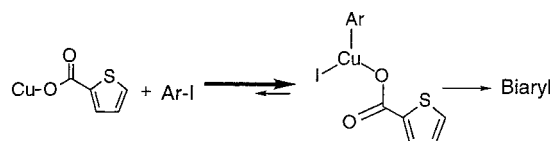
#### Scheme 3



tive coupling required a polar, coordinating solvent such as *N*-methylpyrrolidinone, probably to generate reactive Cu(I) monomers from the insoluble Cu(I) carboxylate polymer.

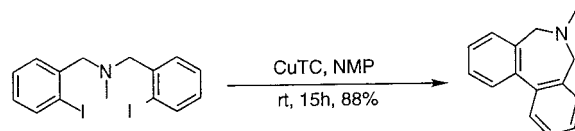
The authors assume that the efficiency of CuTC is probably not due to internal coordination from the sulfur atom to the metal but may be due to an inherent ability of carboxylate as a ligand to stabilize the oxidative addition product (Scheme 4).

#### Scheme 4



The intramolecular reductive coupling has also been successfully studied (Scheme 5).

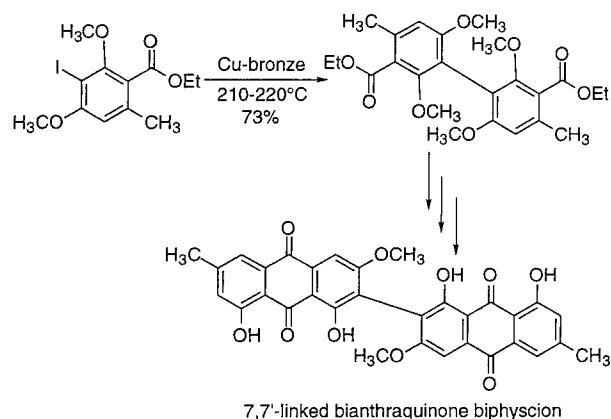
#### Scheme 5



The easy preparation of CuTC, its handling in air, and the high yields of reductively coupled products achieved under mild reaction conditions could make CuTC or other Cu(I) carboxylates the reagents of choice for many Ullmann-like reductive coupling reactions.

Hauser et al. performed the first total synthesis of the 7,7'-linked bianthraquinone biphyscion.<sup>8</sup> The key step was the preparation of symmetrical biphenyl through traditional Ullmann coupling of a protected iodoresorcinol (Scheme 6).

#### Scheme 6

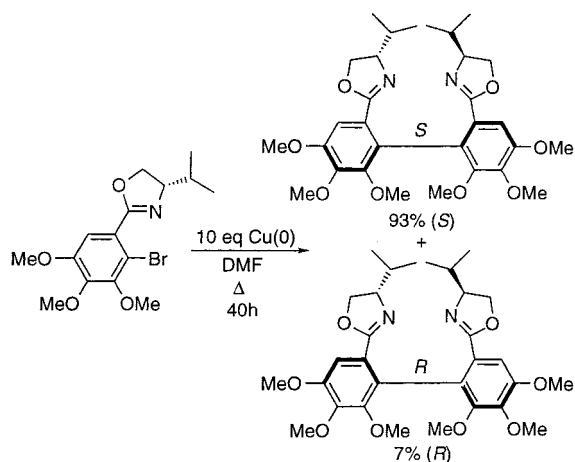


Although steric hindrance can be a problem in Ullmann reactions, coupling proceeded to afford the biaryl in a good yield (73%).

Recently a new trend has appeared using copper-mediated reactions for asymmetrical Ullmann couplings, mainly developed by Meyers et al. This was based on the fact that in many of the natural or synthetic biaryls, bulky ortho-substituents lead to hindrance of free rotation around the biaryl axis and thus to the existence of stable atropisomers. Thus, depending on the substituent, an aryl halide can be converted to a diastereomerically enriched product under equilibrating conditions. This process is referred to as a first-order asymmetrical transformation.

Meyers et al.<sup>9</sup> reported that a thermodynamically controlled resolution appeared to be operative under their reaction conditions so that diastereomerically enriched biaryls are formed (93(*S*)/7(*R*)) and may be readily purified to 100% diastereomeric purity (Scheme 7).

#### Scheme 7



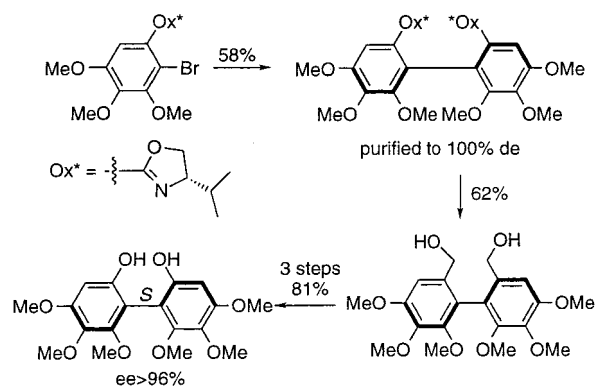
Two factors are mainly responsible for this reasonably effective asymmetrical synthesis. First, although the biaryl is tetrasubstituted, under the reaction conditions rotation is possible around the biaryl axis. Second, the final diastereomeric ratio is the result of chelation control with a Cu(I) and/or Cu(II) species under equilibrating conditions. Indeed, severe steric hindrances between the isopropyl groups of the two oxazoline moieties occur.

Using this methodology, Meyers et al.<sup>10</sup> reported the synthesis of a pure biphenyl diol (*S*), which has functioned as a chiral catalyst in the asymmetrical reduction of unsymmetrical ketones (Scheme 8).

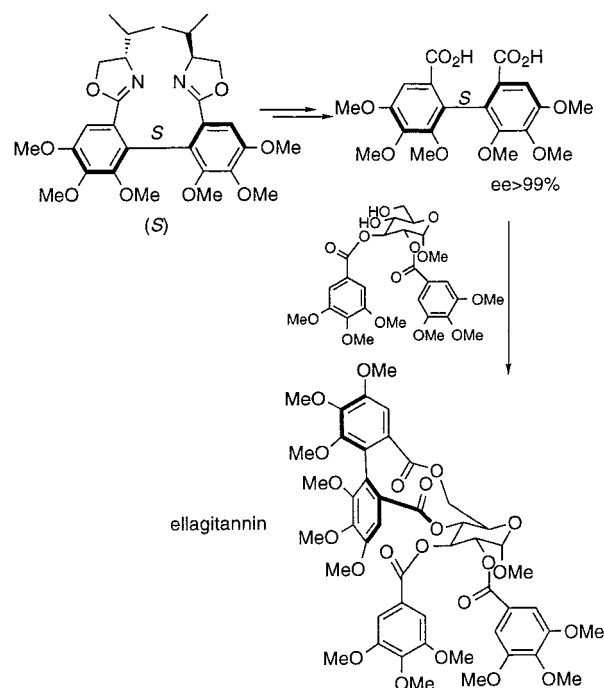
With the same first steps, the authors also described the first asymmetrical synthesis of (*S*)-4,4',5,5',6,6'-hexamethoxy-2,2'-diphenic acid, a ubiquitous subunit in ellagitannins<sup>11</sup> (Scheme 9).

Moreover, Meyers et al.<sup>12</sup> reported the asymmetrical synthesis of a class of chiral binaphthyls which contains substitution in the 8 and 8' positions. The metal is chelated between the two ligands, embedded closer to the binaphthyl framework than in the case of 1,1',2,2'-binaphthyls (BINAP, BINOL),

#### Scheme 8



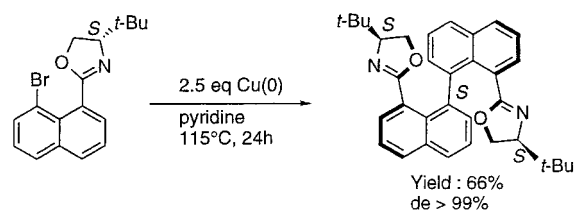
#### Scheme 9



perhaps providing a much more stereochemically biased environment.

Indeed, an oxazoline (*S*), subjected to classical Ullmann conditions, led to bis(oxazoline) (*aSS*) as a single diastereomer and debrominated naphthyloxazoline as a byproduct (Scheme 10).

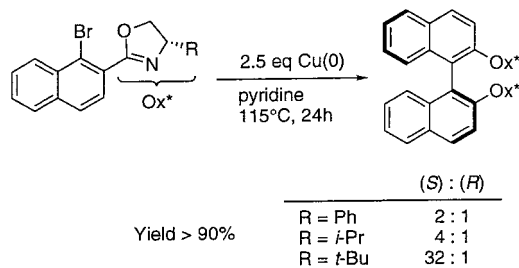
#### Scheme 10



The rotational barrier of atropisomers is less than 20–25 kcal/mol. The difference in stability between the two diastereoisomers appears to be due to the steric interaction of the *tert*-butyl groups. The authors assumed that the addition of steric factors, such as substituents at the 2 and 2' positions of the binaphthyl ring system, could raise the rotational barrier of this system to that of BINAP-type ligands and

could make it usable as a chiral ligand. Thus, Meyers et al.<sup>13</sup> applied their method to binaphthyls substituted in positions 2 and 2' with several oxazolines (Scheme 11).

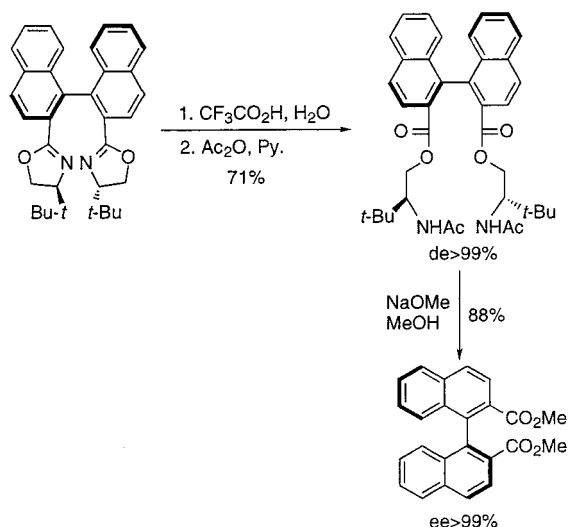
Scheme 11



The diastereomeric ratio of products was found to be sensitive to the size of the (*R*)-substituent in the oxazoline ring. Examining the transition states and copper intermediates, the authors explained that one of the two diastereomeric copper complexes was free of any severe steric interaction due to the close proximity of the (*R*)-substituents of the two oxazolines.

This route was employed to synthesize enantiomerically pure binaphthyl diester or the corresponding acid (Scheme 12) for use as a chiral stationary

Scheme 12



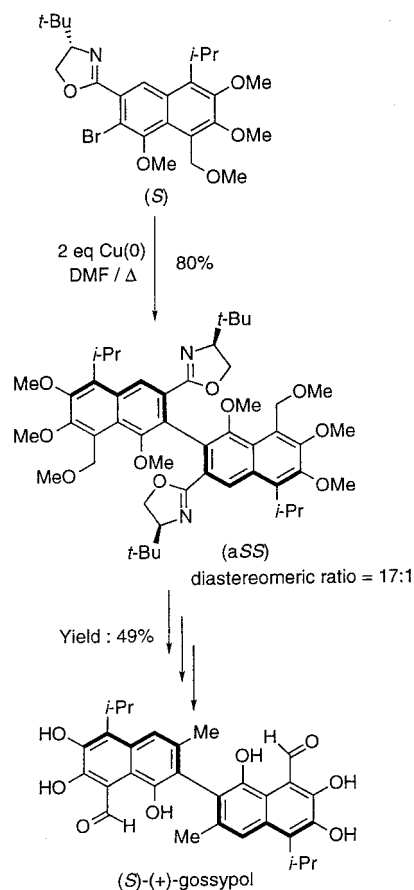
phase in HPLC and GC as well as a selective chiral host for stereoselective inclusion and as a chiral ligand for palladium-catalyzed cyclization.

The authors applied their method to the first asymmetrical total synthesis of (*S*)-(+)-gossypol<sup>14,15</sup> (Scheme 13).

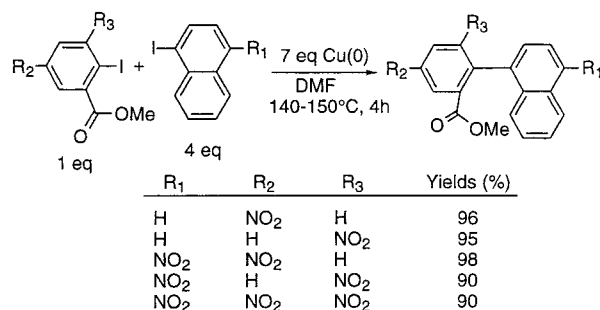
**b. Unsymmetrical Couplings.** To synthesize polynitrobenzanthrones, a new class of suspected mutagens in the atmospheric environment, Suzuki et al.<sup>16</sup> reported an Ullmann cross coupling between nitro-substituted iodobenzoates and iodonaphthalenes (Scheme 14).

To obtain those high yields of unsymmetrical coupling (based on methyl-iodobenzoates), a large excess of iodonaphthalene has to be used. Moreover, the reaction temperature is crucial: below or above

Scheme 13



Scheme 14



optimal temperature, the heterocoupling becomes less competitive and the homocoupling is predominant.

### B. Aromatic Coupling Using Catalytic Amounts of Copper

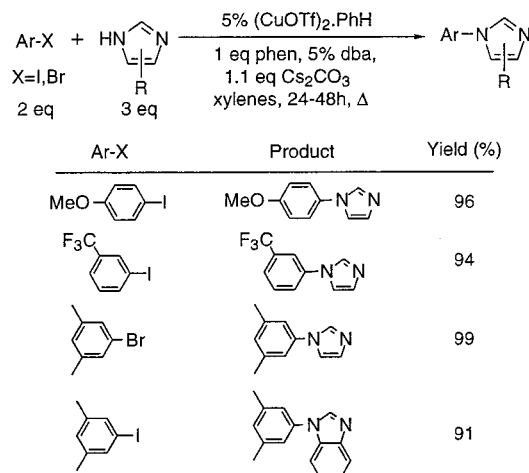
During the past few years, reductive couplings, using catalytic amounts of copper to create aryl–aryl bonds, have drawn little attention from the scientific community.

Two methods for constructing C–N bonds are commonly used: (1) nucleophilic aromatic substitution,<sup>17</sup> which requires that the aryl halide substrate possesses electron-withdrawing substituents, and (2) Ullmann-type coupling of imidazoles with aryl halides, which has a broader substrate scope with respect to the aryl halide. Buchwald et al. used the latter method reporting a copper-catalyzed N-arylation of imidazoles.<sup>18</sup> They found that the coupling proceeds fairly mildly in the presence of 1,10-



phenanthroline (phen) and *trans,trans*-dibenzylideneacetone (dba) as additives, with  $(\text{CuOTf})_2 \cdot \text{benzene}$  as the copper source and  $\text{Cs}_2\text{CO}_3$  as the base, in xylenes at 110–125 °C (Scheme 15).

Scheme 15



The inclusion of additives is one key to the success of the process, and the authors discussed their role. As ligands are known to inhibit copper-assisted coupling reactions,<sup>19,20</sup> it is interesting that this reaction is promoted by adding a 10-fold excess of chelating ligand (relative to the amount of copper). The effect of dba is not easy to explain, and the authors assumed that dba prevents undesirable disproportionation or in some way stabilizes the catalytically active copper(I) species.

The reaction proceeds cleanly with little, if any, formation of arene or symmetrical biaryl byproducts. Aryl iodides undergo coupling with imidazole at 110 °C, and the reactions are completed in 24–30 h, while the use of aryl bromides requires a higher reaction temperature, a higher concentration of the substrates, and longer reaction times. As is usually the case with Ullmann-type coupling processes, the protocol works for both electron-rich and electron-poor aryl halides (the opposite of what would be expected from a nucleophilic aromatic substitution reaction).

## 2. Coupling of Aromatics via Aryl Carbanion

This type of coupling is closely related to the Ullmann reaction but involves the formation of an aryl carbanion as the intermediate. As oxidative addition to the copper is the limiting step in the “classical” Ullmann reaction, preparation of the carbanion provides milder conditions with a higher rate. With this methodology catalytic amounts of copper (generally Cu(I)) can be used, but conversely a stoichiometric (or greater) amount of base or organometallic is required. The reaction requires the reduction of the substrate (formation of the carbanion) and a transmetalation followed by a reductive elimination of the copper intermediate complex.

### A. Use of Stoichiometric Amounts of Copper

**a. Symmetrical Couplings.** During the past decade, various activating groups have been used. We propose to distinguish three families based on the

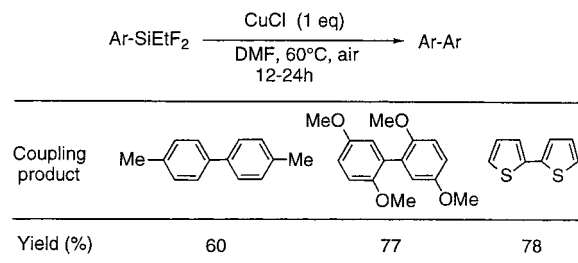
nature of the atom which is substituting the initial halogen atom of the substrate. This atom can be a (1) Si, (2) Sn, or (3) Li atom.

The activation of the substrate with silicon derivatives—fluorosilanes, siloxanes, or silyloxy groups—and trialkylstannane groups leads to smoother conditions and, in most cases, to higher yields.

The lithium derivatives present the additional opportunity of introducing asymmetry to the coupling reactions.

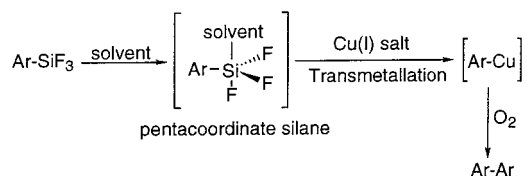
*i. Coupling of Silicon Derivatives.* Mori et al.<sup>21</sup> centered their research interest on the homocoupling reaction of aryl silanes under mild conditions. Using a copper(I) salt in an aprotic polar solvent and under aerobic conditions, they succeeded in homocoupling various aryl silanes (Scheme 16).

Scheme 16



The number of fluorine atoms on silicon is highly crucial: two or three fluorine atoms are essential for the success of homocoupling. Likewise, counterions and the oxidation state of the copper salt dramatically affect the yield of biaryl. CuCl and CuOTf efficiently accelerate the homocoupling reaction. The use of a polar solvent is crucial to promote the reaction. It is assumed that it coordinates with an organosilicon reagent to form the pentacoordinated but tetravalent species, which may behave as a pentavalent organosilicate that is formed by the addition of a fluoride ion to the organosilane and is known to be highly active to transmetalation (Scheme 17).

Scheme 17

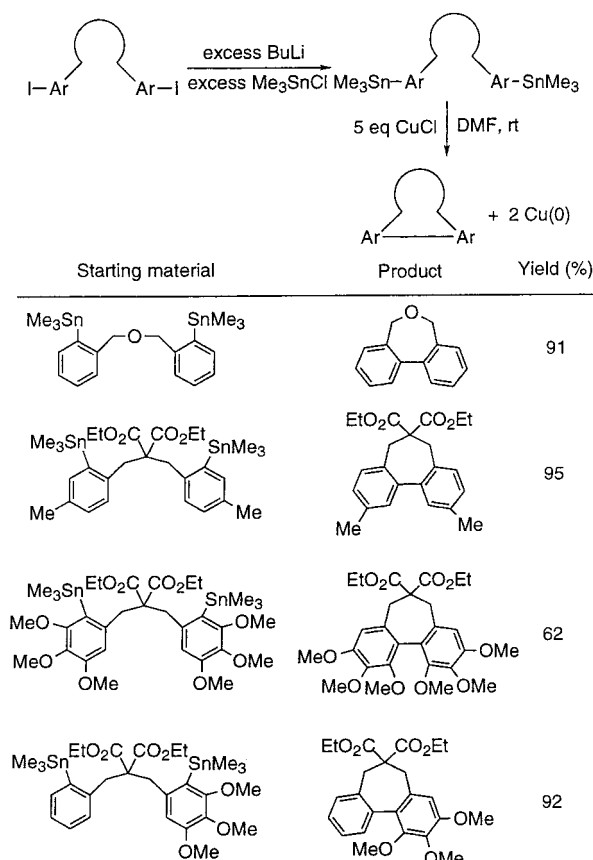


Although mechanistic details of the homocoupling process remain unclear, since the organocopper species could neither be isolated nor detected, these results should give a clue as to the formation of the organocopper species by the transmetalation from silicon to copper.

*ii. Coupling of Tin Derivatives.* Piers et al. developed an intramolecular Cu(I)-mediated coupling of two aryl trimethylstannane functions.<sup>22</sup> Treatment of various substances with an excess of CuCl in dry DMF at room temperature for 30–60 min effects, in each case, oxidative coupling between the two  $\text{sp}^2$  carbon centers bearing the  $\text{Me}_3\text{Sn}$  functions (Scheme 18).

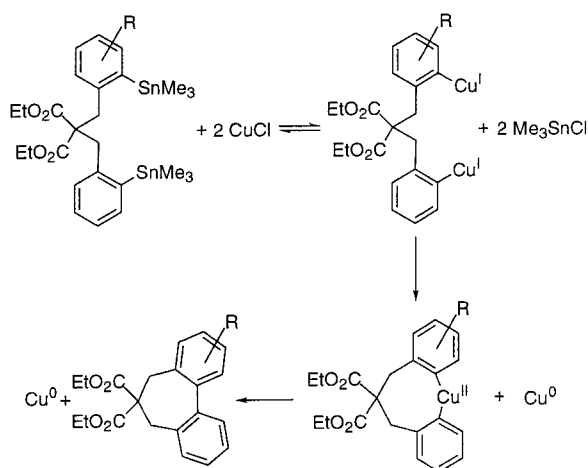


## Scheme 18



The authors used a protocol that gives good yields and avoids the production of polymeric material. Referring to the works of Farina et al.,<sup>23</sup> Scheme 19

## Scheme 19

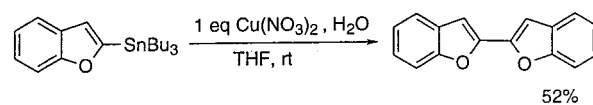


outlines a possible pathway via the oxidative coupling process.

The routine use of 5 equiv of CuCl would facilitate the overall process by shifting the initial equilibrium reaction toward the bis-copper(I) species.

Quayle et al.<sup>24</sup> reported a general method for the preparation of highly substituted buta-1,3-dienes based upon a copper(II)-promoted coupling reaction of alkenyl stannanes. They extended their method to the homocoupling of benzofused heterocyclic systems (Scheme 20).

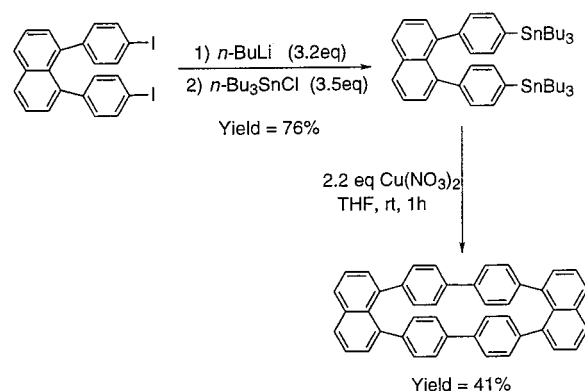
## Scheme 20



This formation of the bis-benzofuran is operationally simple to carry out and occurs at ambient temperature over short reaction times (10–40 min).

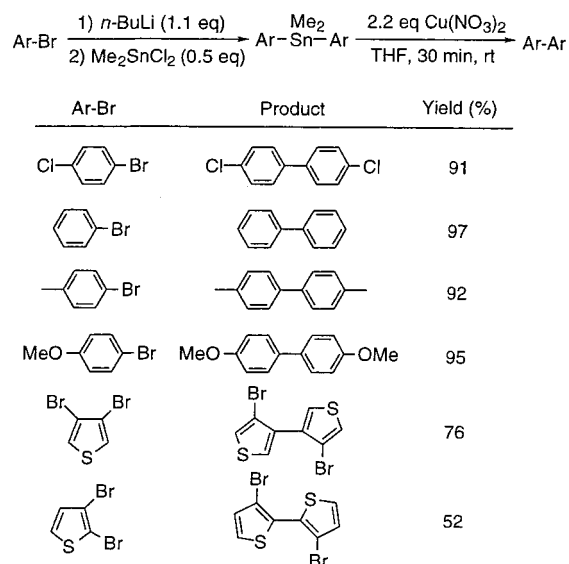
According to the same methodology, Iyoda et al. synthesized in a moderate yield the 1,8-(1,8-naphthalendiyldiyl)bis(4,4'-biphenyldiyl)naphthalene,<sup>25</sup> a very stable strained cyclophane potentially interesting for host-guest chemistry (Scheme 21).

## Scheme 21



The same team has found another method for the synthesis of biaryls and their heteroaromatic analogues using the coupling of diaryldimethyltins with copper(II) nitrate.<sup>26</sup> They applied the reaction, which proceeds smoothly at room temperature under ambient atmosphere, to various kinds of diaryldimethyltins (Scheme 22).

## Scheme 22

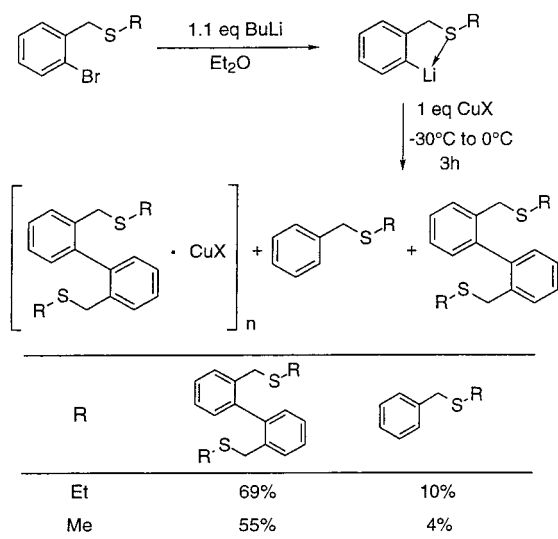


The reaction has also been carried out in the case of diaryldimethyltins containing *para*- or *meta*-substituents. The coupling occurs but the yields are lower. Moreover, it should be noticed that coupling of dibromothiophenes affords biaryl products without loss of the bromo substituents.

The authors assume that the first step of the coupling involves an electron-transfer process and transmetalation to generate an organocopper(II) species and dimethyltindinitrate.

*iii. Coupling of Lithium Derivatives.* The use of phenylcoppers stabilized by sulfur ligands at the *ortho*-benzylic position for the cross coupling was developed by Ziegler et al.<sup>27</sup> several years ago. Toyota et al. reported the results of the reaction and the effects of the intramolecular thioether ligands on the stability and reactivity of organocopper compounds.<sup>28</sup> 2-(Alkylthiomethyl)phenyllithium was reacted with a copper(I) halide to form homocoupled compounds, 2,2'-bis(alkylthiomethyl)biphenyl, benzyl ethyl sulfide, and traces of a copper halide complex of the biphenyl ligand (Scheme 23).

Scheme 23

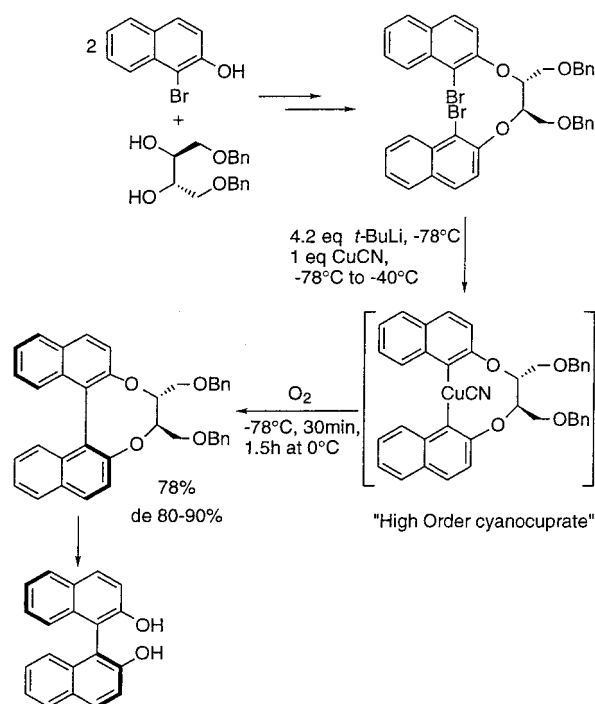


Several copper(I) salts were tested, but CuCl gave the best results, which suggests that CuCl has a low ability to form a complex with the difunctional sulfane ligand as a stable form. With CuBr, the major product is the copper halide complex of a difunctional thioether ligand, an interesting molecule from the standpoint of coordination chemistry because copper(I) ions are able to take a variety of aggregation forms depending on the nature of the ligands. Therefore, the authors investigated the structure and properties of the copper halide complexes.

Lipshutz et al.<sup>29</sup> developed a synthesis of biaryls by intramolecular oxidative couplings of cyanocuprate intermediates. They achieved an asymmetrical intramolecular reaction with the help of optically active auxiliary bridges (lactic, mandelic, or tartaric acid derivatives). They used their method for synthesizing 2,2'-binaphthol (Scheme 24).

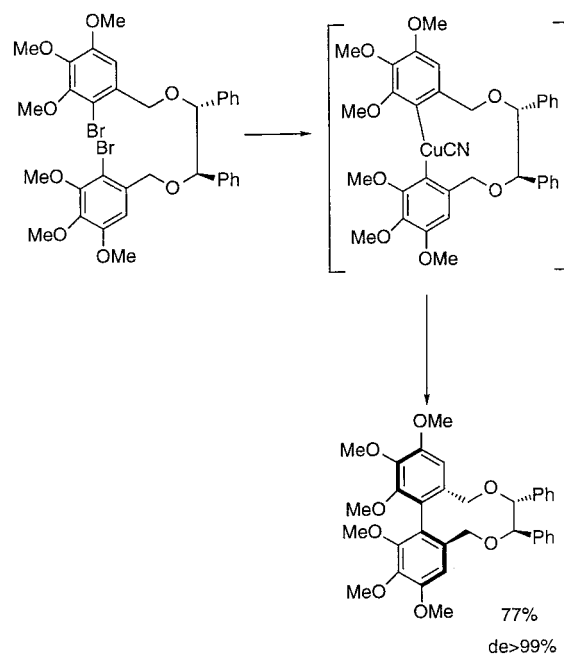
Treatment with *t*-BuLi followed by addition of CuCN presumably leads to the in situ formation of a higher order cyanocuprate, which produces the binaphthyl upon exposure to oxygen. It is interesting that aryl bromide precursors are readily available, nonracemic tethers are derived from inexpensive members of the "chiral pool", and couplings take place at practical temperatures.

Scheme 24



Moreover, this method applies equally to 2,2'-*C*-substituted binaphthyls and appears suited to the synthesis of biaryl portions of several natural products. An approach toward the ellagitannins was achieved by subjecting a dibromodiether to cuprate-induced coupling (Scheme 25).

Scheme 25

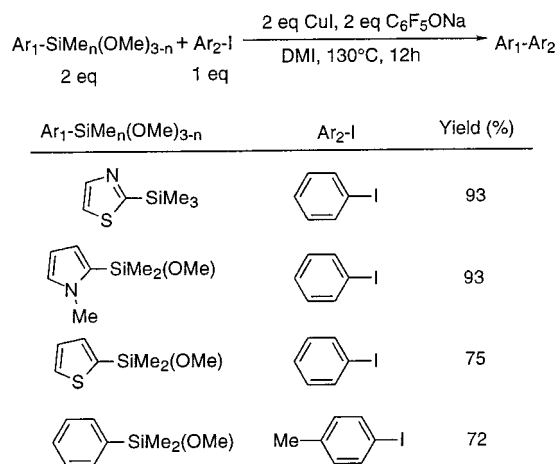


Lin et al.<sup>30</sup> used this asymmetrical intramolecular oxidative coupling to achieve the asymmetrical synthesis of the naturally occurring (+)-kotanin.

**b. Unsymmetrical Couplings.** *i. Coupling of Silicon Derivatives.* Using silyloxy groups, Hosomi et al.<sup>31</sup> achieved a new fluoride ion-free cross-coupling reaction between aryl- or heteroarylsilanes and aryl

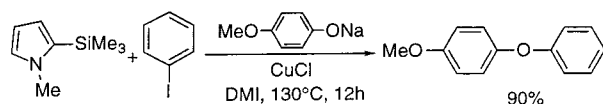
halides mediated by a copper(I) salt. They examined several substrates, copper salts, and solvents, and their best results are depicted in Scheme 26.

Scheme 26



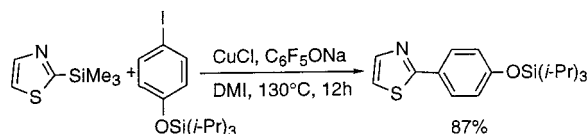
CuOC<sub>6</sub>F<sub>5</sub> is the best promoter for this reaction. The pentafluorophenoxide ion reveals strong affinity to the silicon atom of arylsilanes and accelerates the transfer of the Ar<sub>1</sub> group. Moreover, the authors noticed that other copper(I) alkoxides and aryl oxides such as methoxide, *tert*-butoxide, and phenoxide react faster with the organic halides than the organosilicon compounds (Scheme 27).

Scheme 27



Hosomi et al. also demonstrated the synthetic utility of their fluoride-free cross coupling by expedient reaction of a substrate containing a silyl ether moiety which is easily cleaved by a fluoride ion (Scheme 28).

Scheme 28

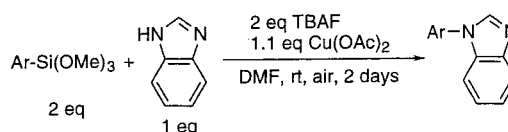


Lam et al. described an interesting copper-mediated C–N bond cross-coupling reaction. They first discovered a new aryl/heteroaryl cross-coupling reaction via the aryl boronic acid/cupric acetate arylation of N–H containing heteroarenes.<sup>32</sup> This reaction proceeds at room temperature when exposed to air for 2 days and provides good yields (50–88%) but needs the presence of a base (either pyridine or triethylamine depending on the substrate).

They recently improved their methodology using hypervalent aryl siloxanes instead of aryl boronic acids and tetrabutylammonium fluoride (TBAF) for C–N bond formation<sup>33</sup> (Scheme 29).

Their new methodology offers the advantage of performing a room-temperature N-arylation in the

Scheme 29

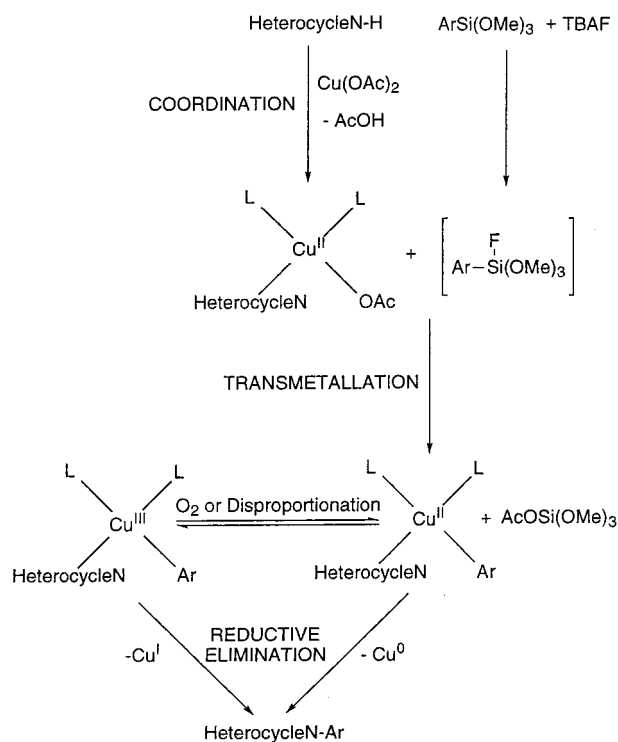


Ar	Yield (%)
Phenyl	83
<i>p</i> -Cl-phenyl	72
<i>p</i> -OMe-phenyl	98

absence of a base. Water does not appear to interfere with this reaction.

The authors believe the mechanism is similar to that postulated for N-arylation with aryl boronic acids<sup>32</sup> (Scheme 30).

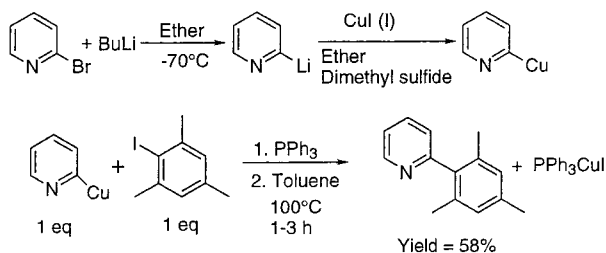
Scheme 30



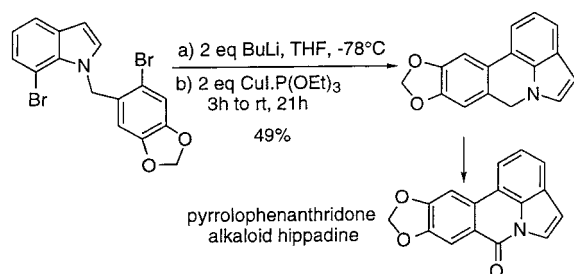
With this method, the authors performed a one-pot N-arylation of benzimidazoles using various iodobenzenes as arylating agents via *in situ* generation of phenyl trimethylsiloxane through the Masuda method.<sup>34</sup> The cross-coupling product is obtained in moderate yields (40–44%).

*ii. Coupling of Lithium Derivatives.* Nilsson et al.<sup>35</sup> found that the reaction of 2-pyridylcopper in the presence of triphenylphosphine gives 50–80% yields of 2-arylpyridines using nonactivated iodoarenes (Scheme 31).

The optimal ratio of triphenylphosphine/pyridylcopper is slightly above 1. The presence of triphenylphosphine seems to stabilize 2-pyridylcopper with respect to thermal decomposition and formation of symmetrical biaryl. With this method, even a crowded trimethyliodobenzene can react in 2 h in an acceptable yield.

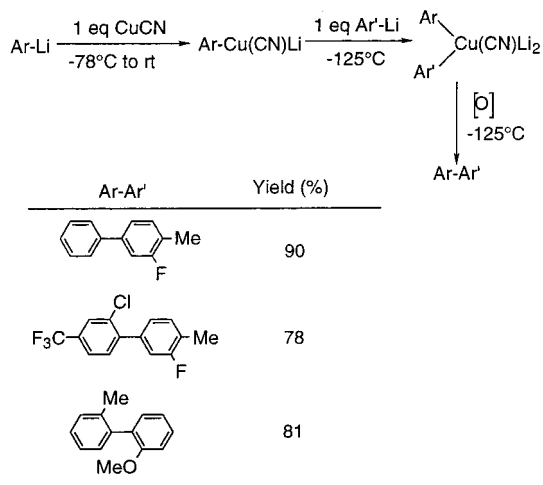
**Scheme 31**

Harrowven et al.<sup>36</sup> described a short synthesis of the pyrrolophenanthridone alkaloid hippadine using a low-temperature Ullmann cross coupling as the key step (Scheme 32).

**Scheme 32**

An intramolecular coupling, akin to this modified Ullmann reaction, allows them to construct the pentacyclic skeleton.

Their interest for the coupling of aryls through oxidation of cyanocuprate intermediates has led Lipshutz et al.<sup>37</sup> to perform the first controlled unsymmetrical biaryl cuprate oxidation. Indeed, at  $-125\text{ }^{\circ}\text{C}$  in 2-methyl-tetrahydrofuran, they “kinetically” generated high-order mixed diarylcuprates. Oxidation at  $-125\text{ }^{\circ}\text{C}$  gives the desired cross-coupling products. They first applied their procedure to the synthesis of biphenyls with good yields (70–90%) (Scheme 33).

**Scheme 33**

Neither steric nor stereoelectronic factors appear to play an important role in these couplings. Various cuprates were tested, but cyanocuprates gave the best results in terms of selectivity. Moreover, the

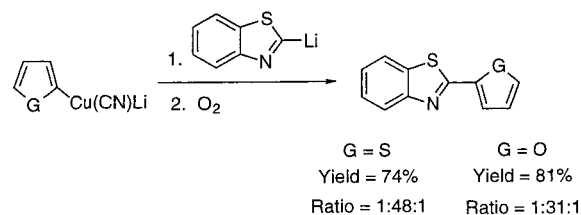
temperature is a far more critical parameter than the concentration at which the cuprate is oxidized.

Extension of the method to both naphthalene and binaphthyl derivatives was investigated. Here again a small steric effect is observed. Likewise, an electron-deficient benzene ring or a heteroaromatic moiety can be attached to the naphthalene ring with good yields (Scheme 34).

**Scheme 34**

Coupling product	Yield
	80%
	81%
	82%
	76%
	80%

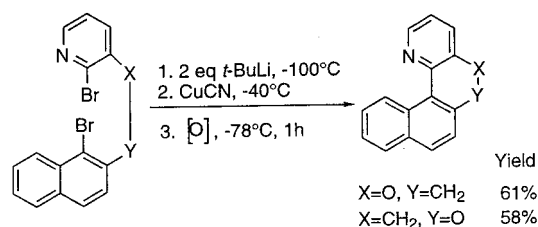
Lipshutz et al. also developed the potential for one or both ligands of copper in the cyanocuprate intermediate (Ar, Ar') to be of an heteroaromatic nature.<sup>38</sup> For the coupling of heterocycles, results are found to be mixed. Very good isolated yields are obtained (87–97%), but the ratio of cross-coupled/homocoupled products is not always advantageous. Upon switching to a benzothiazole reagent, cross-coupled biaryl is formed in good yield and selectivity (Scheme 35).

**Scheme 35**

Couplings under these controlled conditions in the bipyridyl series are unexpectedly random. This is due to the over-riding influence exerted by the pyridyl moiety in perturbing the normally highly ordered mode of kinetic cuprate behavior toward oxidation. The corresponding intramolecular variant is far more consistent and rewarding (Scheme 36). Similar treat-



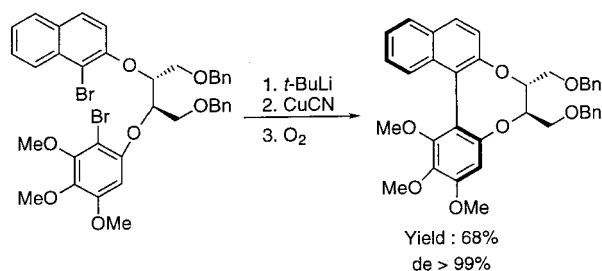
## Scheme 36



ment of a thienyl analogue leads to the expected product with a good yield (72%).

Results obtained with these intramolecular couplings provided strong justifications for applying these concepts to targets containing atropisomers. The asymmetrical synthesis of biaryls by intramolecular symmetrical oxidative coupling has already been discussed (see section II.2.A.a). Lipshultz et al. then applied this method with success to the synthesis of unsymmetrical biaryls<sup>29</sup> (Scheme 37).

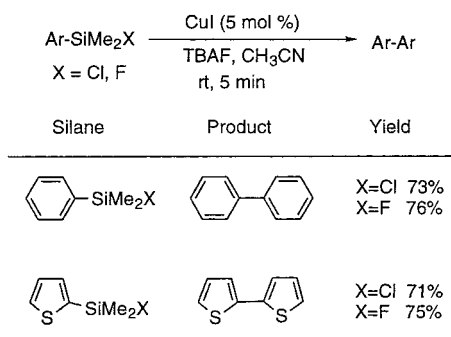
## Scheme 37



## B. Catalytic Amounts of Copper

**a. Symmetrical Couplings.** *i. Coupling of Silicon Derivatives.* Kang et al. reported copper(I)-iodide-catalyzed homocoupling of substituted chloro- or fluoro-dimethylsilanes to form biaryls<sup>39</sup> using tetrabutylammonium fluoride (TBAF) (Scheme 38).

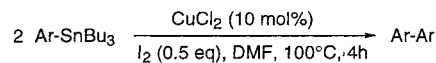
## Scheme 38



Of the catalysts tested, CuI gave the best results. The presence of TBAF is essential as an accelerator for transmetalation<sup>40</sup> in this homocoupling. In considering the likely mechanism, it is presumed that oxidative addition of activated organosilane to Cu<sup>I</sup> salts results in the formation of organo ArCuSiMe<sub>2</sub>X. This is then ready for transmetalation with the pentacoordinate silicate, formed from TBAF and organosilane, to give Ar<sub>2</sub>CuI. This latter molecule undergoes reductive elimination to generate the Ar-Ar bond with the liberation of CuI.

*ii. Coupling of Tin Derivatives.* Kang et al. also carried out an efficient catalytic homocoupling of organostannanes with CuCl<sub>2</sub> slowly adding iodine as the oxidant<sup>41</sup> (Scheme 39).

## Scheme 39

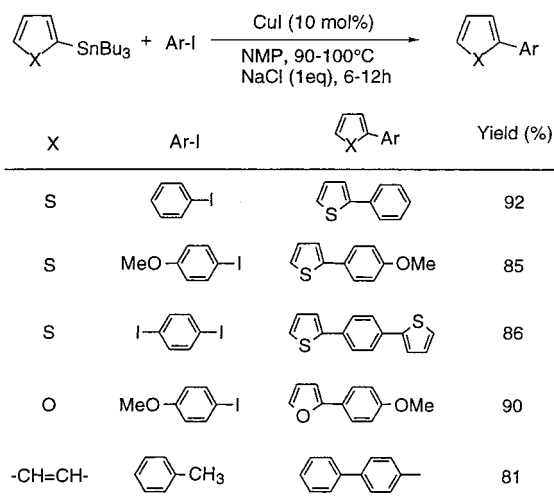


Ar	Yield (%)
Ph	93
2-pyridyl	85
2-furyl	80
2-thienyl	72

Of the suitable catalysts, CuI, CuCl, CuCl<sub>2</sub>, and CuF<sub>2</sub>·2H<sub>2</sub>O tested, CuCl<sub>2</sub> was the best choice.

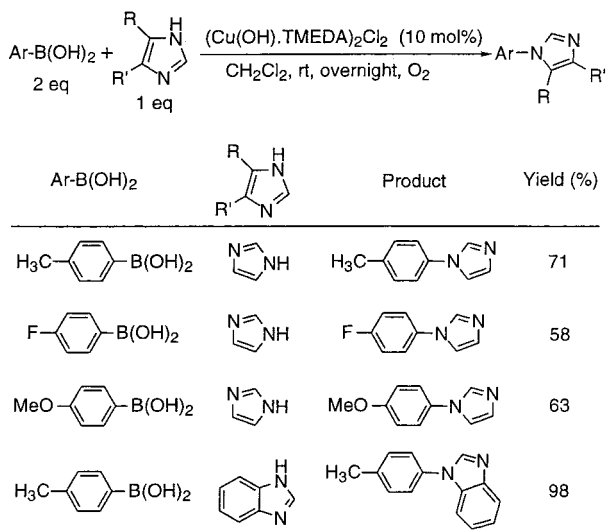
**b. Unsymmetrical Couplings.** *i. Coupling of Tin Derivatives.* Kang et al.<sup>42</sup> reported a cuprous-iodide-catalyzed cross coupling of aryl stannanes with aryl iodides in the presence of sodium chloride (Scheme 40).

## Scheme 40



Initially a series of experiments were performed using different salts. KCl and NaCl are the most preferable. Kang et al. noticed that the addition of NaCl is crucial in these cross couplings. It is presumed that the transmetalation of ArSnBu<sub>3</sub> with cuprate is reversible. *n*-Bu<sub>3</sub>SnI, formed from transmetalation of ArSnBu<sub>3</sub> with CuI, can be converted to *n*-Bu<sub>3</sub>SnCl by adding NaCl. *n*-Bu<sub>3</sub>SnCl does not participate in a back-reaction with cuprate and thus drives the transmetalation favorably.

*ii. Coupling of Boron Derivatives.* Collman et al. developed a copper-catalyzed N-arylation of azoles using aryl boronic acids,<sup>43</sup> akin to a modified Ullmann reaction. Since readily available Cu(OH)Cl·TMEDA has been successfully employed in aerobic oxidative coupling of 2-naphthols,<sup>54,57</sup> the authors assumed that this catalyst could be an excellent replacement for the Cu(II) salts and tertiary amines that are used in Chan and Lam's system.<sup>32</sup> They successfully employed and optimized this catalytic system for the cross-coupling reaction of aryl boronic acids with imidazoles (Scheme 41).

**Scheme 41**

Although a lower yield is found compared to the use of O<sub>2</sub>, the reactions also succeeded under ambient conditions. The authors speculated on a mechanism stemming from Evans' postulate for coupling aryl boronic acids with phenols.<sup>44</sup>

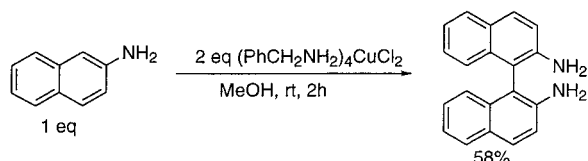
In addition to these examples based on the Ullmann reaction, several couplings of other activated aryls under mild conditions have also been established. López-Alvarado et al.<sup>45</sup> described N-arylation of imidazoles with *p*-tolyllead using a catalytic amount of Cu(OAc)<sub>2</sub> at 90 °C in good yields. However, this method is limited to *p*-tolyllead and produces toxic organolead byproducts.

### 3. Oxidative Aromatic Coupling Using Copper Salts

Copper-mediated or -catalyzed oxidative couplings are one of the ways to obtain biaryls. For the past decade, oxidative couplings of 2-naphthols have been largely employed for the preparation of binaphthols. Due to this, extensive efforts have been made to increase the scope of these methodologies for symmetrical and unsymmetrical couplings including enantioselective reactions.<sup>4,46</sup>

#### A. Use of Stoichiometric Amount of Copper

**a. Symmetrical Couplings.** Smrcina et al. performed a very large study on the synthesis of symmetrical and unsymmetrical binaphthyls. First they developed a facile synthesis of the racemic 2,2'-diamino-1,1'-binaphthyl<sup>47</sup> by oxidation of 2-naphthylamine using (PhCH<sub>2</sub>NH<sub>2</sub>)<sub>4</sub>CuCl<sub>2</sub> (Scheme 42).

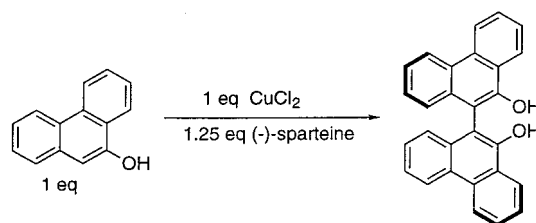
**Scheme 42**

The complexation of copper(II) chloride is a key point in the reaction, since uncomplexed CuCl<sub>2</sub> gave only a 34% yield.

They extended this procedure to the synthesis of enantiomerically pure binaphthyls using inexpensive and commercially available chiral amines.<sup>48,49</sup>

Coupling of 1 equiv of 2-naphthol,<sup>48</sup> using an in-situ-generated complex of 1 equiv of CuCl<sub>2</sub> and 2 equiv of (–)-sparteine, results in the formation of precipitate and mother liquor. The precipitate leads to the isolation of enantiomerically pure (–)-binaphthol with a 14% yield, while the mother liquor gives 42% of (–)-binaphthol of 20% ee.

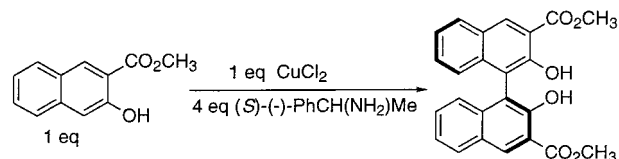
Similarly, a stoichiometric coupling of 9-phenanthrol with CuCl<sub>2</sub> and (–)-sparteine has been achieved leading to (–)-biphenanthrol of 76% ee with an 80% isolated yield<sup>49</sup> (Scheme 43).

**Scheme 43**

However, in both cases, Smrcina et al. observed that the pure (–)-enantiomer could be best obtained by a second-order asymmetrical transformation from racemic species in good yields. Thus, the authors concluded that, in these cases, the enantioselection was mainly controlled via a second-order asymmetrical transformation of the binaphthyl.

Coupling of 1 equiv of 2-naphthylamine<sup>48</sup> with 1.5 equiv of (–)-sparteine and 1 equiv of CuCl<sub>2</sub> gives a precipitate which leads, after crystallization, to pure (–)-2,2'-diamino-1,1'-binaphthyl with a 13% yield. The mother liquor from the reaction furnishes 41% of (+)-2,2'-diamino-1,1'-binaphthyl of 31% ee. Further resolution leads to pure (+)-enantiomer.

Likewise, the coupling of methyl 3-hydroxy-2-naphthoate<sup>49</sup> with CuCl<sub>2</sub> and (S)-(–)-methylbenzylamine (1:4) leads to the isolation of 47% of (–)-binaphthylester (44% ee) from the precipitate, while the mother liquor furnishes (+)-enantiomer of 43% ee with a 40% yield (Scheme 44).

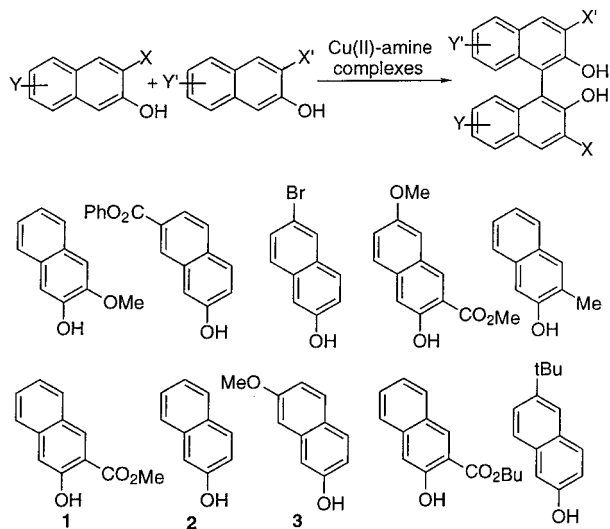
**Scheme 44**

In these cases, the stereodifferentiation can be ascribed to a diastereoselective crystallization of the corresponding Cu(II)–amine–binaphthyl complex.

**b. Unsymmetrical Couplings.** Hovorka et al. studied the direct oxidative coupling of substituted 2-naphthols as a key step toward binaphthol-derived systems. They investigated oxidative cross coupling of various substituted 2-naphthols mediated by different Cu(II) salts.<sup>50</sup> First cross couplings were performed with an excess (4 equiv) of in-situ-formed copper(II) chloride/*tert*-butylamine complex (1:4) in methanolic media under strictly anaerobic conditions

at temperatures of 25–50 °C and with reaction times of 5–150 min. They achieved 12 couplings from 10 substituted 2-naphthols (Scheme 45) with good to

#### Scheme 45



excellent yields (70–97%). In each case, the coupling occurs at the  $\alpha$ -position of the hydroxyl group.

Nevertheless, under comparative oxidative conditions, the selectivity of the cross coupling is dramatically influenced by the substitution of the aromatic rings. At one extreme, the selectivity is excellent (92% for cross coupling of **1** and **3**; 91% for **1** and **2**), while in the other extreme the selectivity does not exceed limits of statistical distribution (47% for **2** and **3**). Using methyl 3-hydroxy-2-naphthoate (**1**) and 2-naphthol (**2**), the influence of the reaction variables on the selectivity of the cross-coupling reaction was examined. It was found that neither temperature and solvent variations nor the structure of the amine ligand had a significant effect.

Cross couplings were performed next with 4 equiv of  $\text{CuCl}(\text{OMe})$  synthesized in or ex situ. Thus, **1** and **2** were coupled selectively to give 86% yield of isolated crossed product. The main advantage of this protocol is its simplicity: the amine which had to be used in excess is not needed and the formation of a voluminous precipitate of  $\text{Cu}(\text{II})$ –amine complex is avoided, enabling a substantial reduction of the reaction volumes.

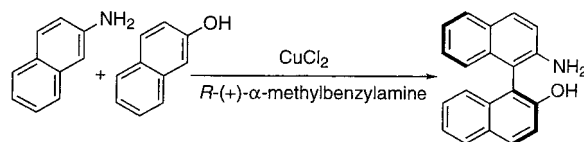
Hovorka et al. were also interested in the mechanism of  $\text{CuCl}_2$ -mediated oxidative couplings.<sup>51</sup> The mechanism is not clear, and essentially three possible routes have been proposed in the literature: (1) homolytic coupling of two radicals ( $X^\cdot + Y^\cdot$ ), (2) ionic reaction ( $X^+ + Y^-$ ), and (3) radical insertion of one of the aryls into the C–H bond of another aryl molecule ( $X^\cdot + Y$ ). Hovorka et al. showed that the model reaction between 2-naphthol and methyl 3-hydroxy-2-naphthoate can be controlled to give either the cross-coupled product or a nonselective mixture of the cross- and homo-coupled products. The copper/ligand ratio was found to be the main controlling factor. They devised a plausible model of a binuclear  $\text{Cu}(\text{II})$  complex explaining the preferential cross coupling: if dimeric complexes  $(\text{ArOCuL})_2$  are considered as intermediates, the coupling would occur as an in-

tramolecular process and the differentiation between pathway 1, 2, and 3 would be “meaningless”.

Using the same procedure as for symmetrical coupling (see section II.3.A.a), Smrcina et al.<sup>47</sup> achieved the cross coupling of 1 equiv of 2-naphthol and 1 equiv of 2-naphthylamine by means of 2.5 equiv of copper(II) chloride in the presence of benzylamine (1:4) at room temperature over 24 h. The racemic cross-coupled product was obtained pure with an isolated yield of 45%.

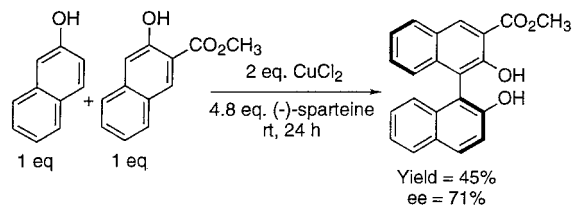
They then carried out the synthesis of enantiomerically pure 2-amino-2'-hydroxy-1,1'-binaphthyl<sup>48</sup> using enantiopure (*R*)-(+)- $\alpha$ -methylbenzylamine (10 equiv) with  $\text{CuCl}_2$  (2.5 equiv). The stereodifferentiation was ascribed to a diastereoselective crystallization of the  $\text{Cu}(\text{II})$ –amine–product complex. The precipitate and the mother liquor, after crystallization, respectively, led to 23% of pure (–)-cross-coupled product and 24% of pure (+)-cross-coupled product (Scheme 46).

#### Scheme 46



A new situation was encountered for the highly chemoselective cross coupling of 2-naphthol with methyl 3-hydroxy-2-naphthoate<sup>49</sup> which displayed a fairly good enantioselectivity (Scheme 47).

#### Scheme 47

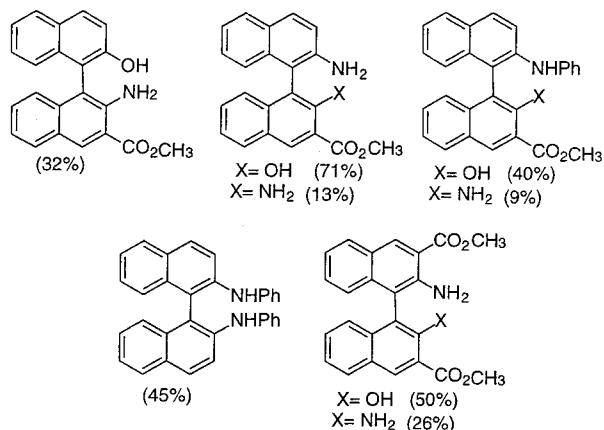


Indeed, the stereodifferentiating process is neither a diastereoselective crystallization nor a second-order asymmetrical transformation. Another mechanism operates in this system: asymmetrical induction in the coupling reaction has been proposed as the most likely one.

Smrcina et al. then extended their method to the selective cross coupling of 2-naphthol and 2-naphthylamine derivatives leading to racemic 2,2',3-trisubstituted and 2,2',3,3'-tetrasubstituted 1,1'-binaphthyls<sup>52</sup> (Scheme 48).

Each product has been synthesized from its respective precursors by the  $\text{CuCl}_2/t\text{-BuNH}_2$ -mediated oxidative cross coupling. Binaphthyls, resulting from the self-coupling, and carbazoles have been identified as byproducts. The nature and number of substituents on the naphthyl derivatives dramatically influence their propensity to cross-couple.

Frontier orbital theory and electrochemical measurements have been employed to explain the observed selectivity. In a coupling reaction with two potential partners A and B, both of them capable of generating a radical, three possible products can be

**Scheme 48**

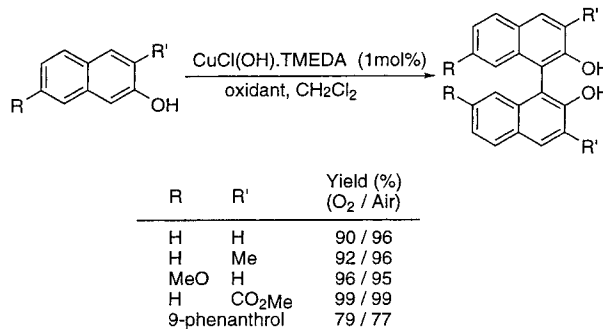
expected, namely, A–A, B–B, and A–B. Assuming that the coupling proceeds as an orbital-controlled process, the choice of the reacting partner for the initially formed radical, e.g.,  $A^*$ , will be determined by the energy difference between the SOMO of  $A^*$  and the HOMOs and LUMOs of A and B. The high-energy SOMO (a nucleophilic radical) is likely to interact with the LUMO of the reaction partner, while the low-energy SOMO (an electrophilic radical) should mix with the HOMO. If the stabilization is greater from the interaction between  $A_{\text{SOMO}}$  and  $B_{\text{HOMO/LUMO}}$ , then preferential formation of the cross-coupled product A–B can be anticipated. Thus, to obtain a high proportion of cross coupling, one partner must be relatively easily oxidized to an electrophilic radical while the acceptor molecule should be capable of electron donation (preferably in an anionic form) with the HOMO close in energy to the SOMO of the radical. Although the mechanism is more complex and the coupling probably occurs in the coordination sphere of copper, it seems that the basic properties of the reaction partners can be approximated by this frontier orbital theory.

**B. Use of Catalytic Amounts of Copper**

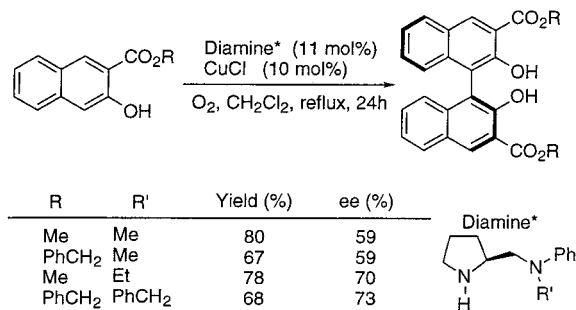
**a. Symmetrical Couplings.** Smrcina et al.<sup>49</sup> carried out one of the first examples of a catalytic, oxidative asymmetrical coupling that creates a binaphthyl system. They proposed a catalytic cycle in order to lend further credence to their mechanistic conclusions (see section II.3.A.a). The crucial point for the design of the catalytic cycle was the reoxidation of Cu(I) to Cu(II). Hovorka et al. reported conditions<sup>50</sup> that were the solution to this issue.

The catalytic self-coupling of 2-naphthol (in form of its sodium salt) is carried out in MeOH with 10 mol % of  $\text{CuCl}_2$ , 20 mol % of (–)-sparteine, and 1.1 equiv of AgCl. The reaction mixture, stirred at room temperature for 72 h, gives rise to (+)-binaphthol (70%; 14 turnovers) of only ca. 3% ee. Although the enantiomeric excess is very low, this experiment demonstrates that the reaction conditions allow for a catalytic process to operate. In this experiment, the oxidation of the copper(I) is performed by the stoichiometric amount of silver, which is the major drawback of this method from an economical point of view.

Koga and Nakajima<sup>53</sup> first developed an efficient catalytic process for the aerobic oxidative coupling of naphthol derivatives by the use of a catalytic amount of  $\text{CuCl-TMEDA}$  (1 mol %) under molecular oxygen or even under ambient conditions (Scheme 49).

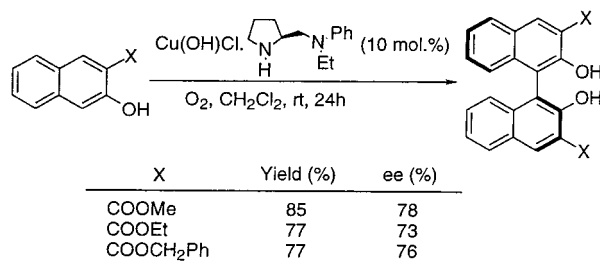
**Scheme 49**

The authors then extended this method to the asymmetrical aerobic coupling<sup>54</sup> of 3-hydroxy-2-naphthoate with a chiral copper-amine complex as a catalyst. They used diamines derived from L-proline because of their availability and their sterically rigid conformation in chelation with various metals (Scheme 50).

**Scheme 50**

They screened several types of ligands and esters, leading them to the conclusion that a secondary nitrogen in the pyrrolidine ring is crucial for asymmetrical induction: the extent of enantioselection is dependent on the bulkiness of  $R'$  substituents on this nitrogen.

They achieved the isolation of a copper-diamine complex by precipitation in hexane. The isolated complex possesses slightly better reactivity, which makes it possible to conduct the reaction at room temperature<sup>55</sup> (Scheme 51).

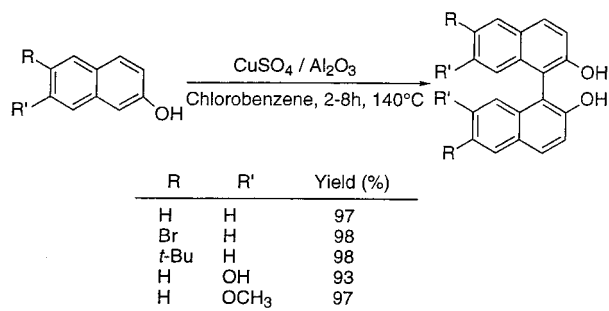
**Scheme 51**



They also carried out an oxidation of naphthols with ketone, amide, alkyl, or alkoxy moieties at the 3-position. Unfortunately it generates the corresponding binaphthols in low enantioselectivities, which implies that the ester moiety is essential for the asymmetrical induction. As the mechanism of this oxidative coupling is unknown, they postulated that their coupling reaction consists of three successive processes: (1) exchange of the hydroxy group on the copper complex for a phenolic hydroxy group followed by the additional coordination of the ester carbonyl to the copper atom, (2) oxidative coupling affording a diketone with central chirality, and (3) transfer of central chirality to axial chirality through keto–enol isomerism along with dissociation of the copper–amine complex.

Pac et al. achieved the coupling of 2-naphthols catalyzed by alumina-supported copper(II) sulfate (SCAT) under aerated conditions<sup>56,57</sup> (Scheme 52).

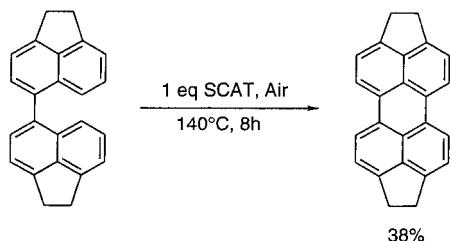
Scheme 52



The supported catalyst can be easily prepared. The remarkable simplicity of both the reaction and the workup procedures is of synthetic significance. Air is essential for the catalysis of the coupling reaction. However, CuSO<sub>4</sub>/Al<sub>2</sub>O<sub>3</sub> can also act as an efficient stoichiometric reagent for the coupling reaction under deaerated conditions. Other similar catalysts were prepared by using solid supports such as acidic and basic alumina, Florisil, Celite, silica gel, and molecular sieves and by supporting Cu(OAc)<sub>2</sub> and CuF<sub>2</sub> on neutral alumina. Nevertheless, their catalytic activities were substantially lower, in most cases, than those of SCAT. What is of interest is that the catalytic activity of SCAT might be restored by appropriate reactivation treatment after oxidation reactions.

The authors then attempted the SCAT-promoted intramolecular dehydrogenative coupling of 5,5'-diacenaphthene<sup>57</sup> as an easy access to perylene with a low yield (Scheme 53).

Scheme 53



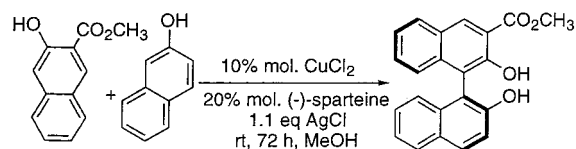
This appears to reflect general limitations of the SCAT catalysis which would arise from steric and

electronic requirements, e.g., adsorption of the reactants on the SCAT surface without steric hindrance, lower oxidation potentials than the limit for one-electron oxidation by Cu(II) of SCAT, and reactivities of the radical cations for the follow-up processes. However, the choice of the metal ions and inorganic solids associated with improvements in preparation of supported catalysts and/or reagents might be able to increase synthetic applicability.

Lakshmi Kantam et al. also developed couplings of 2-naphthols under aerated conditions using Cu-exchanged montmorillonite as a catalyst<sup>58</sup> with similar results to those of Pac et al.<sup>56,57</sup>

**b. Unsymmetrical Couplings.** To lend further credence to their mechanistic conclusions (see section II.3.A.a), Smrcina et al.<sup>49</sup> carried out a catalytic cross coupling of 2-naphthol and methyl 3-hydroxy-2-naphthoate under conditions similar to those employed for the self-coupling of 2-naphthol (see section II.3.B.a). It produced a (–)-cross-coupled product of 32% ee (41%; eight turnovers). This was the first example of catalytic asymmetrical oxidative cross coupling (Scheme 54).

Scheme 54



**c. Oxidative Coupling with FeCl<sub>3</sub>.** Similar to oxidative couplings with copper(II), iron(III) is also used as an oxidative reagent. Indeed, because of its oxidizing properties and its low cost, iron(III) has been used for many years to perform the homocoupling of substrates with low oxidation potential, in particular for the synthesis of 1,1'-binaphthol. Typically the reactions were carried out in organic media using solutions with more than equimolar amounts of FeCl<sub>3</sub>.<sup>59</sup>

Several variants were developed, such as the use of K<sub>3</sub>Fe(CN)<sub>4</sub> by Feringa et al.,<sup>60</sup> but all of these methods suffered from difficulties in the separation of organic and inorganic products, from the formation of quinones as byproducts, and from the disadvantage of requiring (over)stoichiometric amounts of reagent.

Toda et al. reported a solid-state oxidative procedure for the preparation of binaphthol derivatives.<sup>61</sup> They found that the reaction proceeded faster and more efficiently (91–95% yields) in the solid state than in solution and that it could be accelerated by irradiation with ultrasound. Taking advantage of the fact that oxidation of Fe<sup>2+</sup> to Fe<sup>3+</sup> in air occurred easily in the solid state, the authors carried out the coupling reaction at 50 °C over 24 h in the presence of catalytic amounts of FeCl<sub>3</sub>·6H<sub>2</sub>O (0.2 equiv) with a 89% yield. Similarly, Villemin et al. used stoichiometric amounts of FeCl<sub>3</sub> without solvent under microwave irradiation.<sup>62</sup>

Ding et al. carried out the reaction in water.<sup>63</sup> Indeed, the oxidative coupling of 2-naphthols suspended in aqueous Fe<sup>3+</sup> (2 equiv) gave the corresponding 1,1'-binaphthols with yields of 91–95% and proceeded much faster than in homogeneous solution.

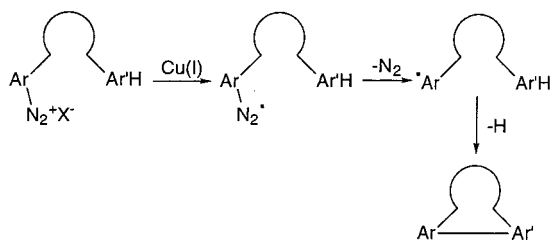
Considering the insolubility of 2-naphthol in water, the authors suggested that the reaction occurs at the surface of the crystalline 2-naphthol via a solid–liquid process.

As they had done with copper,<sup>58</sup> Lakshmi Kantam et al. used heterogeneous catalysis for the oxidative coupling of 2-naphthols.<sup>64</sup> The catalysts were iron supported either on a montmorillonite clay (23.4% Fe<sub>2</sub>O<sub>3</sub>) or an acid-treated mesoporous clay (Fe–K10; 20.4% Fe<sub>2</sub>O<sub>3</sub>). Although both Fe–clays gave high yields of homocoupling products (88–95%), Fe–K10 appeared to have the highest activity. This activity was attributed to the easier access of the catalytic sites on this clay. In both cases the catalyst could be recycled without loss of catalytic properties and the procedure is easy and simple.

#### 4. Aromatic Coupling via Radicals (The Pschorr Reaction) Using Copper Salts

The major use of the copper-mediated reaction is to obtain symmetrical biaryls mainly via intermolecular procedures. Nevertheless, a few cases of intramolecular couplings have been developed, based on the Pschorr reaction. The Pschorr reaction<sup>65</sup> has an even longer history than the Ullmann reaction. It involves the intramolecular substitution of arenes by aryl radicals which are generated by the reduction of arene diazonium salts usually with a copper(I) ion. Aryl diazenyl radicals, intermediates in the reaction, rapidly eliminate nitrogen giving rise to the required aryl radicals for C–C bond formation<sup>3</sup> (Scheme 55).

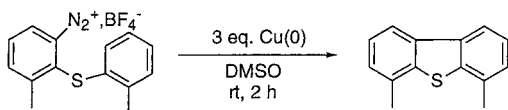
Scheme 55



The Pschorr reaction has two main weaknesses: starting compounds are not always easily prepared and the yields of ring-closed product are often modest.

In the last step of the synthesis of 4,6-dimethyl-dibenzothiophene, Meille et al. achieved an intramolecular cyclization with a suspension of Cu(0)<sup>66</sup> (Scheme 56).

Scheme 56



After recrystallization, a 26% yield is obtained which represents the usual low yield of this method.

#### 5. Synthesis of Oligomers and Polymers Using Copper as a Reagent

The synthesis of films of polyacetylene,<sup>67</sup> with an excess of Ziegler–Natta catalyst, was the discovery which stimulated research into organic conducting

polymers. Exposing these films to iodide vapor, Shirakawa et al.<sup>68</sup> observed a considerable increase in conductivity. This discovery, which represents the beginning of the tremendous story of organic conducting polymers, earned Shirakawa, MacDiarmid, and Heeger the Nobel Prize in Chemistry for the year 2000. Since then, studies have been extended to a wide range of other macromolecules<sup>69,70,71</sup> with the same conjugated structure such as polythiophenes,<sup>72</sup> polypyrroles, poly-*p*-phenylenes, etc. Over the past few years, organic conducting oligomers or polymers have been intensively studied, owing to their fundamental optoelectronic properties and their potential applications ranging from photodiodes<sup>73</sup> to light-emitting devices (LEDs)<sup>74</sup> and thin film transistors (TFTs).<sup>75</sup>

It is now well established that the physical properties of conducting polymers are closely linked to the structure of their monomeric precursor and to their polymerization conditions. The polymerization of organic monomers can be classified into two categories, i.e., the oxidative electrochemical or chemical polymerization and the organometallic couplings.

The electrochemical anodic polymerization has been extensively studied.<sup>76</sup> This method presents the advantage that the doped conducting polymer is directly grafted onto the electrode surface, which is of particular interest for electrochemical applications or in situ characterization by electrochemical analyses. Many of the chemical polymerizations are based on the oxidative coupling of monomeric precursors using oxidants such as FeCl<sub>3</sub> or CuCl<sub>2</sub>. The polymers obtained by these methods are often high-molecular-weight polymers with a rather low amount of irregular couplings.

On the other hand, organic conductive polymers can be synthesized by organometallic couplings. The Ullmann, Kumada–Corriu, Stille, Heck, or Suzuki-coupling reactions have been performed to obtain polymers and will each be discussed in a section of the review. Usually these methods generate more regioregular head-to-tail polymers with high molecular weights and conductivities.

Among conjugated oligomers or polymers, polypyrroles and polythiophenes have attracted great attention for their chemical stability, ease of functionalization, and variety of useful properties. This section will deal with the synthesis of such polymers and oligomers using copper as the reagent. Since its behavior for oxidative coupling is similar to that of copper and since it is largely used for chemical polymerization, iron will also be discussed as a reagent.

The classical Ullmann reaction (see section II.1) has allowed the synthesis of various polymers, especially polymers from monomers bearing an electron-withdrawing group.

The oxidative coupling of activated aryls using copper or iron has also been performed to obtain mainly oligomers.

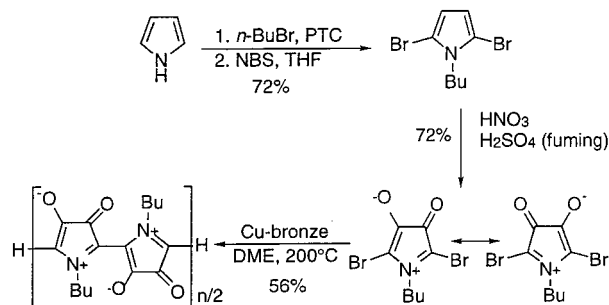
Last but not least, chemical polymerization with FeCl<sub>3</sub> has been widely developed. Nowadays this methodology suffers from its lack of regioregularity (only 80% of the synthesized polymers are regioregu-

lar). Nevertheless, this method is also suitable for the synthesis of well-defined oligomers.

### A. The Ullmann Reaction

In an effort to maximize the extended  $\pi$ -conjugation in polymers and to study their corresponding optical and electronic properties, Tour et al.<sup>77</sup> performed the synthesis of a zwitterionic pyrrole-derived polymer using the Ullmann reaction (Scheme 57).

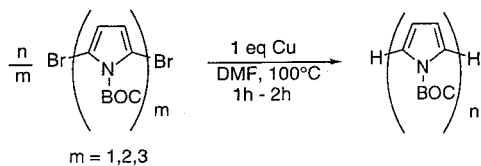
**Scheme 57**



The use of DME as the solvent was crucial since common solvents of the classical Ullmann coupling (DMF, pyridine) did not allow polymerization. After 18 h of reaction, fractional precipitation produced a polymer with a polydispersity (PD) of 1.15–1.25 with a number-average molecular weight of 3910 g/mol (i.e., 26 zwitterionic repeating units were formed). No bromide content was detected, which is a commonly observed feature of Ullmann reactions<sup>78</sup> since the excess Cu(0) carries out oxidative additions on aryl bromide locations with subsequent end-group protonations on workup or from the solvent.

To study and synthesize well-defined 2,5-linked polypyrroles, Groenendaal et al.<sup>79</sup> also used the Ullmann coupling reaction. They first synthesized three *N-t*-BOC-protected monomers of various sizes: 2,5-dibromopyrrole, 5,5'-dibromo-2,2'-bipyrrole, and 5,5''-dibromo-2,2':5',2''-terpyrrole. The polymerization of the monomers was carried out at 100 °C under inert atmosphere (Scheme 58).

**Scheme 58**

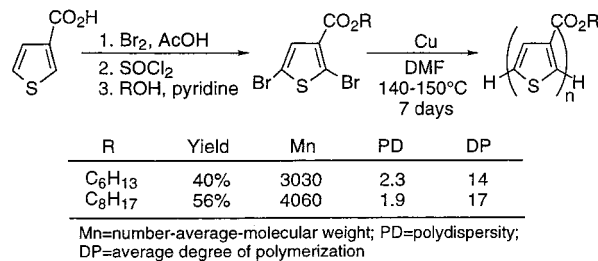


After analyses by HPLC, they found that in the case of the pyrrole monomer 25 different oligomers with up to 25 pyrrole repeating units were formed while 8 different oligomers with up to 16 repeating units were obtained starting from bipyrrole monomer and up to 24 units starting from terpyrrole monomer. This difference may be due to the lower reactivity and the higher stability of the longer monomers. Their observations have led the authors to propose a chain-reaction mechanism for the oligomerization of *N-t*-BOC-2,5-dibromopyrrole.

Looking for a general synthesis of polythiophenes bearing a carbonyl group (or other strongly electron-

withdrawing substituents) directly attached to the 3-position of the thiophene ring, Pomerantz et al.<sup>80</sup> naturally thought about using the Ullmann reaction (Scheme 59).

**Scheme 59**



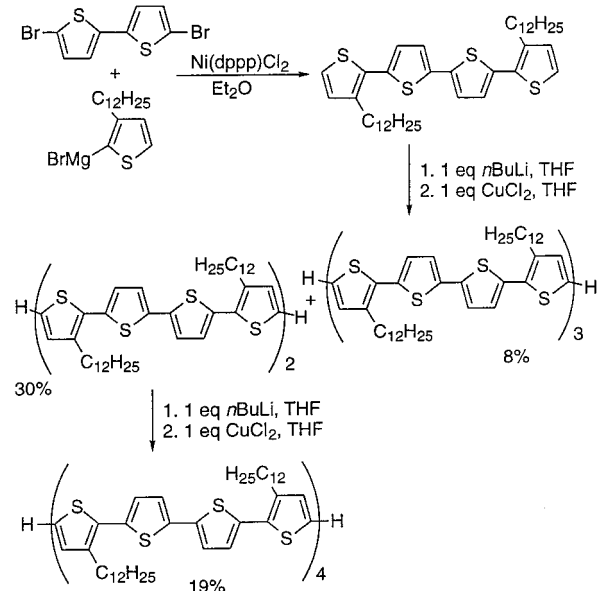
Furthermore, the authors showed that polymers obtained by this route had better properties (i.e., lower polydispersity and longer conjugation lengths) than polymers prepared by a Ni(0) coupling reaction.

### B. Oxidative Coupling of an Activated Aryl

#### a. Using Copper as the Oxidative Reagent.

Interested in the synthesis of structurally defined conjugated oligomers with dimensions on the nanometer scale, Bäuerle et al.<sup>81</sup> performed the synthesis of a homologous series of isomerically pure  $\alpha$ -linked oligo(alkylthiophenes). In particular, they synthesized and isolated a sedicithiophene which should be 64 Å when extended. Their monomeric precursor, a quaterthiophene, was synthesized using a nickel-catalyzed coupling. The conversion of this monomer to higher homologues was carried out by oxidative dimerization of the lithiated compound with CuCl<sub>2</sub> (Scheme 60).

**Scheme 60**

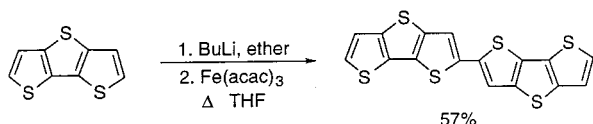


Owing to their solubility, each oligomer was obtained in pure form by repeated chromatography. The authors then studied their physical properties and obtained the first STM images of physisorbed two-dimensional crystalline layers of the oligomers with submolecular resolution.



**b. Using Iron as the Oxidative Reagent.** Looking for new organic conductors for thin film transistor (TFT) applications, Li et al. produced the "dimerization" of a fused thiophene derivative<sup>82</sup> using ferric acetylacetonate as the oxidative coupling reagent (Scheme 61).

Scheme 61



This dimer,  $\alpha,\alpha'$ -bis(dithieno[3,2-*b*:2',3'-*d*]thiophene), was found to have an unusual  $\pi$ -stacked structure and a wide HOMO–LUMO gap, which induces a high mobility and a very high On/Off ratio for the material.

### C. Chemical Polymerization Induced by Iron

In the 1980s, conducting polymers raised huge interest. However, their insolubility in any solvent has been a serious restriction to their practical applications. That is the reason many teams have worked to synthesize soluble polythiophenes, mainly obtained with monomeric thiophene precursors bearing an alkyl chain in the 3-position.

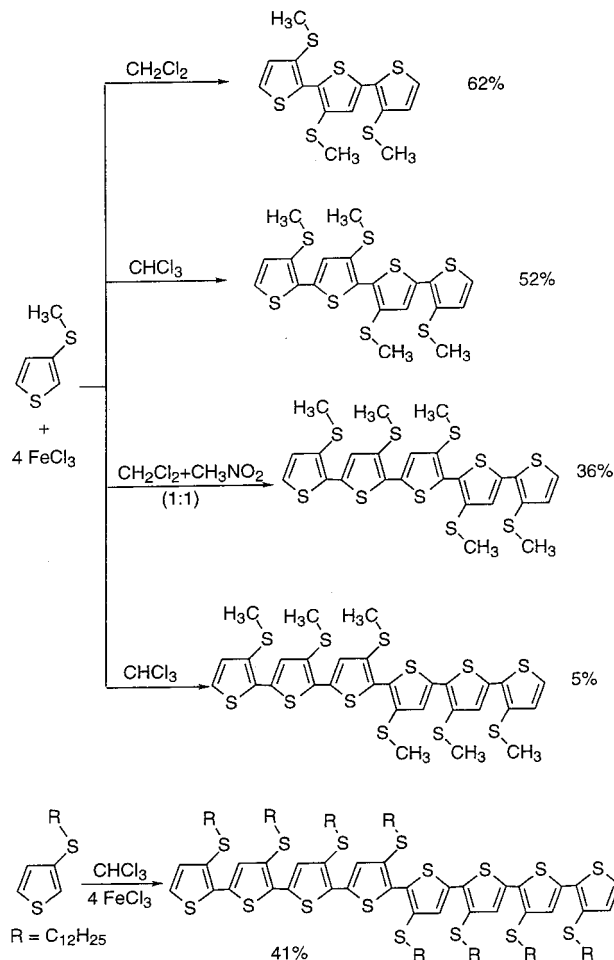
In 1986, a few months after Sato et al.<sup>83</sup> and Lemaire et al.<sup>84</sup> reported the electrochemical polymerization of polythiophene, Sugimoto et al.<sup>85</sup> achieved the first chemical polymerization of 3-alkylthiophene utilizing 4 equiv of  $\text{FeCl}_3$  as the oxidative reagent in chloroform. From this experiment, chemical polymerization of various 3-alkylthiophenes has been performed. Nevertheless, the reaction mechanism of the chemical polymerization is still unclear and subject to controversial interpretations.<sup>86,87</sup> Wegner et al.<sup>88,89</sup> carried out a complete study of several well-characterized poly(3-alkylthiophenes) concentrating their attention on the structural regularity and molecular weight of the polymers. Indeed, those two factors drastically influence the overall performance of a polymer with regard to conductivity in combination with useful mechanical properties. Thus, Wegner et al. synthesized soluble high-molecular-weight polymers which have rather a low amount of irregular couplings (ca. 20%).

To bypass this lack of regioregularity, Zagórska et al.<sup>90</sup> performed the chemical polymerization of 4,4'-dialkyl-2,2'-bithiophenes using the classical conditions of Sugimoto. With this kind of monomer, the coupling results in a regular structure equivalent to alternating tail-to-tail and head-to-head couplings of monomeric 3-alkylthiophenes. However, since the regioregularity of polymers synthesized by oxidative chemical polymerization can hardly exceed 80%, this method is not used very much for the synthesis of polymers but is used for the synthesis of well-defined oligomers.

Barbabella et al.<sup>91</sup> made a remarkable study of the regioselective oligomerization of 3-(alkylthio)thiophenes with ferric chloride. Whereas in the same experimental conditions 3-alkylthiophenes always lead to high-molecular-weight polymers,<sup>92</sup> the au-

thors observed the formation of regioregular  $\alpha$ -conjugated oligothiophenes, from trimer to octamer, depending on the length of the alkyl chain and the solvent used (Scheme 62).

Scheme 62



Theoretical calculations of the coefficients of the HOMO orbitals of the monomer and of the corresponding head-to-head, head-to-tail, and tail-to-tail 2,2'-bithiophenes and calculations of the coefficients of the SOMO orbitals of the corresponding radical cations showed that the regioselectivity of the oligomers is due to the strong orienting effect of the substituent and to the stability of the radical cations formed during the oxidative process.

Working on the dodecyl and hexyl derivatives of 1,3-dithienylbenzo[*c*]thiophene, Mohanakrishnan et al.<sup>93</sup> achieved their oligomerization to dimers and trimers (with yields of, respectively, 62.5% and 12.5% for the dodecyl derivative and 43% and 23% for the hexyl one).

The same reaction with a dithienylbenzo[*c*]thiophene functionalized with silyl groups on the  $\alpha$ -position at each end leads to a dimer with a good yield (66%).

### III. Nickel-Promoted Aryl–Aryl Bond Formations

Nickel-catalyzed aryl–aryl bond formations have been studied especially since the discovery by Kumada<sup>94,95</sup> and Corriu,<sup>96</sup> in 1972, of an efficient method for the formation of C–C bonds by nickel-catalyzed



coupling of Grignard reagents with organohalides. This reaction, further developed by using complexes of Pd and other group-VIII metals, is highly selective, allowing the formation of symmetrical and unsymmetrical biaryls in high yields, and is furthermore run under mild conditions. These types of reactions have since been widely studied with, for example, organozinc, organoboron, and organotin reagents showing similar high efficiency as well as improved compatibility with many functional groups present in the substrates. Kalinin<sup>97</sup> extensively reviewed the application of these methods to the functionalization of heterocyclic compounds in 1991. We will focus here on the use of nickel complexes as promoters for the coupling of two aromatic rings over the past 10 years. We will first describe reactions where nickel is used in stoichiometric amounts (Ni(0) as the preformed or in situ prepared reagent) and then transformations involving catalytic amounts of nickel. Here again these reactions involve an additional reducing agent or the use of organometallic aromatic derivatives (see, as described above, the “Kumada–Corriu” reaction).

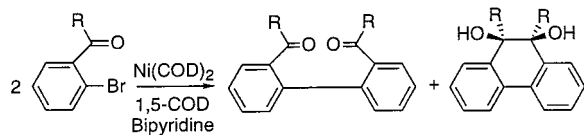
## 1. Aromatic Coupling Involving Stoichiometric Amounts of Nickel

Ni(0)-mediated aryl–aryl bond formations have been described for the homocoupling of haloaryl compounds and proved to be very efficient for the preparation of bi-, oligo-, and polyaryls. Examples where stoichiometric amounts of preformed Ni(0) reagents have been used were reported by Semmelhack et al.<sup>98</sup> This procedure was later extended to the preparation of the in situ active form of nickel (use of Ni(II) and an additional reducing agent) by Kende et al.<sup>99</sup> Such examples are now seldom found in the literature because the pendant reaction, i.e., nickel used in catalytic amounts, offers much more interest in terms of both cost and ease of preparation.

### A. Nickel(0) Used as a Preformed Reagent

To illustrate this reaction, we mention the homocoupling experiments, reported by Scherf et al.,<sup>100</sup> of 2-carbonyl-substituted bromobenzenes with Ni(COD)<sub>2</sub> (bis(1,5-cyclooctadiene)nickel(0)). This reagent had to be used in excess (1.2–2.2 equiv of per aryl–aryl bond formed) to allow high yields of the desired product. Interestingly, the use of Ni(0) allowed the formation of a subsequent *cis*-pinacol cyclization (Scheme 63) according to the experimental procedure

#### Scheme 63



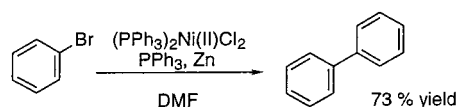
(amounts of the metal introduced or the rate of addition of the coupled material).

### B. Use of Additional Zinc or Other Reducing Agents

Many recent examples use Ni(0) prepared in situ, for example, by using stoichiometric amounts of a Ni(II) salt in the presence of a reducing agent. Indeed,

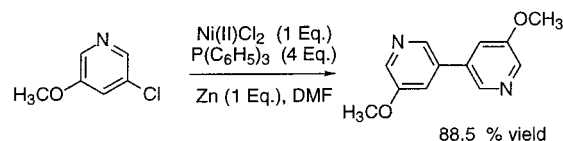
zerovalent nickel reagents are air-sensitive, need to be prepared by sophisticated techniques, and thus remain difficult to handle. As already mentioned, Kende et al.<sup>99</sup> reported a simple method to generate in situ tris(triphenylphosphine)nickel(0), the reactive species undergoing further oxidative additions with aryl halides. They were able to reduce bis(triphenylphosphine)nickel(II) dichloride with zinc in the presence of stoichiometric amounts of triphenylphosphine and to use the solution of zerovalent nickel complex for biaryl formations (Scheme 64).

#### Scheme 64



This procedure was tested for the homocoupling of bromo- and iodobenzene derivatives in DMF to give the expected biaryls with a modest to good yield (up to 85%). Tiecco and Testaferri<sup>101</sup> further improved this procedure by preparing the active Ni(0) complex directly from nickel(II) chloride, triphenylphosphine, and zinc, avoiding the ex situ preparation of the complex Ni[P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>2</sub>Cl<sub>2</sub>. They then applied this method to the synthesis of various symmetrical bipyridines and biquinolines. They successfully tested the homocoupling of bromo and chloro derivatives with good yields (up to 89%, Scheme 65). The major

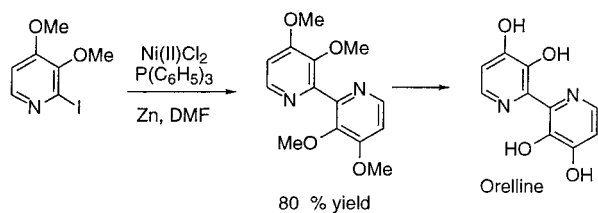
#### Scheme 65



drawback of the above-described method is certainly the necessity for large amounts of triphenylphosphine that require subsequent separation by chromatography. A transposition of this method to the industrial scale is therefore hardly conceivable.

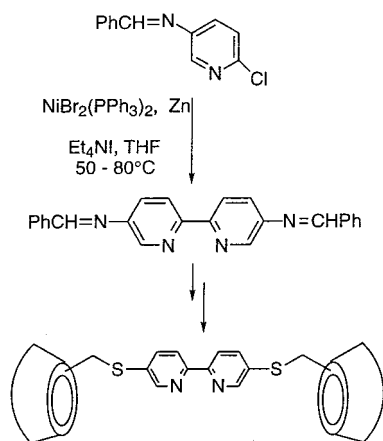
This method has been widely used for the synthesis of symmetrical nitrogen-containing aromatic derivatives. Quéguiner et al.<sup>102</sup> tested this homocoupling reaction to build the 2,2'-bipyridyl structure of the alkaloid orelline (Scheme 66). The target molecule

#### Scheme 66



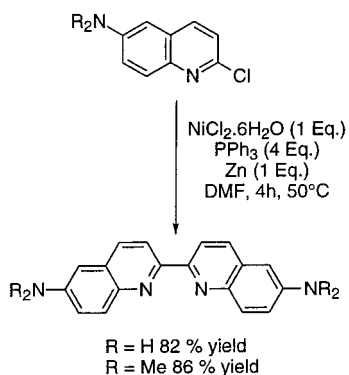
was obtained via the nickel–phosphine complex-mediated homocoupling of 2-iodo-3,4-dimethoxy-5-pyridine in a 80% yield.

Zhang and Breslow<sup>103</sup> used this methodology to prepare 5,5'-diamino-2,2'-bipyridine. This intermediate was further modified to act as a linker between a  $\beta$ -cyclodextrin dimer (Scheme 67). This catalyst

**Scheme 67**

precursor was then used as an enzyme mimic with a metallobipyridyl-linking group for ester hydrolysis with good turnover.

Recently, Janiak et al.<sup>104</sup> described the preparation of 6,6'-diamino-2,2'-biquinoline derivatives by coupling the corresponding 6-chloroquinolines (Scheme 68) in the presence of  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{PPh}_3/\text{Zn}$  in DMF

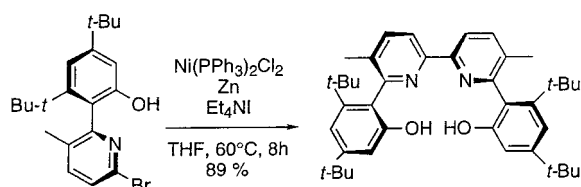
**Scheme 68**

(called NiCRA for nickel-containing complex reducing agent).

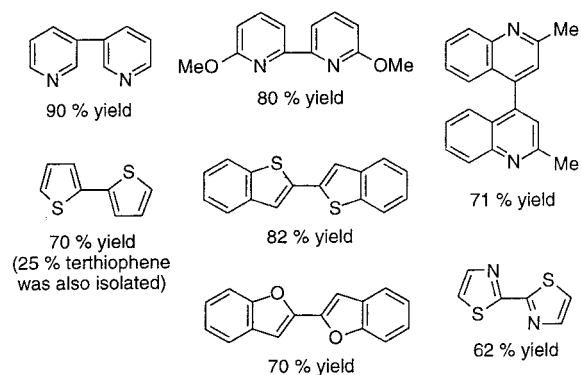
Chan used this method for the synthesis of a new type of chiral atropisomeric 2,2'-bipyridine for application in asymmetric cyclopropanation.<sup>105</sup>

This type of coupling was very recently performed by Howarth et al.<sup>106</sup> employing the ionic liquid  $[\text{bmim}]\text{PF}_6$ , where  $[\text{bmim}]^+$  is the 1-butyl-3-methylimidazolium cation. These types of liquids may provide an alternative to classical solvents for minimizing industrial wastes, since they are nonvolatile and immiscible with a wide range of organic solvents (thus easily reusable). The authors tested the coupling of a variety of aryl bromides (bearing electron-donating or -withdrawing substituents) to occur in the ionic liquid  $[\text{bmim}]\text{PF}_6$  with a mixture of  $(\text{PPh}_3)_2\text{NiCl}_2$ , Zn and  $\text{PPh}_3$  as the catalyst. The yields obtained were comparable to those generally obtained in the more classical DMF, but the ionic liquid containing the spent catalyst could be reused by reforming the Ni(0) active species without adding further  $(\text{PPh}_3)_2\text{NiCl}_2$ , although there was a small decrease in the yield of the coupling reaction.

Fort et al.<sup>107</sup> prepared a number of nitrogen-, sulfur-, or oxygen-containing bis-heteroaromatic or

**Scheme 69**

bis-heterocyclic derivatives by homocoupling the corresponding halogenated compounds using a similar procedure. In these cases, the authors assumed mixtures of sodium hydride, sodium alkoxide, and  $\text{Ni}(\text{OAc})_2$  to be the best activating agents to perform these couplings of organic halides. In Scheme 70,

**Scheme 70**

some examples of biaryl structures obtained by this procedure are given. Couplings occurred in good to excellent yields whatever the nature of the halide, the main side reaction being the reduction of the C-halogen bond.

Attempts to use these reagents in catalytic amounts failed, due to the significant reduction of the starting material by excess sodium alkoxide or sodium hydride added to regenerate the catalytic system.

This list of examples is certainly not exhaustive but is however representative of the large use of the  $\text{NiCl}_2/\text{Zn}$  system for the preparation of symmetrical biaryls, especially pyridine derivatives.

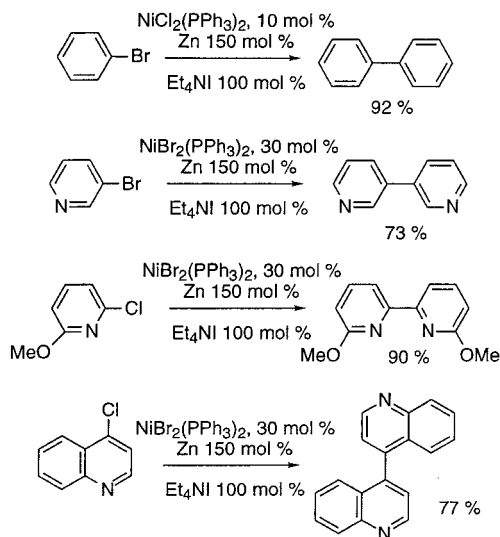
## 2. Aromatic Coupling Involving Catalytic Amounts of Nickel

In recent years, many more methods involve the use of nickel in catalytic amounts to promote efficient biaryl cross coupling. The aforementioned methodology, i.e., the homocoupling of aryl halides, has been adapted to the use of Ni(II) in catalytic amounts through the presence of a chemical reducing agent (mostly zinc) or the help of electrons provided by a cathode. We will first report some examples to illustrate the coupling reactions leading to the synthesis of symmetrical biaryls classified according to the nature of the reducing species used. Subsequently, we will examine cross-coupling reactions between aryl halides, organometallic derivatives, and catalytic amounts of Ni(II) species for providing unsymmetrical compounds. Recent examples will be summarized according to the nature of the coupling aryl nucleophiles (organozinc, Grignard, or borane derivatives).

## A. Homocoupling of Aryl Halides

**a. Use of Zinc as the Reducing Agent.** Since the discovery of Kende that Ni(0) generated in situ was efficient for the homocoupling of aryl bromides, many alternatives and improvements to this nickel-catalyzed coupling reaction have been performed.<sup>108</sup> Kumada and Tamao<sup>109</sup> were, for example, able to perform this transformation by using catalytic amounts of Ni(II) complex and stoichiometric amounts of zinc in the presence of triphenylphosphine. Iyoda et al.<sup>108</sup> further improved this methodology by generating the active Ni(0) complex from NiX<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and zinc in the presence of Et<sub>4</sub>Ni. This nickel catalyst was efficiently prepared in THF without additional triphenylphosphine and allowed the homocoupling of aryl chlorides, bromides, and iodides. The authors tested their procedure for the coupling of numerous biaryls and bipyridines with good yields (Scheme 71).

## Scheme 71

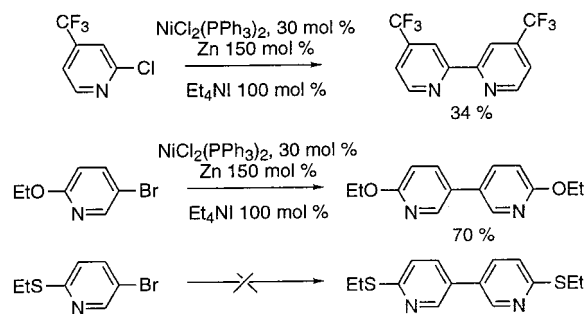


A larger amount of catalyst had to be used for the coupling of halopyridines since the corresponding bipyridines formed stable complexes with nickel.

The authors discussed the possible mechanisms involved in the transformations which remain still, however, controversial. As key steps, the simplest mechanism involved the oxidative addition of aryl halides to Ni(0), the formation of diaryl–nickel(II) species via metathesis, and reductive elimination. Colon,<sup>110</sup> Amatore, and Jutand<sup>111</sup> proposed nickel(I) and nickel(III) species as privileged intermediates. The role of the ammonium iodide is also not well understood, but iodide anions accelerate coupling reactions markedly. It has been proposed that iodide may act as a bridging ion between nickel and zinc in the electron-transfer processes.<sup>111</sup>

The aforementioned procedure described by Iyoda et al. has been applied for the homocoupling of 2-chloro(trifluoromethyl)pyridines toward the preparation of bis(trifluoromethyl)-2,2'-bipyridines.<sup>112</sup> The yields remained moderate (up to 34%, Scheme 72), probably because of the reduced electron density on the pyridine ring. Constable et al.<sup>113</sup> reported studies concerning the synthesis of dinucleating ligands for copper, including 3,3'-bipyridine units. These com-

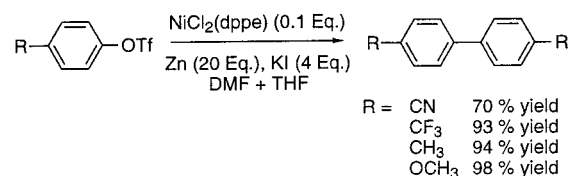
## Scheme 72



pounds were prepared according to Iyoda's procedure for the coupling of substituted 3-bromopyridines. Yields of desired products (Scheme 72) were higher than in the preceding example. The halopyridine derivatives tested bore an electron-donating substituent and gave rise to bipyridines with lower complexing properties. It is interesting to note that the homocoupling was not successfully achieved when the halopyridine was functionalized with a sulfur-containing group. The authors observed that the coupling of 5-bromo-2-ethylsulfanylpyridine led to a large number of organic products, most of them arising from desulfurization processes. These relatively mild coupling conditions were thus not compatible with the coupling of thioethers, probably due to the desulfurization capabilities of the active catalytic nickel species.

This procedure has been performed with aryl triflates in the presence of zinc powder<sup>114</sup> either with a palladium(II) or nickel(II) complex. The synthesis of 1,1'-binaphthyl was reported in a good yield (82–92%) from 1-naphthyl triflate using either NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> or NiCl<sub>2</sub>(dppe) as a catalyst in the presence of zinc and potassium iodide as additives. Interestingly, both complexes were also able to catalyze the homocoupling of 1-naphthyl tosylate. The scope of this methodology has been studied with the synthesis of functionalized symmetrical biaryls. In most cases, nickel was found to be more efficient than palladium, especially when the aryl derivative was substituted with an electron-donating group (Scheme 73).

## Scheme 73

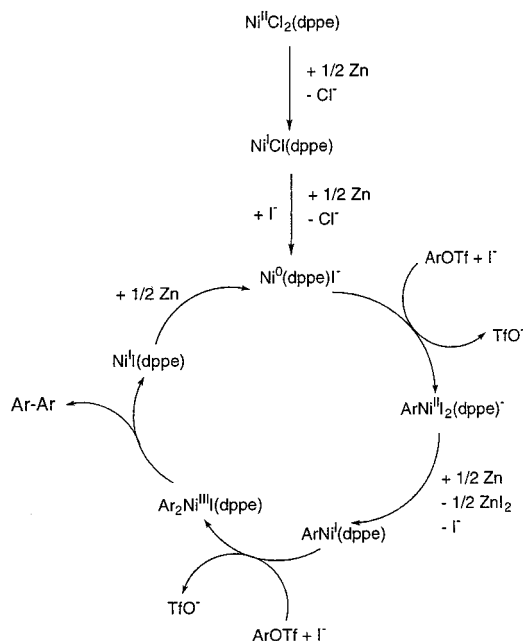


Jutand and Mosleh studied this reaction and proposed a mechanism<sup>115</sup> (see Scheme 74) for the nickel dimerization of aryl triflates with zinc as an electron supplier.

They suggested the single-electron reduction of the intermediate ArNi<sup>II</sup>XL<sub>2</sub> complex by zinc to be the rate-determining step. Iodides should be effective both for forming a pentacoordinated species ArNi<sup>II</sup>-XIL<sub>2</sub><sup>-</sup> and for stabilizing the Ni(0) species. This group also tested less reactive 1-naphthol derivatives for the homocoupling under these conditions and found a decreasing reactivity for NiCl<sub>2</sub>(dppe) as the catalyst



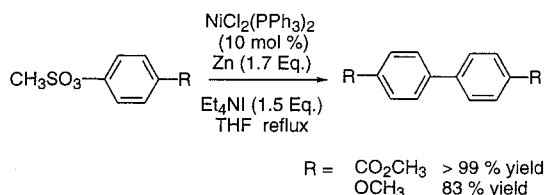
## Scheme 74



The authors attempted to perform the synthesis of enantiopure atropoisomers by using optically active ligands on the metal in order to perform asymmetric homocoupling. They were, however, unable to run such a reaction with *ortho*-substituted aryl triflates and BINAP as the chiral ligand due to steric hindrance around the metal.

Percec et al.<sup>116</sup> demonstrated that aryl mesylates were able to undergo Ni(0)-catalyzed homocoupling reactions under mild conditions. The highest yields were obtained when the aryl group had electron-withdrawing substituents in the *para*-position (Scheme 75).

## Scheme 75



The authors studied in detail the influence of the electronic and steric effects of substituents attached to the aryl sulfonates as well as the effects of the polarity and dryness of the solvent, halide ion source, and concentration of the catalyst and ligand. In all cases, high yields were obtained with aryl mesylates, but they remained less reactive than aryl triflates.

**b. Other Chemical Reducing Agents.** Recently, Fort et al.<sup>117</sup> reported that lithium hydride could be efficiently used as a reducing agent in the liganded Ni(0)-catalyzed homocoupling of haloaryls. They found that biphenyls were obtained in good to excellent yields (up to 92% isolated yield) by refluxing various aryl halides in THF, in the presence of Ni(OAc)<sub>2</sub>, and an excess of *t*-BuOLi activated LiH. Optimization of the reaction indicated that a 20-fold molar excess of

LiH and 2-fold molar excess of *t*-BuOLi relative to Ni(0) were necessary.

It is noteworthy that couplings were not efficient with substrates bearing sulfur-containing substituents, because they suffered from a competitive desulfurization under these conditions. When aryl chlorides were used as coupling precursors, a higher concentration of the catalyst (20 mol %) was needed: the authors proposed that the regeneration of the catalyst was inhibited by in-situ-generated LiCl. It is obvious that oxidative addition of nickel into a carbon-halogen bond is more difficult with a chlorine atom. Considering the amounts of the catalyst and associated reducing agent, this method appears competitive when examined in relation to several of the previously described experiments in which zinc and nickel are simultaneously used.

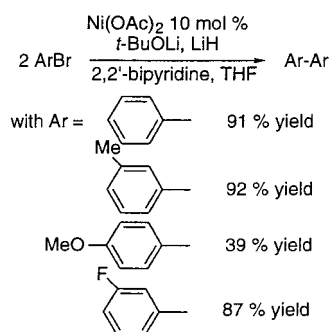
**c. Electroreductive Homo or Cross Coupling of Aromatic Halides.** The homocoupling toward the synthesis of biaryls has been similarly studied using electrochemical reduction instead of zinc powder as the chemical reductant. This was again partly the work of Jutand and Mosleh,<sup>114,118</sup> who were essentially studying the palladium-catalyzed electro-synthesis of biaryls from aryl triflates. Troupel et al.<sup>119</sup> studied the analogous nickel(II)-catalyzed reaction for the electro-synthesis of biaryls from haloarenes. They performed the electroreduction of Ni(II) to Ni(0) in the presence of triphenylphosphine. They proved that the oxidative addition of PhX to zerovalent nickel was obtained directly by electrolysis at the formation potential of Ni(0). In the mixed solvent, THF-HMPT, with an excess of triphenylphosphine and LiClO<sub>4</sub> as the electrolyte, modest to high yields of biaryls were obtained from phenyl chloride (82%), phenyl bromide (58%), and phenyl iodide (22%). This order of reactivity is obviously the inverse to that observed in most of the previously described examples and could be ascribed to the anodic reaction in the electrolytic cell. From a synthetic point of view, this observation is potentially of particular interest for electroorganic chemistry.

The authors performed additional reductive couplings of organic halides in polar aprotic solvents,<sup>120</sup> where zerovalent nickel-2,2'-bipyridine (Ni-bpy) was electrogenerated as the active catalyst. They were able to replace DMF or NMP, generally used as the solvents to perform such transformations, by mixtures of EtOH/DMF or EtOH/MeOH.<sup>121</sup> Recently, by replacing bipyridine by 2,2'-dipyridylamine (dpa) as a nitrogenous bidentate ligand, they were able to run the same type of transformations in a cheap and safe solvent like EtOH<sup>122</sup> (Scheme 77).

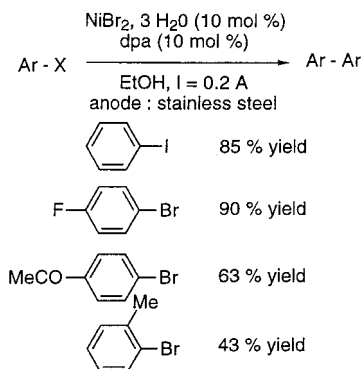
These transformations were performed in an undivided cell with a stainless steel rod as the anode surrounded by a nickel grid as the cathode. During the electrolysis, the potential of the cathode was around -0.9 V vs SCE, corresponding to the reduction of the divalent nickel-dpa complex. Under these conditions, the yields of biaryls were either equal or higher than those previously obtained with a Ni-bpy catalyst. It is also worth noting that *ortho*-substituted aromatic halides can be coupled, however in moderate yield, with this system. Demnitz et al.<sup>123</sup>



## Scheme 76



## Scheme 77

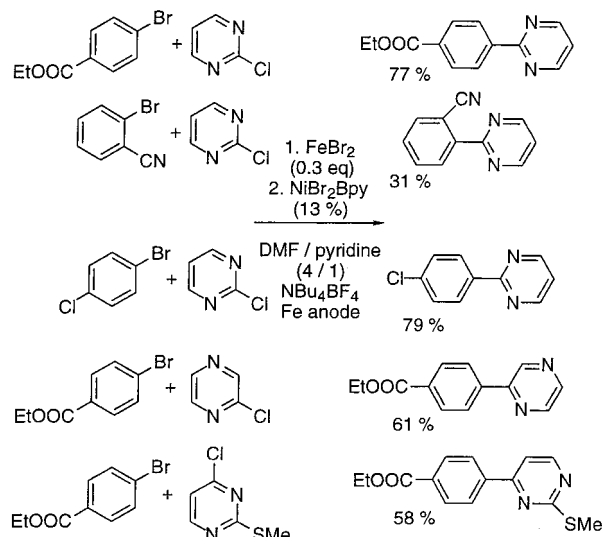


reported analogously the reductive homocoupling of 6-bromopicoline to provide 6,6'-dimethyl-2,2'-bipyridine in high yields. Several groups attempted to optimize the method for the preparation of highly reactive nickel to perform analogous transformations. Yasuhara et al.<sup>124</sup> reported an efficient preparation involving the electrolysis of a DMF solution containing  $\text{Bu}_4\text{NBF}_4$  as the supporting electrolyte in an undivided cell with a platinum cathode and a nickel anode. The subsequent reaction of various iodoaryls with the aforementioned electrogenerated nickel gave the corresponding biphenyls in good yields.

Very recently, Périchon et al.<sup>125</sup> performed efficient electrochemical cross couplings between functionalized aryl halides and 2-chloropyrimidine or 2-chloropyrazine (in equimolar quantity) leading to the preparation of unsymmetrical biaryls in good yields (Scheme 78). Iron salts as additives were necessary for this reaction. In their absence, the *N*-containing heterocycles were probably so strongly ligated to the nickel catalyst that the catalyst became inefficient, and only reduction products from the reagents were observed.

The iron salts were formed by the oxidation of an iron anode along with the reduction of 1,2-dibromoethane prior to the introduction of the reagents. The authors assumed  $\text{ArNiX}$  to be the first intermediate formed, which further reduced to  $\text{ArNi}$ , which then reacted preferentially with 2-chloropyrimidine or 2-chloropyrazine, in an  $\text{S}_{\text{N}}\text{Ar}$ -like process. Under these reaction conditions, unsymmetrical-substituted biaryls were obtained with good yields. The authors successfully applied this procedure under similar conditions to the electro-synthesis of functionalized 2-arylpyridines from functionalized aryl and pyridine halides.<sup>126</sup>

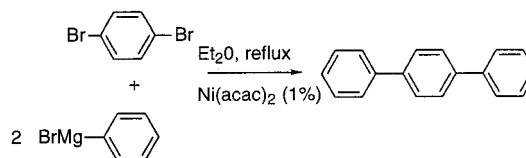
## Scheme 78



## B. Cross-Coupling Reactions between Aryl Halides and Organometallic Reagents

**a. Organomagnesium Derivatives.** Kumada<sup>94</sup> and Corriu<sup>96</sup> simultaneously described the rapid and efficient coupling between aromatic halides and aromatic Grignard reagents catalyzed by a nickel catalyst. Corriu<sup>96</sup> described nickel(II) acetylacetonate to be the most effective catalyst for the coupling reactions between aromatic Grignard reagents and olefinic halides (various *trans*-stilbenes in high yields 50–75%). This team also reported the synthesis of *p*-terphenyl in an 80% yield (Scheme 79) by reacting

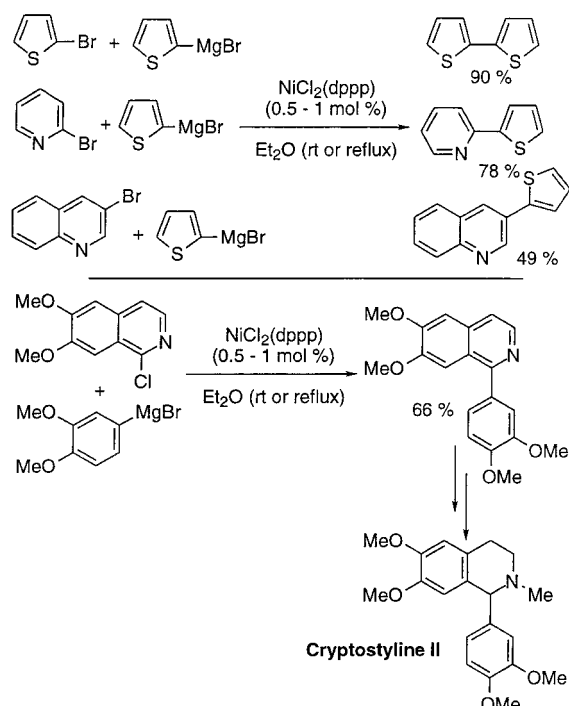
## Scheme 79



*p*-dibromobenzene.

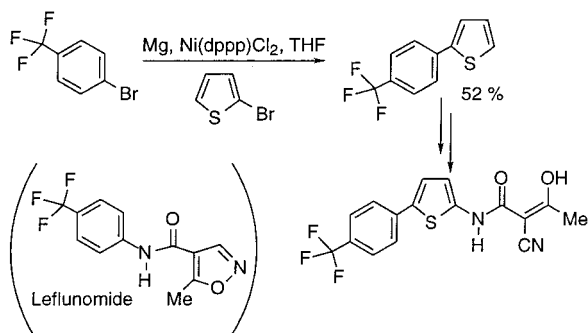
At the same time, Kumada<sup>95</sup> studied this reaction by using dihalodiphosphenickel. His group found that bidentate diphosphine ligands exhibited remarkable catalytic activity (i.e.,  $\text{NiCl}_2(\text{dppp})$  and  $\text{NiCl}_2(\text{dppe})$ ). They concluded that the *cis*-configuration of the two phosphine groups in the diorganonickel intermediate was of major importance. They especially noticed the high reactivity of chloride derivatives as a remarkable feature. This group later extended the scope of this nickel-catalyzed Grignard cross coupling to numerous examples of the arylation of haloheterocyclic compounds.<sup>127</sup> In the presence of catalytic amounts of  $[\text{NiCl}_2(\text{dppp})]$ , bromothiophenes, halopyridines, haloquinolines, and haloisoquinolines reacted with aryl (and also alkyl) Grignard reagents at either room or ether-refluxing temperature to give cross-coupling products. Some representative examples are reported in Scheme 80. The authors found applications of this method for the synthesis of some substituted isoquinolines as precursors for the preparation of isoquinoline alkaloids of pharmaceutical interest, such as cryptostyline II.

## Scheme 80



This aryl–aryl cross coupling has been widely applied as a key step in the total synthesis of numerous biologically active targets. As an example, Axton et al.<sup>128</sup> produced this reaction (Scheme 81) in

## Scheme 81

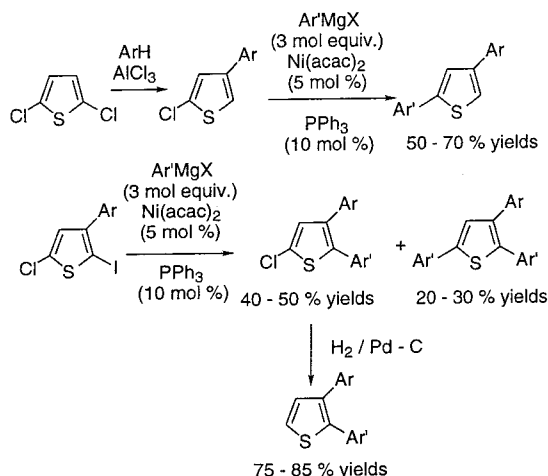


the preparation of novel immunosuppressive butenamides to mimic the metabolic product of leflunomide.

This method has also been applied to the preparation of 3-alkylthiophenes. These building blocks are useful precursors for the synthesis of poly(3-substituted)thiophenes which are soluble organic-conducting polymers. The monomeric alkylthiophenes were generally prepared by a Grignard cross-coupling reaction between alkylmagnesium bromides and 3-bromothiophene in the presence of a nickel catalyst.<sup>129,130</sup> It was however noticed<sup>131</sup> that this method was of little interest for practical applications because of the significant formation of 3,3'-bithiophene. This byproduct resulted from the homocoupling of the bromothiophene. This methodology has however been used for the synthesis of unsymmetrical 2,3-diaryl- and 2,4-diarylthiophenes (Scheme 82) starting from 2,5-dichlorothiophenes.<sup>132</sup>

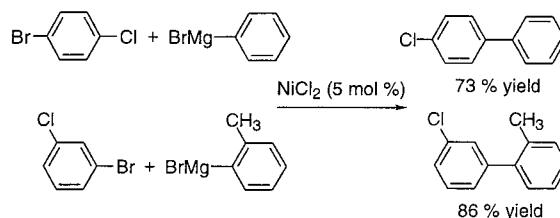
It should be noted that most of the reported reactions were performed using  $\text{NiX}_2\text{L}_2$ -type cata-

## Scheme 82



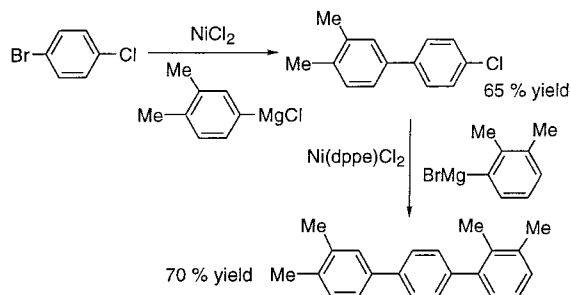
lysts. Ikoma et al.<sup>133</sup> reported that nickel(II) chloride in the absence of ligands was an efficient catalyst for the aryl cross-coupling reaction between haloarenes and Grignard reagents when bromine compounds were used as substrates, whereas chloroarenes were not transformed. With this halogen-selective catalyst, they were thus able to study the intramolecular halogen selectivity for the coupling of *p*- and *m*-bromochlorobenzenes.<sup>134</sup> In all cases, the reactions catalyzed by  $\text{NiCl}_2$  gave higher yields of chlorobiphenyls than those catalyzed by phosphine-ligated nickel complexes (Scheme 83).

## Scheme 83



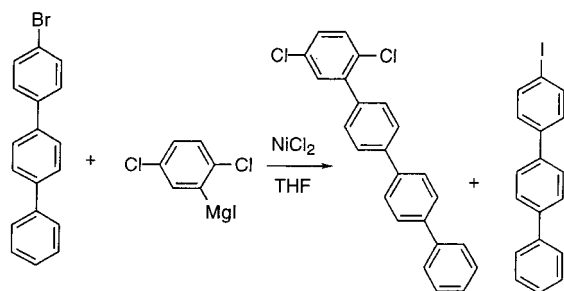
Interestingly, with successive cross couplings by  $\text{NiCl}_2$  and  $\text{Ni}(\text{dppe})\text{Cl}_2$ , they synthesized, in two steps, an unsymmetrical 2,3,3',4'-tetramethyl-*p*-terphenyl, which is a monomer for an important heat-stable polymer (Scheme 84).

## Scheme 84



Using this procedure, Wang and Pomerantz<sup>135</sup> prepared a quaterphenyl as the monomer for the preparation of luminescent and electrically conducting polymers. The synthesis, described in Scheme 85, was performed with the production of a substantial amount (40–45%) of a side product resulting from

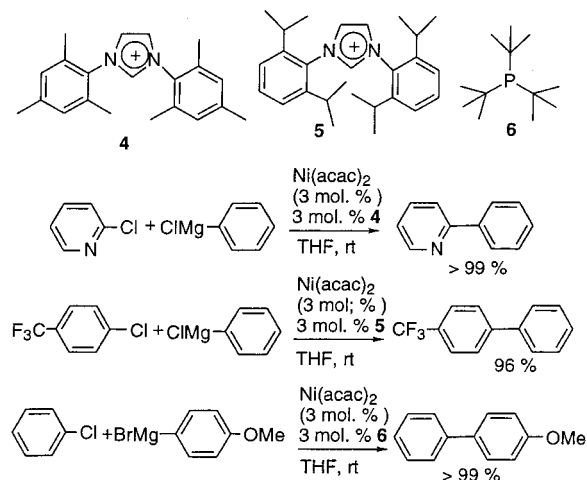
## Scheme 85



the exchange of halogen in this  $\text{NiCl}_2$ -catalyzed Grignard reaction. The authors experimented with other aryl halides and Grignard reagents in order to understand this new phenomenon. The same reaction mixture, using  $\text{Ni(II)}$  and ligands, did not lead to halogen exchange. They thus postulated that in this case the phosphine was too strongly bonded to the nickel to be displaced by an iodide. Indeed, in any plausible mechanistic proposition, the iodide must be bonded to the nickel in order to exchange with an aryl bromide during the reaction. The mechanistic complexities of this reaction are not yet completely resolved.

Very recently, Herrmann et al.<sup>136</sup> published an article describing the nickel-catalyzed cross coupling of aryl chlorides, not usually described as reactive substrates, with aryl Grignard reagents. This cross coupling occurred using conveniently available imidazolium salts **4** and **5** in Scheme 86 as well as tri-

## Scheme 86

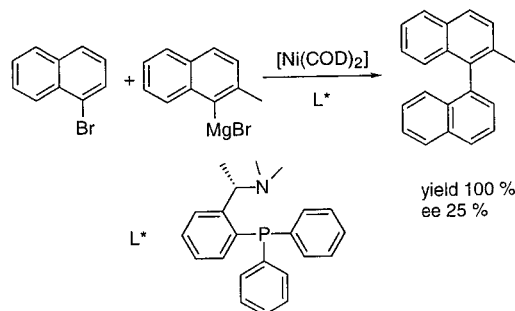


(*tert*-butyl)phosphane **6** as efficient ligands for nickel(II) diacetylacetonate. The authors claimed that the analogous palladium systems do not efficiently catalyze the reaction under these mild conditions. Using  $^{13}\text{C}$  NMR experiments with ligand **4** or **5**, they identified the formation of an imidazolin-2-ylidene complex of nickel(0).

Nowadays, enantioselective versions of this cross-coupling reaction are being used for the preparation of optically active biaryls that are significant as chiral auxiliaries for a variety of synthetic asymmetric reactions. As an example, Yamagishi et al.<sup>137</sup> studied the cross-coupling reaction of aryl halides and aryl Grignard reagents to prepare biaryls by the asym-

metric formation of the  $\text{C}_1\text{--C}_1'$  bond. They extended their reaction to the preparation of various biaryl compounds using nickel diaminophosphine catalysts. The results obtained for the asymmetric version of this transformation remained modest. Only 25% ee could be reached in the nickel-catalyzed cross-coupling reaction between 1-naphthyl bromide and 2-methyl-1-naphthylmagnesium bromide (Scheme 87).

## Scheme 87

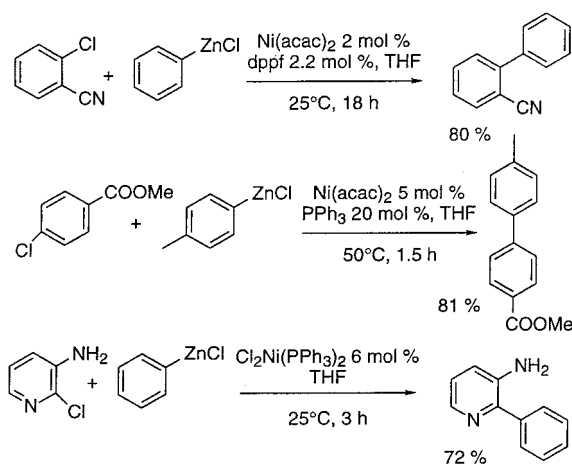
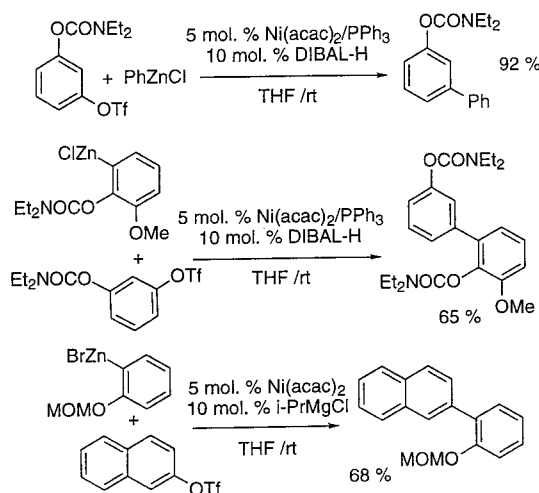


Considering both the huge success of biaryl structures as backbones for the preparation of new chiral ligands and the difficulty of their synthesis, further attempts to perform this Grignard cross-coupling reaction in an asymmetric manner will probably be published soon.

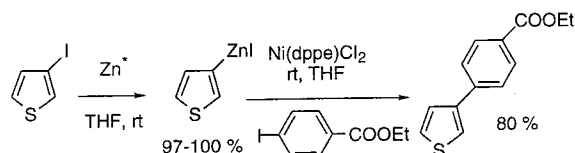
**b. Organozinc Derivatives.** Negishi<sup>138,139</sup> first reported the synthesis of unsymmetrical biaryls via the Ni- or Pd-catalyzed coupling of aryl zincs with aryl bromides or iodides. Stanforth<sup>140</sup> recently reviewed the wide application of this methodology for the synthesis of biaryl compounds. Recently, much effort has been directed toward the use of less expensive substrates (aryl chlorides instead of aryl bromides or iodides) or the use of more functionalized aryl derivatives. The structure and reactivity of both aryl zincs and nickel catalysts are still being studied and optimized today.

Miller and Farrell<sup>141</sup> were able to perform this cross coupling efficiently using various aryl chlorides as substrates and bearing a wide range of functional groups. Indeed, a variety of functional groups tolerate aryl zinc compounds but are, on the contrary, Grignard sensitive, especially the nitrile, carbonyl, and ester groups. Miller et al. also described the coupling of aryl zincs with “unactivated” aryl chlorides (i.e., not containing activating electron-withdrawing substituents), such as 4-chlorotoluene (75% biaryl formation with  $\text{PhZnCl}$ ). This methodology is interesting since substrates may be totally derived from inexpensive and readily available aryl chloride starting materials. Some examples of this transformation are summarized in Scheme 88. Aryl zinc derivatives can be prepared by transmetalation of the corresponding arylmagnesium chlorides or aryllithiums with  $\text{ZnCl}_2$  or by direct oxidative metalation of aryl halides.<sup>142</sup>

Simultaneously Snieckus<sup>143</sup> and Koch<sup>144</sup> described the nickel(0)-catalyzed cross coupling of aryl triflates with organozinc reagents under similar conditions to those described above, providing a general regioselective method for the synthesis of functionalized biaryls with good yields.

**Scheme 88****Scheme 89**

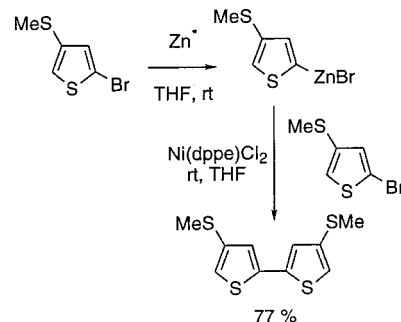
Rieke et al.<sup>145</sup> were interested in the chemistry of 3-substituted thiophenes, very useful synthons (precursors for soluble conducting organic polymers) for both the materials and pharmaceutical fields. One of the most used procedures for preparing these substrates involves the formation and subsequent reaction of 3-thienyl organometallics with electrophiles. Thus, Rieke zinc ( $Zn^*$ ) was prepared through the reduction of  $ZnCl_2$  by Li using naphthalene as an electron carrier in THF. The activated metal then underwent oxidative addition to 3-iodothiophene to form 3-thienylzinc iodide as a regioselective reagent in THF at room temperature. This substrate then underwent cross-coupling reactions with different aromatic halides using  $Ni(dppe)Cl_2$  as the catalyst (Scheme 90). As already observed with other com-

**Scheme 90**

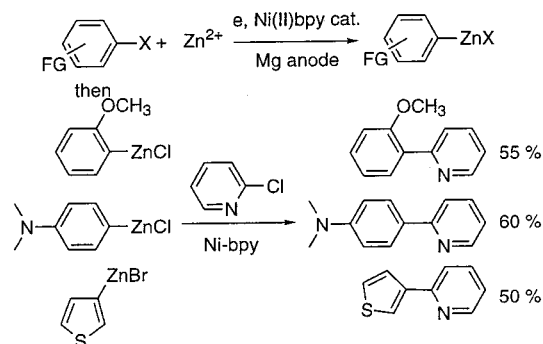
pounds, the reactivity of the organozinc species was found to be substrate dependent and aromatic halides with an electron-withdrawing group in the *para*-

position were found to be more active than the corresponding halides with an electron-donating group (*p*-tolyl iodide led to the corresponding 3-tolylthiophene with only a 40% yield).

Folli et al.<sup>146</sup> successfully applied this methodology to the synthesis of  $\alpha,\alpha'$ -bithienyls with  $\beta$ -thiomethyl substituents (Scheme 91).

**Scheme 91**

Périchon et al.<sup>147</sup> reported the electrochemical preparation of an aryl zinc compound followed by its reaction with 2-chloropyridine. Both reactions were catalyzed with the same nickel(II)-bipyridine complex, and 2-arylpriidines were obtained in good yields (Scheme 92, up to 60%).

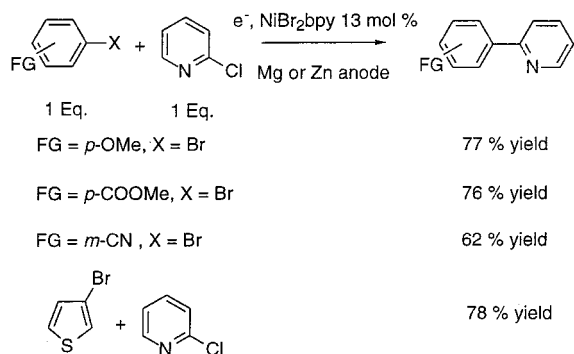
**Scheme 92**

The efficiency of the catalysis with nickel salts is not improved when another aryl is used instead of 2-chloropyridine as the aryl halide added in the second stage, and a catalytic amount of palladium phosphine is required to give unsymmetrical biaryls in good yields. In this article, the authors were also able to demonstrate that the arylation of 2-halopyridines could be more effectively conducted in one operation by nickel-catalyzed electroreduction of 1/1 mixtures of an aryl (or heteroaryl) halide and either 2-chloro- or 2-bromopyridine, according to the reactivity of the aryl halide. This method is analogous to the electrochemical cross couplings mentioned in the section III.2.A.c of this article. Because of the difference in reactivity of the two aryl halides involved in the reaction, it is worth noting that the cross coupling did not result in a statistical product distribution but led to good yields for the formation of the cross-coupling products (30–80%, Scheme 93).

**c. Borane Derivatives.** Grignard and organozinc reagents are among the most prone to transmetalation, which is often regarded as the rate-determining step. Boronic acids, on the other hand, are consider-

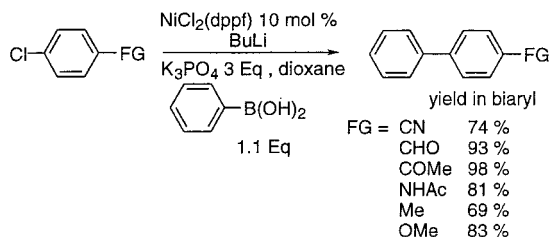


## Scheme 93



ably less reactive. The method known as the Suzuki reaction involves the palladium-catalyzed cross-coupling reaction of organoboron compounds (aryl boronic acids and their esters) with aromatic organic electrophiles (mostly halides and triflates)<sup>148</sup> in the presence of a base. The most reactive, and therefore most often used aryl halides in Suzuki reactions, are aryl bromides and iodides. One of the challenges in extending the application of the Suzuki-type cross couplings was to test these reactions with less reactive aryl sulfonates and aryl chlorides, which showed poor reactivity toward oxidative addition in the catalytic cycle. This could be achieved with the synthesis of biaryls via nickel(0)-catalyzed cross-coupling reactions between aryl chlorides and aryl boronic acids.<sup>149</sup> Ni(0) has a standard  $E^{\text{ox}}$  much lower than that of Pd(0); in other words, Ni(0) is a stronger nucleophile than Pd(0). The authors first described that phenylboronic acid reacted in high yields with both chloroarenes having an electron-withdrawing or -donating group. The electron-deficient chloroarenes gave yields of biaryls often exceeding 95%. For the substrates bearing an electron-donating group, even if the yields were slightly lowered, they remained better for the nickel catalysis than for the palladium one. The highly active nickel(0) catalyst was prepared in situ by treating the nickel chloride complexes with butyllithium via a transmetalation and reductive elimination or  $\beta$ -hydride elimination sequence. Some representative results are reported in Scheme 94.

## Scheme 94

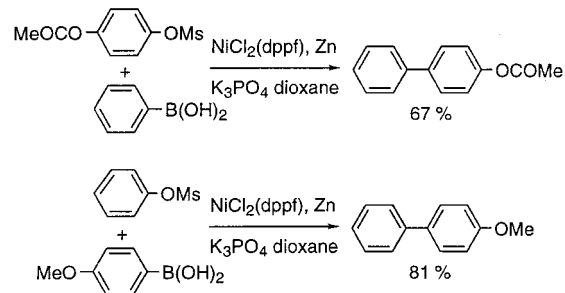


The authors further extended the scope of this nickel-catalyzed cross-coupling reaction to the use of functionalized aryl boronic acids with representative chloroarenes.<sup>150</sup> Chloroindole and chlorothiophene were thus successfully coupled with phenylboronic acid. When the aryl boronic acids were substituted with electron-withdrawing groups, however, the yields in cross-coupling products were lowered due to the C–B bond cleavage with the base. In these cases, it

was possible to lower the deboronation by using dimethoxyethane as the solvent. The authors also concluded that the nickel catalysis was more sensitive to the steric hindrance of both aryl boronic acids and chloroarenes than the palladium catalysis. The Hammett plot of the substituent effect of chloroarenes revealed that the reaction involved a rate-determining oxidative addition of chloroarenes to the nickel(0) complex.

Percec et al.<sup>151</sup> developed this reaction under similar conditions to those of the cross-coupling reaction between aryl mesylates or tosylates and aryl boronic acids. In this case, the active Ni(0) catalyst was generated in situ from  $\text{NiCl}_2(\text{dppf})$  and Zn. The authors demonstrated that this reaction was highly regioselective and could be successfully performed in the presence of various functional groups. They studied the influence of the effects of the substituent of the aromatic substrates, the nature of the leaving group, the solvent, and the type of catalyst and base on the reaction yield. The highest yields (Scheme 95)

## Scheme 95

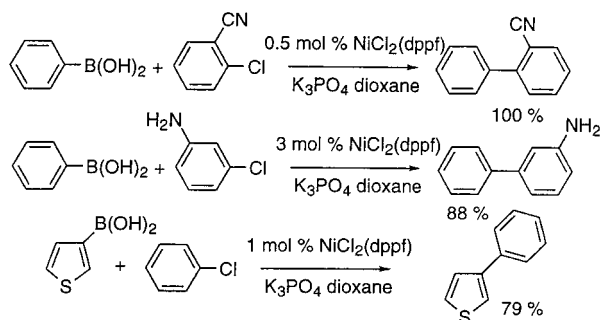


were obtained by using 10 mol % of  $\text{NiCl}_2(\text{dppf})$ , 3 equiv of  $\text{K}_3\text{PO}_4$  and 1.7 equiv of Zn in dioxane at 95 °C. The authors further argue that this reaction is cost saving when using nickel precursors instead of palladium. Moreover, this methodology extended the application of such cross couplings because the substrates used, i.e., mesylate derivatives, are readily obtainable from substituted phenols, hydroquinones, and bisphenols.

Indolese<sup>152</sup> then reported a convenient procedure for this cross-coupling reaction that did not need an activating agent to reduce the nickel catalyst (i.e., butyllithium or other various organometallics). He was able to raise the turn over number to 200 compared to 10 in the previous studies. Contrary to the preceding conditions and here in the case of chloroarenes, the catalyst ( $\text{Ni}(\text{dppf})\text{Cl}_2$ ) performed much better when the reducing agent was omitted. No explanations concerning possible mechanisms for this transformation are found in the report. As shown in Scheme 96, unsymmetrical biaryls with both electron-withdrawing and electron-donating groups were obtained in high yields. In general, the reactions were very clean, where less than 10% homocoupling (of the phenylboronic acid) could be observed. The nickel complexes involved in this transformation are interestingly air stable and can be used without any activation. This method allowed an easy and economical synthesis of unsymmetrical biaryls.

Further improvements have since been reported for this reaction, where new catalysts have been devel-

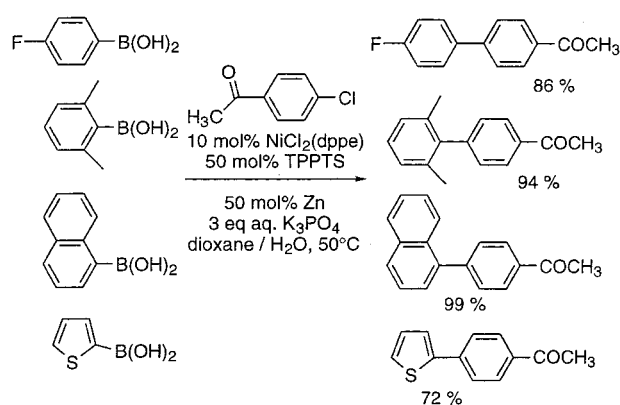
## Scheme 96



oped such as phosphine-free nickel complexes. Lead-beater and Resouly<sup>153</sup> were thus able to prepare  $\text{NiCl}_2(\text{NET}_3)_2$  and  $\text{NiCl}_2(\text{bipy})$  by reacting anhydrous  $\text{NiCl}_2$  with 2 equiv of the monodentate ligand triethylamine or 1 equiv of the bidentate ligand 2,2'-bipyridine. They studied the different parameters of the reaction (effect of base, catalyst concentration, solvent, and reaction time) for the test coupling of 4-bromotoluene and phenylboronic acid. The use of dioxane as a polar, weakly coordinating solvent and potassium phosphate as the base produced both high rate and yield from the reaction. The best yields were moreover obtained with 3–6 mol %  $\text{NiCl}_2(\text{NET}_3)_2$  as the catalyst. The authors proposed that these results may involve the relatively high rate of dissociation of a triethylamine ligand compared to one of the pyridyl group of bipyridine. By performing some screening experiments, it was concluded that better yields were obtained with aryl bromides in which the C–Br bond is more easily activated under the mild conditions used. As already reported in other Suzuki-type reactions, the effects of both electron-donating or -withdrawing groups on the rate of the reaction or yield of biaryls were inconsequential. The best yield of 4-phenyltoluene (84%) was obtained for the coupling of 4-iodotoluene with phenylboronic acid using 3 mol %  $\text{NiCl}_2(\text{NET}_3)_2$  as the catalyst and  $\text{Na}_3\text{PO}_4$  as the base in dioxane at 95 °C for 16 h.

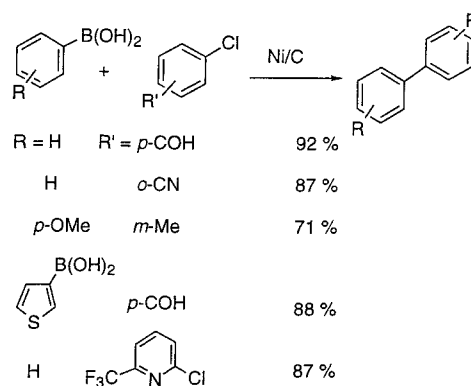
Another approach for the cross coupling of chloroarenes with boronic acids has been developed by Genêt et al.<sup>154</sup> by using a water-soluble nickel catalyst. Heating a mixture of  $\text{NiCl}_2(\text{dppe})$  with sodium triphenylphosphinotrimetasilate (TPPTS) and zinc in water preformed this nickel(0) complex. The addition of phenylboronic acid and the chosen aryl chloride (in dioxane) to this solution as well as 3 equiv of  $\text{K}_3\text{PO}_4$  led to the desired coupling. Aromatic chlorides substituted in the *para*-position with an electron-withdrawing group underwent clean cross coupling (yields up to 85%). The selectivities were very high since only traces of the homocoupling products could be detected. The authors then studied the cross-coupling reactions between 4-chloroacetophenone and substituted aryl boronic acids (see Scheme 97). They were able to use aryl boronic acids bearing electron-withdrawing or -donating substituents, sterically hindering groups, and also heteroaromatic substrates. They demonstrated this method to be valuable for laboratory synthetic applications by the preparation of 2-*p*-tolylbenzotrile in a 70% yield as an important pharmaceutical intermediate.

## Scheme 97



Lipshutz et al.<sup>155</sup> described the use of nickel on charcoal as a heterogeneous catalyst to effect efficient Suzuki biaryl couplings. Several couplings involving a variety of aryl boronic acids and aryl chlorides were performed in high yields under optimized conditions ( $\text{Ni/C}$  6–10 mol %, 4 equiv of  $\text{PPh}_3$ ,  $\text{K}_3\text{PO}_4$ ,  $\text{LiBr}$  in refluxing dioxane). Some representative examples are given in Scheme 98. The authors are still studying

## Scheme 98

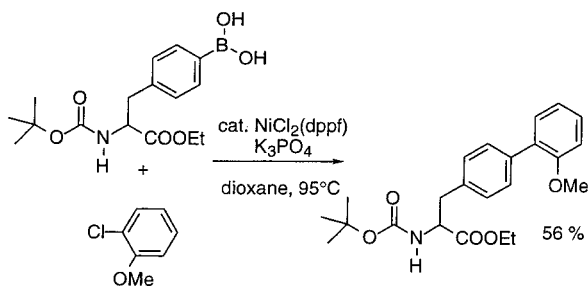


the nature of the active catalyst, which is very sensitive to the amount and the nature of phosphine present, since bidentate ligands inhibit the completion of the reaction. No experiments have yet been described for the reuse of this heterogeneous catalyst, but the authors assume the catalyst leach from the solid support to be very low.

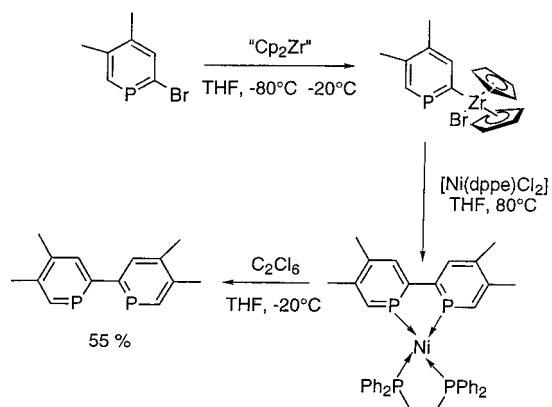
The nickel-catalyzed Suzuki-coupling reaction provided an application for the preparation of 4-substituted phenylalanine derivatives. Firooznia et al.<sup>156</sup> studied the coupling of boronate esters with aryl chlorides by palladium catalysis and the similar reaction of the free boronic acid by nickel complexes. The nickel catalysis led to slightly better yields than the corresponding Pd-catalyzed reactions, but the advantages of this method are questionable since boronate esters are more readily accessible, easier to purify, and more stable than boronic acids.

**d. Zirconocene Derivatives.** As a marginal example, Mathey and Le Floch<sup>157</sup> observed the nickel(II)-promoted homocoupling reaction of 2-(phosphinyl)halogenozirconocene complexes. This group was interested in the synthesis of functional biphosphinines as ligands for homogeneous catalysis. The efficient synthesis of 2,2'-biphosphinines is described

## Scheme 99



## Scheme 100

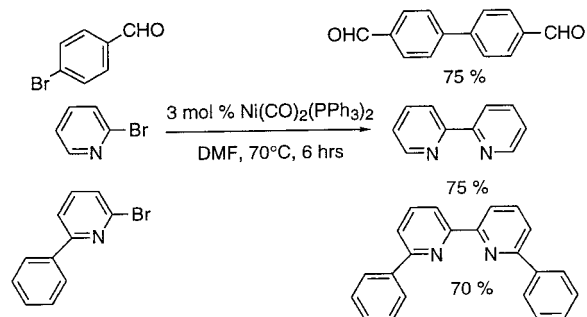


in Scheme 100, where the key steps of the process involve a double C–Zr to C–Ni bond metathesis, leading to an intermediate Ni(II) complex, followed by a classical reductive elimination favored by the imposed *cis* stereochemistry. The oxidation of the obtained nickel complex was performed using hexachloroethane to give the free bisphosphinine (up to 55% yield) with the release of [Ni(dppe)Cl<sub>2</sub>].

### 3. Use of a Nickel Catalyst without Coreducing Agent

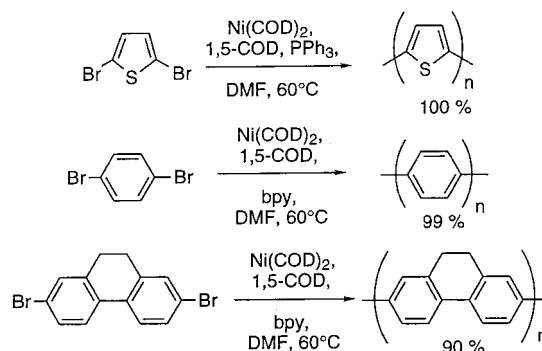
The zerovalent nickel complex Ni(CO)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was used in catalytic amounts for the homocoupling of aryl halides or halopyridines.<sup>158</sup> The authors studied the effects of solvent, halides, and substituents on the coupling reaction and found polar solvents such as DMF or DMSO to accelerate the reaction rate and increase the yields. Under these mild conditions, aryl bromides reacted better than aryl chlorides and electron-withdrawing substituents allowed the formation of biaryls in higher yields (Scheme 101). This

## Scheme 101



methodology was applied to the cross coupling of pyridine derivatives to yield a range of oligopyridines with good yields (up to 75%): unlike most of the

## Scheme 102



previous studies concerning metal-mediated polypyridine synthesis, the heterocycle here seemed not to coordinate and was easily obtained from the reaction mixture.

This is, to our knowledge, the only example where Ni(0) is used in catalytic amounts without the addition of a specific reducing agent as cocatalyst. How the catalytic system is regenerated in the reaction course is not discussed in this article. Our own experience in the case of palladium-catalyzed couplings led us to suspect the reductive properties of the solvent itself.

### 4. Nickel-Promoted Oligomerization and Polymerization

The various procedures above have been applied for the nickel-promoted preparation of aryl oligomers and polymers. Some examples will now be discussed following the same classification.

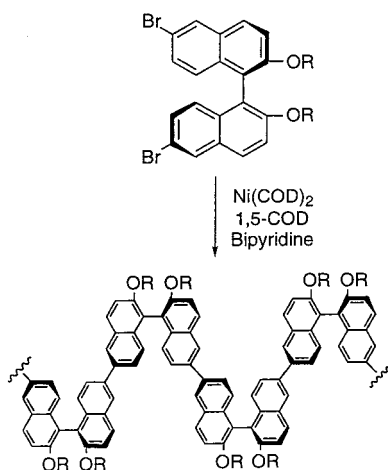
Homocoupling reactions with preformed nickel(0) in stoichiometric amounts have been applied to the preparation of  $\pi$ -conjugated poly(thiophene-2,5-diyl), poly(*p*-phenylene), by dehalogenative polycondensation of the corresponding 2,5-dihaloderivatives.<sup>159</sup> This Ullmann-type polymerization occurred with zerovalent nickel complexes, typically a mixture of bis(1,5-cyclooctadiene)nickel(0) and neutral ligands (mainly triphenylphosphine).

These coupling reactions proceeded under mild conditions and could be applied to a wide range of aromatic compounds, under various reaction conditions to provide high yields of  $\pi$ -conjugated polymers. This procedure has been successfully applied to the polymerization of 6,6'-dibromo-1,1'-bi-2-naphthol derivatives,<sup>160</sup> where Ni(0) complexes were used as promoters (Scheme 103).

The corresponding polymer could be obtained with a 58% yield and a molecular weight of 15 000 g/mol.

Oligo- and polymerization reactions involving catalytic amounts of nickel have also been extensively studied. Wei et al.<sup>161</sup> used this procedure for the synthesis of a series of  $\alpha,\omega$ -aldehyde-capped thiophene oligomers with a maximum of six thiophene units. This team aimed to prepare functionalized electroactive oligomers to be further incorporated into the backbone of conventional polymers. The final step of the reaction involves the homocoupling of a bromo-oligothiophene in the presence of zinc, nickel(II) chloride, and triphenylphosphine in DMF with good yields.

## Scheme 103



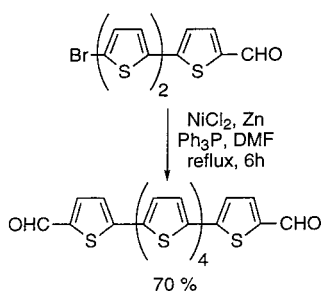
Huang et al.<sup>162</sup> very recently described the synthesis of an efficient green electroluminescent-conjugated polymer: poly[2,7-bis(4-hexylthienyl)-9,9-dihexylfluorene]. The synthetic approach toward this polymer is based on an aryl cross coupling between thierylzinc chloride and a dibromofluorene derivative catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> in a high yield (89%). The polymerization step is successfully performed (60% yield) through a nickel-catalyzed reductive homocoupling. The soluble electroluminescent material thus obtained showed high absolute photoluminescence quantum efficiency (around 32%) compared with other polythiophene derivatives.

The Grignard cross coupling between various aryl halides has also been applied to the preparation of oligomers (via stepwise coupling) or polymers (via coupling of bifunctionalized monomers).

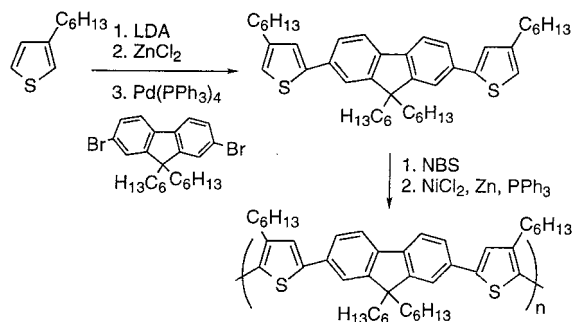
Ishikawa and Tanaka were interested in the chemistry of organosilicon polymers since they are used as photoresists, precursors of ceramics, and conducting and photoconducting materials. They thus reported the synthesis of poly[(disilanylene)oligophenylenes] with a different number of phenylene groups and poly[(silylene)biphenylenes] by the nickel-catalyzed coupling reactions of di-Grignard reagents.<sup>163</sup>

Many more examples are to be found in the chemistry of thiophene derivatives. Jayasuriya and Kagan<sup>164</sup> also used the Grignard cross-coupling reaction to prepare various bi- and terthienyls to study their phototoxicity. Their starting material was 3-thienylmagnesium bromide, prepared by transmetalation of 3-lithiothiophene with magnesium bromide etherate. The NiCl<sub>2</sub>(dppp)-catalyzed coupling reaction of

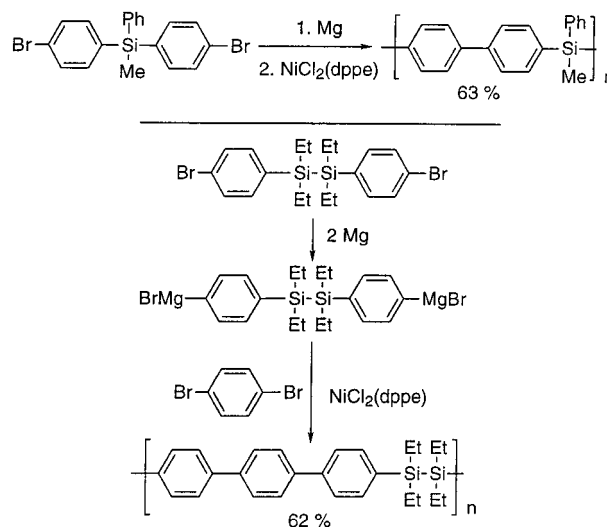
## Scheme 104



## Scheme 105



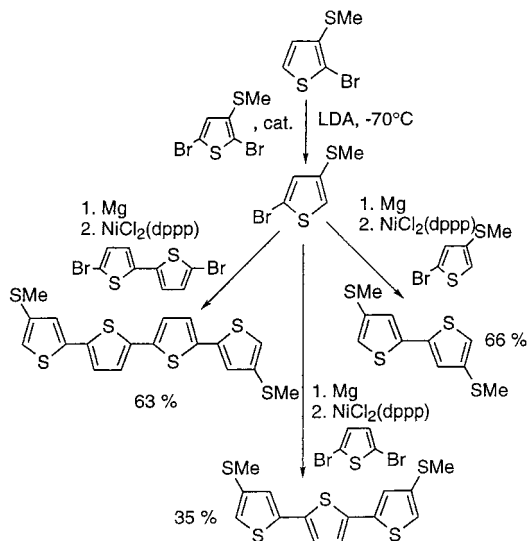
## Scheme 106



this Grignard reagent with 3,4-, 2,4-, and 2,3-dibromothiophene gave the expected products in yields varying between 61% and 85%.

This methodology was also followed by Bäuerle et al.<sup>165</sup> for the synthesis of methylthio-oligothiophenes, which present interesting biological activities as herbicides (Scheme 107). They are furthermore mono-

## Scheme 107



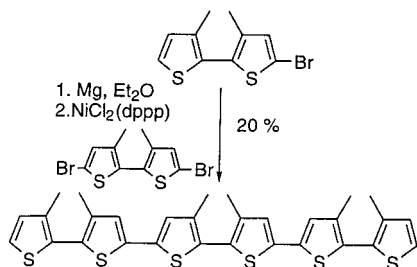
mers for the preparation of stereoregular polymers with appreciable conjugation length, exhibiting electronic properties that are dominated by the donor



strength of the substituents. Using Grignard cross coupling catalyzed by  $\text{NiCl}_2(\text{dppp})$ , they were able to prepare a tetramer with a 63% yield.

Longer oligothiophenes, i.e., sexithiophenes, were prepared by Barbarella et al.<sup>166</sup> using a nickel-phosphine-catalyzed Grignard coupling (Scheme 108).

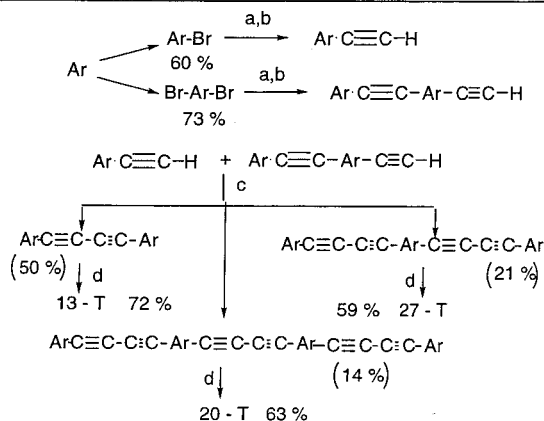
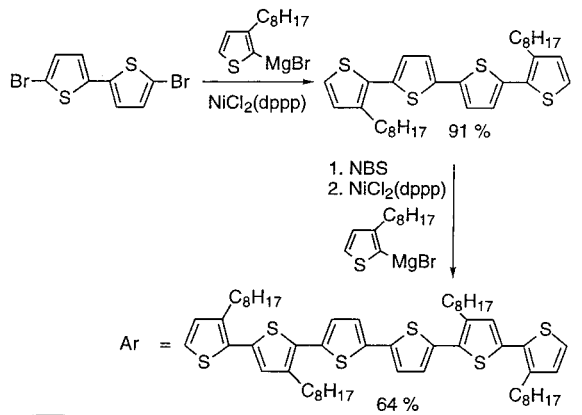
#### Scheme 108



Similar reactions were performed with isomeric 4,4'-dimethyl bithiophene derivatives to yield the desired corresponding sexithiophene in only 8% yield. This result also shows the importance of the steric effect during aryl-aryl bond formation catalyzed by Ni(0).

Otsubo et al.<sup>167</sup> prepared longer oligothiophenes (eicosamers and heptacosamers, i.e., respectively 20-mer and 27-mer) to study the correlation between the chain length and electronic properties. They prepared the key intermediate (tetraoctyl-substituted sexithiophene) on a large scale by conventional Ni(II)-catalyzed aryl Grignard cross coupling with a high overall yield (60%, Scheme 109). Because the syn-

#### Scheme 109

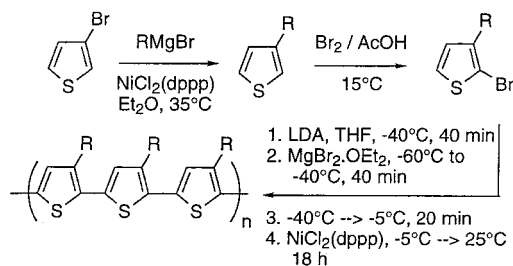


a.  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{CuI}$ ,  $\text{Me}_3\text{SiC}\equiv\text{CH}$  b.  $\text{KOH}$   
c.  $\text{Cu}(\text{OAc})_2$ , pyridine d.  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ ,  $\text{KOH}$

thesis of long oligothiophenes requires several difficult purifications, they chose, as the last reaction, to perform an eglinton coupling followed by a sodium sulfide-induced 1,3-butadiyne cyclization. This method avoids the contamination with analogous oligomeric byproducts. By this methodology, the oligomers were synthesized in good yield and high purity and their structures were characterized by NMR and MS spectroscopic measurements as well as by elemental analyses.

Grignard cross coupling is a method of choice for the step-by-step preparation of oligothiophenes. Yamamoto et al.<sup>168</sup> were one of the first groups to use this reaction for the preparation of poly(thiophenes) by chain growth polymerization. They synthesized highly regular poly(2,5-thienylene) in a 61% yield by the polycondensation of 2,5-dibromothiophene in the presence of magnesium catalyzed by  $\text{NiCl}_2(\text{bpy})$  (2,2'-bipyridine) (whereas palladium catalysis remained ineffective). McCullough et al.<sup>169</sup> modified this method to prepare structurally homogeneous soluble poly(3-alkylthiophenes), starting from nonsymmetrical 3-alkylthiophenes (Scheme 110). Indeed, a structur-

#### Scheme 110

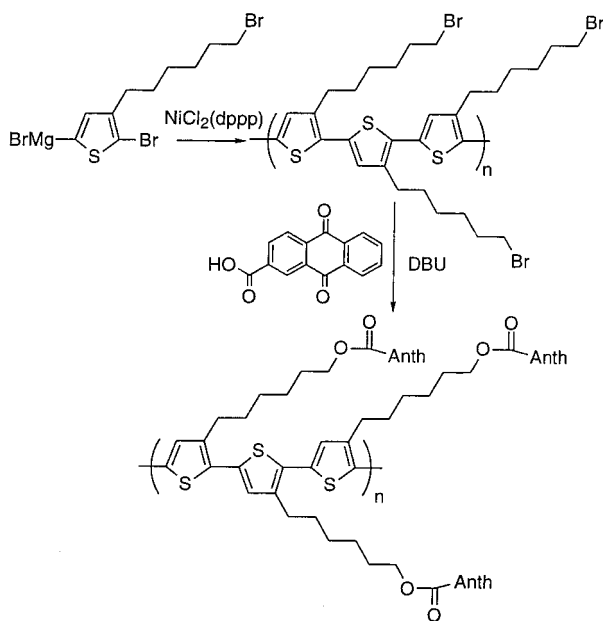


ally homogeneous head-to-tail arrangement (regular 2,5-couplings between adjacent thiophene rings) is necessary to obtain optimal electronic and optical properties.

This procedure requires the preparation of pure 2-bromo-3-alkyl-5-bromomagnesiathiophene by the selective metalation of 2-bromo-3-alkylthiophene at the 5-position, followed by trapping the 2-bromo-3-alkyl-5-lithiothiophene with magnesium bromide etherate. The cross coupling is then performed in situ, catalyzed by  $\text{NiCl}_2(\text{dppp})$ , leading to the formation of head-to-tail coupled poly(3-alkyl-thiophenes), with yields varying from 33% to 69%, depending on the length of the alkyl substituent in position 3. By NMR analysis the authors were able to determine that 93–98% of the desired regiochemistry was found in the polymers. Several groups have used this method to synthesize various regioregular poly(3-substituted)thiophenes. Trznadel et al.<sup>170</sup> synthesized poly(hexylthiophenes) and then performed several sequences of extractions to recover fractions of poly(3-hexylthiophene) differing in their molecular weight. They studied the effect of molecular weight on their spectroscopic and spectroelectrochemical properties. This methodology was also applied to the synthesis of regioregular polythiophenes containing pendant functional groups. For example, Iraqi et al.<sup>171</sup> polymerized 3-(6-bromohexyl)thiophene and reported the

subsequent reaction with 2-carboxyanthraquinone. NMR studies on the polymer in chloroform confirmed that 87% of the total number of thiophene chains were grafted to an anthraquinone group (Scheme 111). They were interested in the binding of redox-

Scheme 111

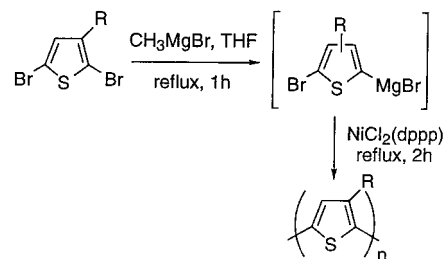


active and mesogenic groups to organic conjugated polymers for their potential electrocatalytic, photochemical, and electronic applications.

Janssen et al.<sup>172</sup> have recently been interested in functionalizing end groups of poly(3-alkylthiophenes) in view of their grafting onto surfaces or extending the range of the applications of these materials. The authors were able to determine (by MALDI-TOF mass spectrometry) that polymers obtained by the above-mentioned McCullough's method contained a significant amount of bromine (1–2 wt %), i.e., that the polymer chains terminated with 0, 1, or 2 bromine atoms. They carried out a successful post-polymerization reaction of the obtained polymers with a thiophene Grignard reagent and the addition of fresh catalyst. The main difficulty of this method is the preparation of 2-bromo-3-alkyl-5-bromomagnesiathiophene in very high purity, which is required in order to obtain long and regular poly(3-alkylthiophene) chains. McCullough proposed a simple method to prepare regioregular polymers using Grignard metathesis, which avoids the limiting step.<sup>173</sup> The synthesis involves the treatment of 2,5-dibromo-3-alkylthiophene (much easier to obtain in high purity) with an equimolar amount of commercially available methylmagnesium bromide to produce a mixture of Grignard derivatives as regiochemical isomers. Their treatment with  $\text{NiCl}_2(\text{dppp})$  produced head-to-tail-coupled regioregular poly(3-alkylthiophenes) (Scheme 112).

The regioselectivity of the Grignard metathesis step is about a 80:20 mixture of isomers, resulting in a 99% head-to-tail coupling for the formation of the polymer. This enhanced selectivity can only be a consequence of the catalytic step, and the mechanism

Scheme 112



for this reaction is still being investigated by the authors. The very high sensitivity of the Grignard cross-coupling reaction to the steric hindrance is probably one of the important factors that control this selectivity.

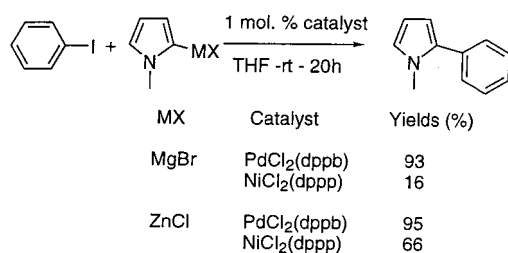
Chen and Rieke<sup>174</sup> developed a similar method, successfully applied to the synthesis of regioregular head-to-tail poly(3-alkylthiophenes). The authors added active zinc<sup>175</sup> to 2,5-dibromo-3-hexylthiophene to give a quantitative yield of the mono-organozinc thiophene with a regioselectivity of 90% for the formation of 2-bromo-5-(bromozincio)-3-hexylthiophene. Interestingly, the polymerization of this monomer in the presence of a catalytic amount of  $\text{Pd}(\text{PPh}_3)_4$  yielded the corresponding polymer with a totally regiorandom structure, whereas the use of  $\text{Ni}(\text{dpe})\text{Cl}_2$  as catalyst delivered, under identical conditions, a regioregular head-to-tail polymer. It is argued that the smaller ionic radius of  $\text{Ni}^{2+}$  vs  $\text{Pd}^{2+}$  along with the higher steric demands for *dppe* indicate that the degree of stereoregularity is controlled by steric congestion in the transmetalation step.<sup>176</sup>

#### IV. Aromatic Coupling Using Palladium as the Catalyst

As shown in the previous section, the use of nickel instead of copper dramatically increased the possibilities of aryl–aryl bond formation. This progress included the easy syntheses of dissymmetrical-hindered biaromatics of many types bearing several (but not all) types of substituents and was mainly due to the association of a nickel catalyst to other organometallic species such as magnesium or zinc derivatives.

Twenty years later it seemed obvious that changing from nickel to palladium would not only enable further improvement but also the use of an increasing variety of nucleophiles (organometallic reagents). Of course, at the beginning of the 1980s, the chemistry of transitional metals was not as developed, and it is not surprising that the first results with palladium were duplicates of the results obtained with nickel-catalyzed Grignard cross coupling. In many cases, but not all, palladium catalysts proved to be as efficient as nickel ones.

In 1981, Kumada<sup>177</sup> studied the efficiency of palladium as the catalyst in the cross-coupling reaction of aryl–magnesium bromides or aryl–zinc chlorides with organic halides. For the synthesis of 2-phenyl 1-methyl pyrrole, the author obtained better results with palladium as the catalyst than with nickel

**Scheme 113**

(Scheme 113). Kumada, in this early work, also showed the possibility of using heteroaryl halides such as 3-bromothiophene, 2-bromopyridine, or 3-bromopyridine.

Both Grignard reagents and zinc derivatives were used for palladium-catalyzed aryl–aryl bond formation. However, the success of palladium is mainly due to the possibility of using a greater number of other nucleophiles, mainly organometallics. Indeed, in the past few years, mercury, silicon, germanium, lead, bismuth, antimony, copper, manganese, zirconium, tin, and boron derivatives have been used in association with palladium in order to perform aryl–aryl bond formation.

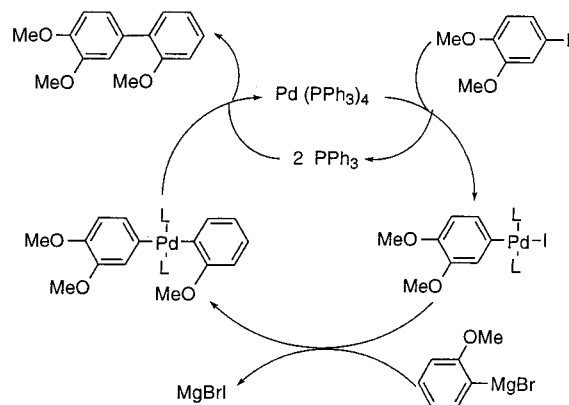
Obviously, tin and boron derivatives have led to much more efficient and useful methods, and the so-called Stille and Suzuki reactions are now part of the classical and general tools of organic synthesis. Indeed, the association of an organometallic compound with low-reactivity (of higher electronegativity in the Pauling scale) and very efficient palladium catalysts have given rise to very selective and efficient aryl–aryl bond formations. In this section, we will describe results obtained with all types of organometallics because in some cases even exotic reagents seem to present drastic advantages and are potentially useful. However, the major part will deal with the two last-named reactions.

Some new results have just appeared in which no other organometallic compounds are needed and only palladium catalysts are used to perform the aryl–aryl bond formation. In these methods, regeneration of the active palladium species is generally obtained due to organic reduction even if this is not always well established.

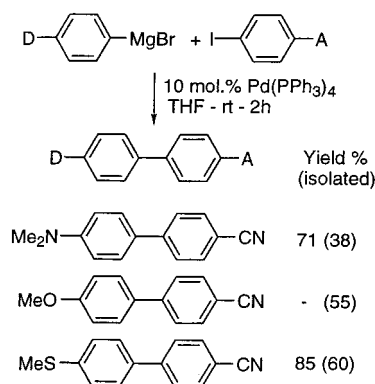
## 1. Palladium-Catalyzed Coupling of Grignard Reagents

The efficiency of Grignard reagents for aromatic palladium-catalyzed cross coupling was first shown in 1976.<sup>178</sup> The authors proposed a mechanism similar to the currently accepted scheme of the nickel-catalyzed process.<sup>94</sup> This mechanism involves a series of two-electron oxidation and reduction steps. Widowson and Zhang<sup>179</sup> studied the synthesis of highly functionalized biaryls. They also studied the mechanism of the reaction, and their proposal was in accordance with the previous one (Scheme 114).

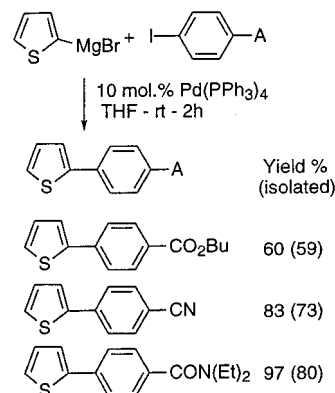
In 1990, Jutand et al.<sup>180</sup> studied the synthesis of 4,4'-unsymmetrically substituted biphenyls to obtain a conjugated polarizable relay, such as D–Ar–Ar'–A in which D is an electron donor and A an electron acceptor. They obtained such compounds by a pal-

**Scheme 114**

ladium-catalyzed cross coupling of magnesium derivatives ( $pD-C_6H_4-MgX$ ) with aryl halides ( $pX'-C_6H_4-A$ ) (Scheme 115).

**Scheme 115**

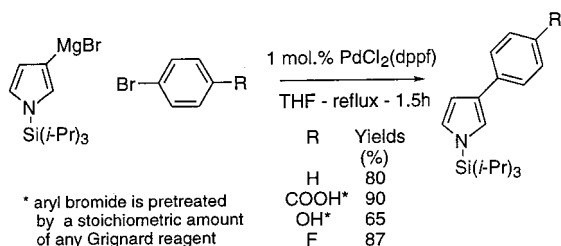
They extended their method to the synthesis of arylated thiophenes (Scheme 116).

**Scheme 116**

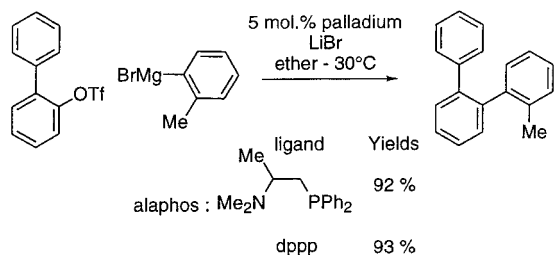
However, the use of Grignard reagents requires the carbon–halogen bond in the acceptor aryl halide to be considerably more reactive than the acceptor group itself. This often limits the halides to iodides and often rules out the use of reactive acceptors such as nitro or esters.

In 1993, the use of palladium-catalyzed cross coupling of 3-pyrrolylmagnesium bromide allowed the synthesis of 3-substituted pyrroles (Scheme 117).<sup>181</sup>

The cross coupling of aryl triflates containing sterically demanding groups in the *ortho*-position has

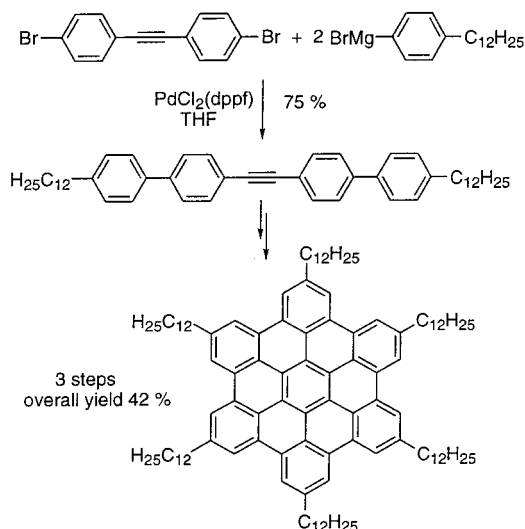
**Scheme 117**

since been performed,<sup>182</sup> with special emphasis on the ligand effects. The most effective catalysts are dichloro-[(2-dimethylamino)propyldiphenylphosphine]palladium ( $\text{PdCl}_2(\text{alaphos})$ ) and dichloro[1,3-bis(diphenylphosphino)propane] palladium ( $\text{PdCl}_2(\text{dppp})$ ) (Scheme 118). In the case of *alaphos* as the ligand,

**Scheme 118**

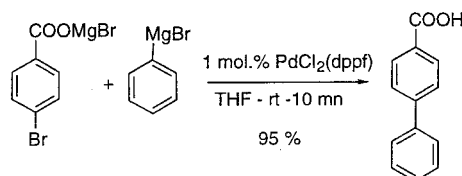
no enantiomeric excess has been reported for the hindered, potentially atropisomeric, biaromatic products. These results are similar to those obtained in the case of nickel(0)-catalyzed reactions.

The use of organomagnesium compounds has recently allowed the synthesis of substituted hexa-*peri*-hexabenzocoronene (Scheme 119). This compound

**Scheme 119**

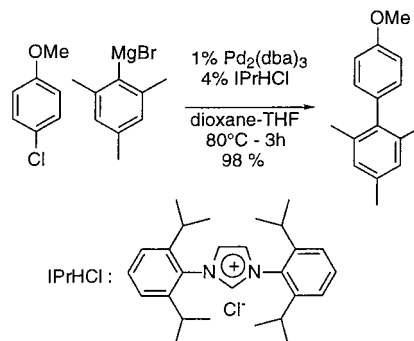
presents interesting physical, electronic, and optoelectronic properties.<sup>183</sup>

In 1997, Bumagin<sup>184</sup> performed the cross coupling of organomagnesium compounds with aryl halides containing carboxy, hydroxy, or amine groups. With palladium as the catalyst, these organometallic species can be directly used without the protection of the functional substituent (Scheme 120). However, a 2- or 3-fold excess of Grignard reagent is needed because

**Scheme 120**

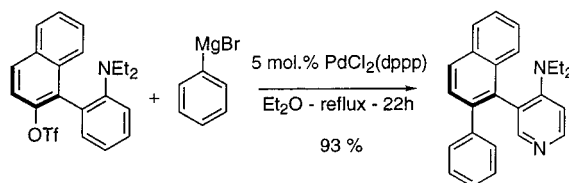
the acidic function reacts leading to the corresponding bromomagnesium benzoate which is then involved in the cross-coupling reaction.

Recently, Nolan et al. studied the efficiency of cross-coupling Grignard reagents with aryl chlorides.<sup>185</sup> This became possible with a  $\text{Pd}_2(\text{dba})_3/\text{imidazolium chloride}$  ( $\text{IPrHCl}$ ) system as the catalyst (Scheme 121). This type of ligand exhibits a consider-

**Scheme 121**

able stabilizing effect in organometallic systems. The described methodology enables biaryl syntheses in good to excellent yields.

Palladium-catalyzed cross coupling of Grignard reagents has been applied to the synthesis of axially chiral analogues of 4-(diethylamino)pyridine (Scheme 122).<sup>186</sup>

**Scheme 122****2. Palladium-Catalyzed Coupling of Zinc Derivatives**

Because of their higher selectivity (lower reactivity) compared to Grignard reagents, organozinc reagents are widely used for transition-metal-catalyzed coupling reactions with a variety of organic electrophiles.<sup>187</sup>

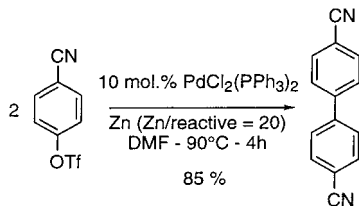
**A. Aryl Homocoupling of Zinc Derivatives**

During the homocoupling of organometallic compounds, transition metals, such as palladium, act as reducing agents, and then the reaction would inevitably involve a stoichiometric amount of palladium. Thus, stoichiometric amounts of auxiliary reducing agents are added to reduce the use of palladium to a catalytic amount. The principal auxiliary used is zinc. In 1993, it was used in association with palladium



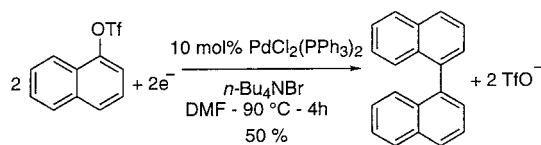
as the catalyst for aryl triflate homocoupling.<sup>114</sup> The authors described a procedure where zinc was used as a chemical reducing agent similar to the electrochemical procedures. The use of a large quantity of zinc (ratio zinc/reactive of 20) allows the synthesis of biaryls with a good yield but drastically limits practical applications (Scheme 123).

#### Scheme 123



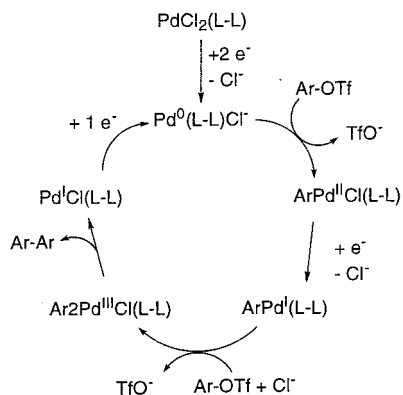
The same authors then also performed mechanistic studies based on palladium-catalyzed electro-synthesis of binaphthyls (Scheme 124).<sup>115</sup> For the electro-

#### Scheme 124



chemical synthesis, they proposed a mechanism involving only single electron transfers (Scheme 125)

#### Scheme 125

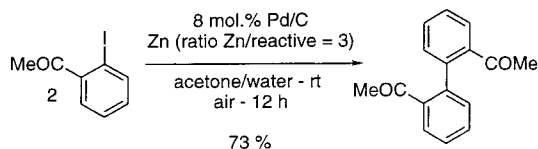


and considered that the same process occurs in zinc-assisted reactions.

In this particular case, the generally better results obtained with zinc than with the electrochemical method could suggest the formation of an aryl–zinc derivative as the intermediate.

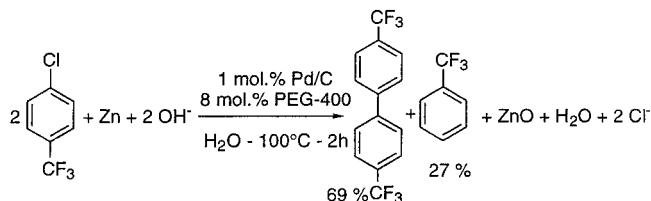
In a more recent study, Li et al.<sup>188</sup> developed a similar method with zinc (ratio Zn/aryl halide = 3) and palladium as the catalyst in the presence of air. They succeeded in biaryl syntheses with good to excellent yields (Scheme 126).

#### Scheme 126



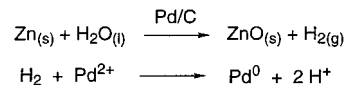
The authors described the reaction as a palladium-catalyzed zinc-mediated aryl halide coupling. However, as previously suggested, a zinc derivative could be the intermediate for the reaction. Sasson et al. studied the mechanism of a palladium-catalyzed aryl homocoupling in the presence of zinc and water.<sup>189</sup> Their methodology was similar to the previous one, but they replaced acetone by poly(ethyleneglycol) and a base (Scheme 127).

#### Scheme 127



The authors observed that without water no reaction occurs. This was also observed by Li et al.<sup>188</sup> Whenever they excluded water and the reaction occurred in dry acetone or acetonitrile, they observed only a 7–8% conversion. Sasson et al.<sup>189</sup> concluded that the conversion was due to the 8 mol % of palladium introduced, which functioned as a stoichiometric reagent because it could not be regenerated in the absence of water. They considered that the key reaction occurred between water and zinc and then the dihydrogen formed reacted with Pd(II) species to regenerate Pd(0) (Scheme 128).

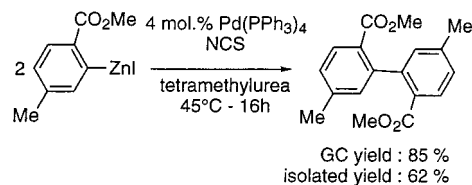
#### Scheme 128



They considered zinc as a reducing agent for palladium. The use of hydrogen as the reducing agent in similar conditions for the same reaction had already been described by the same group.<sup>190</sup>

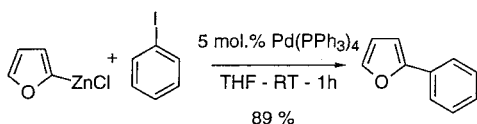
Recently Takagi reported the use of *N*-chlorosuccinimide (NCS) as the auxiliary oxidant.<sup>191</sup> Using a molar ratio ArZnI/NCS/Pd = 2/1.1/0.04, they prepared various functionalized biaryls in good to excellent yields even with substituents at the *ortho* position (Scheme 129).

#### Scheme 129



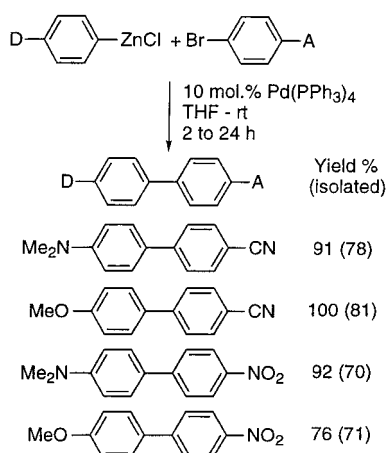
### B. Aryl Cross Coupling of Zinc Derivatives

Concerning palladium-catalyzed aryl cross coupling, the use of zinc derivatives has been studied by Negishi et al.<sup>192</sup> since 1982. The subject of this work was the formation of carbon–carbon bonds on heteroaryl compounds, including the cross coupling with aryl moieties (Scheme 130). The difficulties in the preparation of aryl zinc derivatives<sup>193</sup> is the

**Scheme 130**

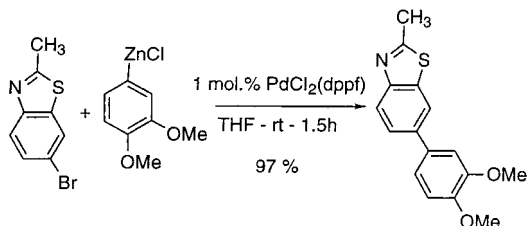
limiting factor in the development of aryl cross couplings using this type of organometallic. Other heterocycles have also been used such as thiophenes or pyridines.

In 1990, zinc derivatives were used by Jutand et al.<sup>180</sup> to obtain 4,4'-unsymmetrically substituted biphenyls with a potential in nonlinear optics. The lower reactivity of organozinc compounds compared with Grignard reagents allows the use of various functional groups on the aryl moiety (Scheme 131).

**Scheme 131**

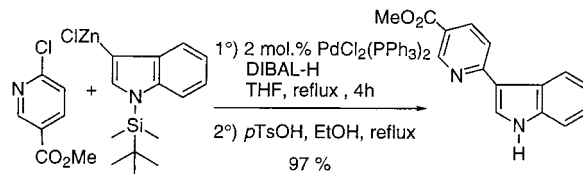
With the same method, the authors also obtained biaryls containing a heterocycle in good to excellent yields.

In 1993, Bumagin<sup>181</sup> studied the reaction of 6-bromo-2-methylbenzothiazole with aryl zinc chloride in the presence of a catalytic amount of  $\text{PdCl}_2(\text{dppf})$  complex. This reaction led to 6-aryl-2-methylbenzothiazoles in high yields (Scheme 132).

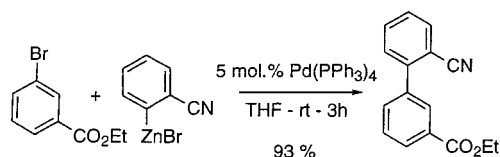
**Scheme 132**

The cross coupling of various heteroaryl halides with 1-(*tert*-butyldimethylsilyl)-3-indolylzinc chloride in the presence of palladium is an efficient method for the synthesis of 3-(2-pyridyl)indoles (Scheme 133).<sup>194</sup>

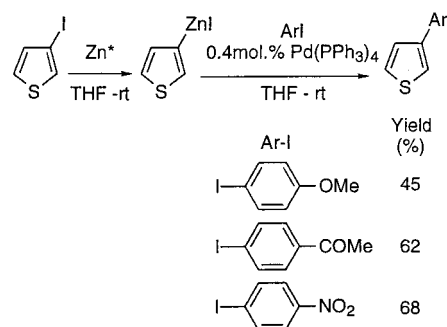
Traditionally, aryl zinc reagents are prepared by metal-exchange reactions of aryllithiums or arylmagnesium halides with zinc halides. In 1998, Miller and Farrell reported the palladium-catalyzed cross coupling of Grignard reagents or lithium derivatives with aryl halides in the presence of zinc salts.<sup>193,195</sup>

**Scheme 133**

The reaction failed in the absence of zinc salts. Such observations suggest an initial step of in-situ formation of zinc derivatives. The formation of aryl zinc derivatives by metal-exchange reactions of aryllithiums or arylmagnesium halides with zinc halides limits the functions which can be tolerated. In 1990, Knochel et al.<sup>196</sup> reported the direct synthesis of aryl zinc halides by the oxidative addition of active metal zinc onto highly functionalized aryl or heteroaryl halides. In 1991, Rieke et al.<sup>175</sup> used a similar technique to obtain functionalized aryl zinc halides. The authors also successfully tested the reactivity of these compounds in palladium-catalyzed cross couplings with aryl halides. The procedure was efficient even with a substituent in the *ortho*-position (Scheme 134).

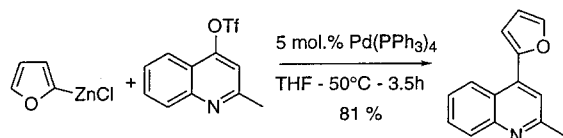
**Scheme 134**

These studies have been extended to 3-arylated thiophenes.<sup>197,198</sup> The arylation occurs in moderate to good yields (Scheme 135).

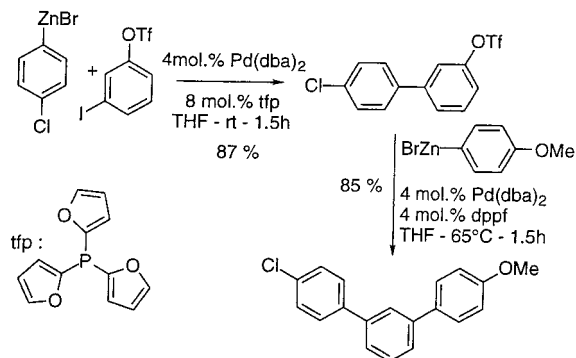
**Scheme 135**

Yamanaka and Sakamoto extended this technique to the formation of heteroaryl-zinc halides.<sup>199,200</sup> Their method allows easy and efficient synthesis of unsymmetrical heterobiaryls such as 2,3'-bipyridine. Zinc-containing compounds can also be used for aryl cross coupling with aryl bearing a leaving group other than halides. In 1990, Cacchi et al. showed the efficiency of the cross coupling of zinc derivatives with aryl triflates.<sup>201</sup> Their method allowed the synthesis of 2-aryl-furans (Scheme 136).

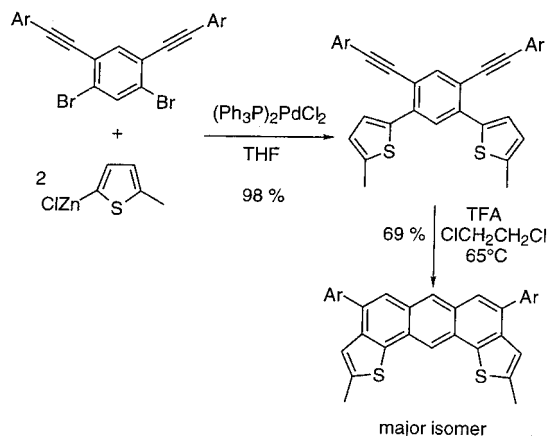
In 1996, Knochel et al.<sup>202</sup> developed reaction conditions enabling the selective coupling of aryl zinc reagents with aryl halides at room temperature. In the case of aryl triflates, a temperature of 65 °C is required. The difference in reactivity of iodide and

**Scheme 136**

triflate allowed for an efficient multicoupling reaction (Scheme 137).

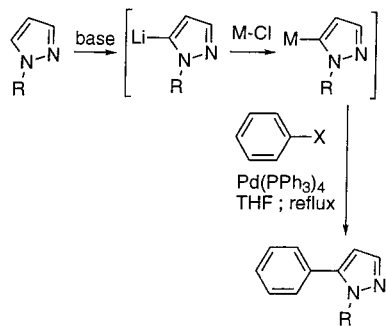
**Scheme 137**

More recently, the same group also studied the reaction of aryl nonaflates.<sup>203</sup> The excellent selectivity between nonaflate and iodide groups allowed the synthesis of products including three different aryl moieties. In 1991, Roth et al.<sup>204</sup> used fluorosulfonate as the leaving group for palladium-catalyzed cross couplings with aryl zinc chlorides. Fused polycyclic aromatics were synthesized by cross coupling of thienyl zinc chloride with aryl halides.<sup>205</sup> These structures were obtained in a two-step process of aryl cross coupling and cyclization (Scheme 138).

**Scheme 138**

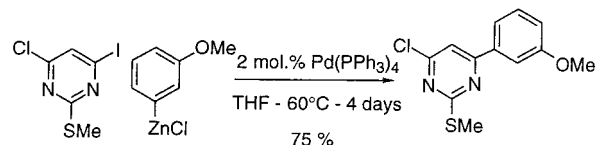
The reaction of zinc derivatives has been compared with that of tin-containing compounds for the synthesis of 5-arylpurazoles.<sup>211</sup> In this case, the zinc allows better yields than tin (Scheme 139). In 1998, Vedsø et al.<sup>207</sup> used a similar procedure for the one-pot preparation of 5-aryl-substituted 1-(benzyloxy)pyrazoles.

Zinc derivatives have also been compared with Suzuki or Stille reactions. In 1994, Quéguiner et al.<sup>208</sup> studied the synthesis of 4-chloro-6-aryl-2-thiomethylpyrimidine-5-carbonitriles. In most cases, the authors used a Suzuki cross coupling. However, they

**Scheme 139**

R	Base	M-Cl	X	Yields (%)
Me	<i>n</i> -BuLi	<i>n</i> -Bu <sub>3</sub> SnCl	I	22
Me	<i>n</i> -BuLi	ZnCl <sub>2</sub>	I	57
Me <sub>2</sub> NSO <sub>2</sub>	LDA	ZnCl <sub>2</sub>	Br	75

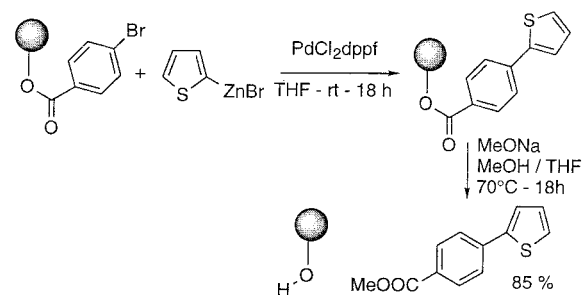
did not succeed in the synthesis of the 3-methoxyphenylboronic acid. In this case, they had to use the *m*-anisylzinc chloride to achieve the aryl cross coupling (Scheme 140).

**Scheme 140**

For the synthesis of new 2-aryl-thieno[3,2-*b*]thiophenes, Kirsch et al. studied the cross coupling of zinc-containing compounds in comparison with Suzuki and Stille methods.<sup>209</sup> The best result was obtained with the zinc derivative and 4-iodo-nitrobenzene.

### C. Use of New Technologies in Aryl–Aryl Bond Formation Using Zinc Derivatives

Like other reactions, the cross coupling of aryl zinc halides has followed recent technical developments. Both solid-phase synthesis and perfluorinated solvent were tested in order to facilitate catalyst or substrate separation. In 1996, a reaction on a solid support was reported.<sup>210</sup> The aryl halide presented an acidic function which allowed linkage to Merrifield's resin (Scheme 141). After the cross-coupling reaction, the

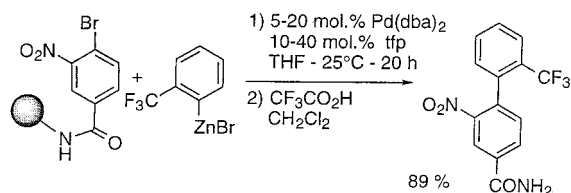
**Scheme 141**

resulting biaryl was cleaved from the resin by *trans*-esterification.

Knochel et al.<sup>211</sup> used either Rink or Wang resins for solid-phase synthesis of polyfunctional aromatics. The aryl halide was linked to the rink-MBHA resin,

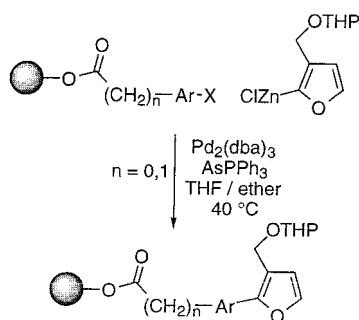
then it was able to react smoothly with various aryl zinc bromides in the presence of a catalytic amount of  $\text{Pd}(\text{dba})_2$  and tri-*o*-furylphosphine (Scheme 142).

Scheme 142



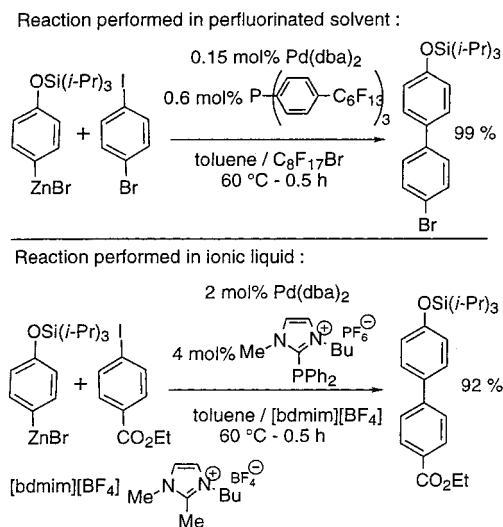
Recently, Han et al.<sup>212</sup> used a zinc derivative to develop a divergent protocol for the solid-phase synthesis of highly substituted biaryl-furan derivatives. The initial step of the synthesis was a cross coupling of a zincate with a supported aryl halide catalyzed by  $\text{Pd}_2(\text{dba})_3$  in the presence of  $\text{AsPPh}_3$  (Scheme 143).

Scheme 143



Knochel et al. studied the cross coupling of organozincs in various media such as perfluorinated solvents<sup>213</sup> or ionic liquids.<sup>214</sup> They developed the use of a fluorinated phosphine as an efficient ligand for palladium in fluorinated solvents. The complex has been used with success as a catalyst for cross coupling of aryl iodides with aryl zinc bromides in a perfluorinated biphasic system<sup>213</sup> (Scheme 144). In the same manner, they prepared a new ionic phosphine ligand to perform cross couplings in ionic liquids<sup>214</sup> (Scheme 144).

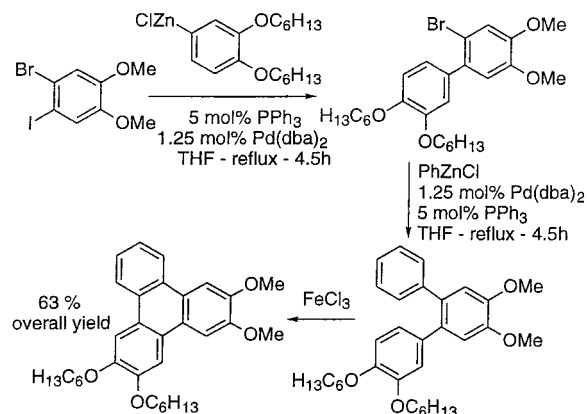
Scheme 144



#### D. Applications of Zinc Derivatives in Multistep Synthesis

The cross coupling of aryl zinc halides has found various applications. In 1994, Jackson et al.<sup>215</sup> developed a flexible synthesis of non  $C_2$ -symmetric substituted triphenylenes. The methodology used the different reactivities of bromides and iodides in two successive palladium-catalyzed cross couplings and then a ferric oxidative coupling (Scheme 145). An-

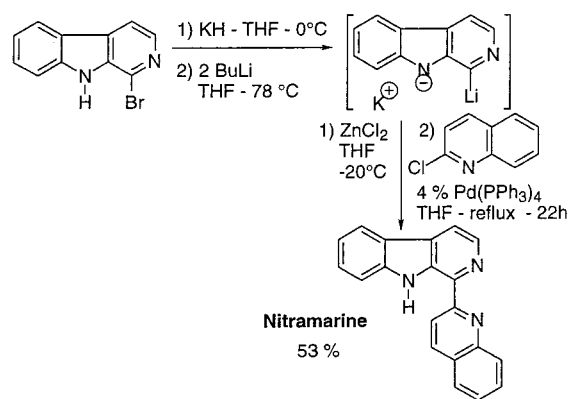
Scheme 145



other way to obtain such triaryl systems was recently studied by Takagi et al.<sup>216</sup> The authors performed a consecutive cross coupling of *o*-phenylenedizinc compounds with aryl halides in the presence of  $\text{Pd}(0)$ -tris(2,4,6-trimethoxyphenyl)phosphine with excellent yields.

Palladium-catalyzed cross coupling of zinc-containing compounds has very often been involved in many total syntheses. The synthesis of 1-substituted  $\beta$ -carboline, representing a large class of biologically active alkaloids, has been achieved by the use of zinc derivatives.<sup>217</sup> More specifically, the authors obtained nitramarine in a 53% yield (Scheme 146). Koch et

Scheme 146

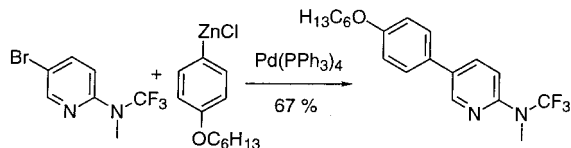


al. used a directed metalation associated with a palladium-catalyzed cross-coupling approach for the direct synthesis of pharmacologically active *ortho*-substituted biaryls.<sup>218</sup> This work deals with aryl oxazolines and benzamides, and the authors succeeded in a short and efficient synthesis of the hypolipidemic xenalipine.



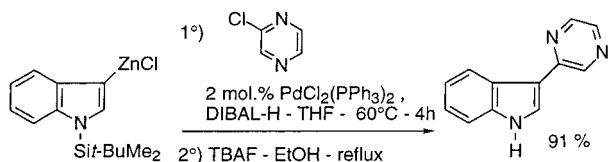
In 1995, Kuroboshi and Hiyama<sup>219</sup> studied the synthesis of trifluoromethylamino-substituted pyridines and pyrimidines. Using a palladium-catalyzed cross coupling, they performed the first synthesis of liquid crystal compounds containing a trifluoromethylamino group (Scheme 147).

Scheme 147



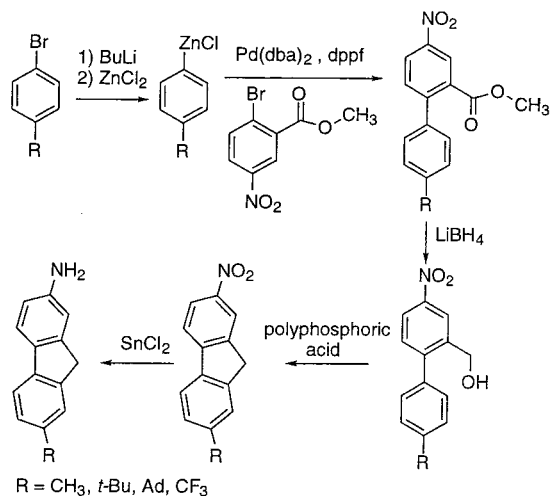
Amat and Bosch<sup>220</sup> applied palladium-catalyzed heteroarylation of 2- and 3-indolylzinc chlorides to indole alkaloid syntheses. For their study, the authors synthesized several substituted indoles by the cross coupling of various heteroaryls with indole (Scheme 148).

Scheme 148



More recently, the palladium-catalyzed cross coupling of zinc-containing aromatics has been used as the key step for the regioselective synthesis of substituted nitro- or aminofluorenes (Scheme 149).<sup>221</sup>

Scheme 149

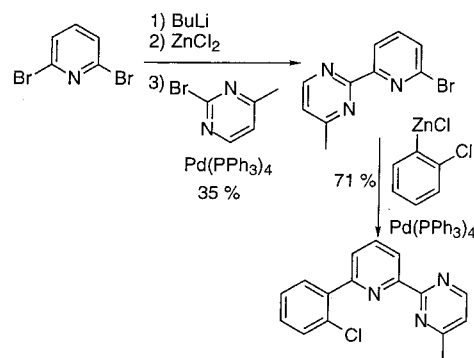


Such a palladium-catalyzed cross coupling has been used for the synthesis of substituted pyridylpyrimidine fungicides (Scheme 150).<sup>222</sup>

### 3. Palladium-Catalyzed Coupling of Mercury Derivatives

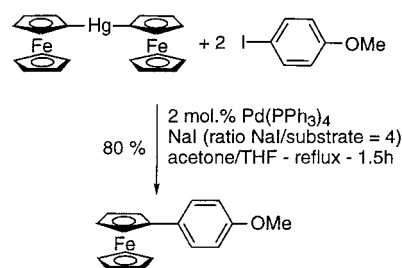
Despite ecological problems, mercury derivatives exhibit good stability which presents specific advantages. Recently, the cross coupling of bis(ferrocenyl)-mercury with aryl and heteroaryl iodides has been

Scheme 150



shown to be convenient for the synthesis of monoaryl-substituted ferrocenes in high yields (Scheme 151).<sup>223</sup>

Scheme 151



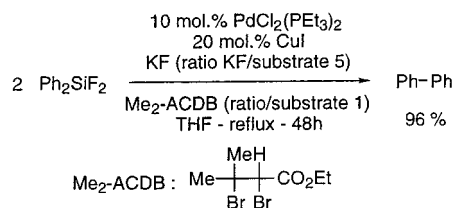
### 4. Palladium-Catalyzed Coupling of Silicon Derivatives

Organotin compounds have been widely used for palladium-catalyzed aryl cross coupling (Stille reaction). Other compounds bearing a metal from the same group IVa have also been studied for this reaction. Among them, the most studied element of the group is silicon.

#### A. Homocoupling of Aryl Silanes

One example was recently published showing the preparation of symmetrical biaryls by palladium-catalyzed homocoupling of organosilicon compounds (Scheme 152).<sup>224</sup> For this reaction, the addition of a

Scheme 152



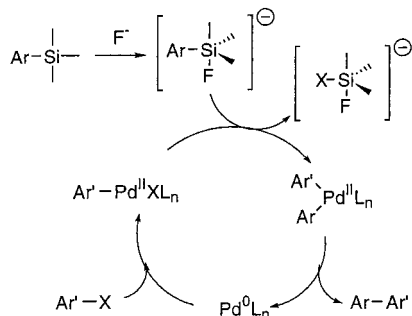
dibromide was needed as an oxidant for the regeneration of Pd(II) complexes.

#### B. Cross Coupling of Aryl Silanes

The cross coupling of aryl-, alkenyl-, allyl-, and alkylsilanes has been developed as an alternative to the cross coupling of magnesium, boron, zinc, and tin alkyls. The regioselectivity of the palladium-catalyzed cross coupling of silanes with organic halides was reported in 1995.<sup>225</sup>

The palladium-catalyzed cross-coupling reaction of organosilicon compounds has been largely studied by Hiyama and Hatanaka since 1988.<sup>226–232</sup> They described the commonly accepted mechanism<sup>226</sup> for the palladium-catalyzed cross-coupling reaction of aryl(halo)silanes with aryl halides which involves three steps (Scheme 153). The first one is an oxidative

Scheme 153

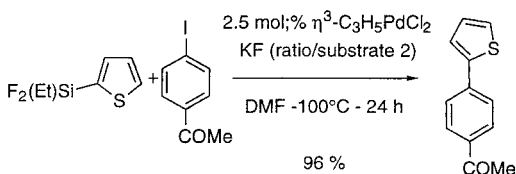


addition of the aryl halide to the palladium(0) complex. Then there is a transmetalation of the generated aryl–palladium(II) complex with an anionic pentacoordinate aryl(fluoro)silicate which is formed by the nucleophilic attack of the fluoride ion on the aryl(halo)silane. Finally, a reductive elimination of the bis(aryl)palladium(II) complex occurs.

The intermediacy of a hypervalent pentacoordinate aryl silicate by the reaction of a silane derivative with an activating ion is common to all types of silane derivatives used for cross coupling. As a general rule, the researchers have tried to find less expensive activating ions or more selective silicon species. This evolution has replaced fluoride by hydroxide and halogenosilanes successively by alkoxy- and alkylsilanes.

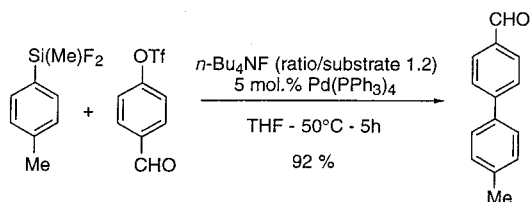
One of the first studies concerned the aryl–aryl cross coupling of ethyl(2-thienyl)difluorosilane and ethyl(phenyl)difluorosilane with aryl halides (Scheme 154).<sup>227,228</sup>

Scheme 154

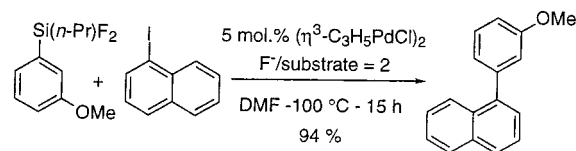


This method has been extended successfully to the reaction of aryls containing either electron-donating or -withdrawing groups and to the use of aryl triflates (Scheme 155).<sup>229</sup> The authors also synthesized substituted heterobiaryls in moderate to good yields.<sup>230</sup>

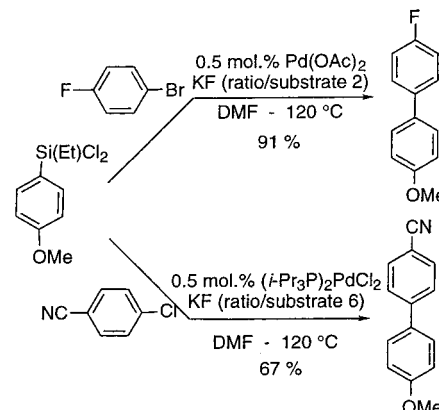
Scheme 155



Scheme 156



Scheme 157



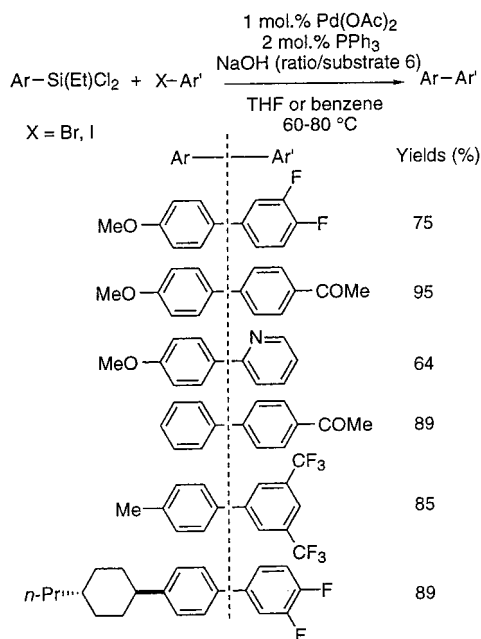
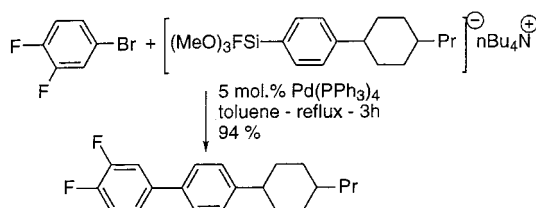
The cross coupling of aryl(halo)silanes with aryl halides is a general and practical route to functionalized biaryls.<sup>226</sup> The optimal conditions for the cross coupling of aryl fluorosilanes with aryl iodides involve 5 mol % of ( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>PdCl)<sub>2</sub> as the catalyst in DMF and a potassium fluoride/substrate ratio of 2 (Scheme 156).

Aryl chlorosilanes are pretreated with KF and can then react smoothly with aryl bromides at 20 °C in DMF in the presence of Pd(OAc)<sub>2</sub> (0.5 mol %) and PPh<sub>3</sub> (0.5 mol %).<sup>226</sup> The cross coupling of organochlorosilanes with aryl chlorides generally involves 0.5 mol % of [(i-Pr<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>] as the catalyst but requires a large excess of potassium fluoride.<sup>231</sup> This reaction seems to be a practical and reliable synthesis of highly functionalized biaryls. 4,4'-Disubstituted bi-phenyls for liquid crystals were obtained from various types of aryl(chloro)silanes.

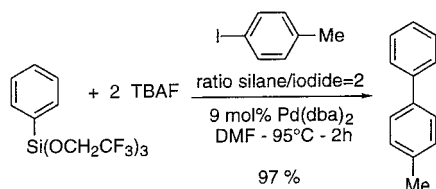
The method has been improved by the use of hydroxide ions (OH<sup>-</sup>) instead of fluoride salts.<sup>232</sup> These conditions allowed the cross-coupling reaction in THF or in benzene at 60–80 °C (Scheme 158). Elimination of fluorides as the promoter is of major economic interest for practical applications.

In 1997, Shibata et al.<sup>233</sup> developed a cross-coupling reaction of aryl–trialkoxysilanes with aryl bromides. The authors prepared a new type of pentacoordinate aryl silicate by the reaction of aryl–trimethoxysilane with a fluoride ion source which was often a tetra-alkylammonium salt (Scheme 159).

To study coupling conditions, they chose 4-(*trans*-4-*n*-propylcyclohexyl)-3',4'-difluorobiphenyl as the model compound. This product was used in active-matrix-liquid-crystal displays. They attempted the cross coupling of 4-(*trans*-4-*n*-propylcyclohexyl)phenyltrimethoxysilane with 1-bromo-3,4-difluorobenzene with different palladium catalysts in various solvents. Their best results were obtained with Pd(PPh<sub>3</sub>)<sub>4</sub> or Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> (5/15) in a THF/toluene mixture or in toluene (Scheme 160).

**Scheme 158****Scheme 159****Scheme 160**

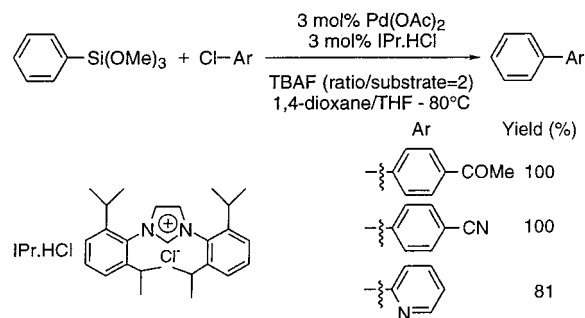
Recently, DeShong et al.<sup>234</sup> studied the same type of cross coupling. They presented this method as a viable alternative to the Stille and Suzuki protocols. The procedure involved the use of a hypervalent silicate derivative generated in situ (Scheme 161). In

**Scheme 161**

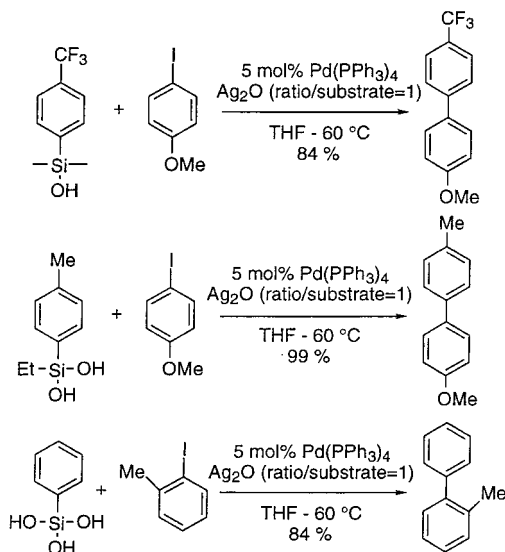
their studies, the hypothesis of the hypervalent silicate anion as the intermediate (Scheme 159) has been supported by the lack of reactivity of aryl silanes.

Recently, phenyl(trimethoxy)silane has been reported to react with aryl chlorides or bromides with the palladium/imidazolium chloride (IPr·HCl) system as the catalyst (Scheme 162).<sup>235</sup>

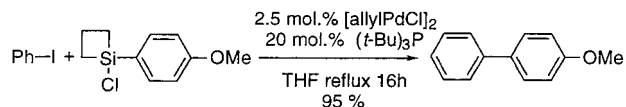
Silanols have also been used by Mori for aryl cross coupling.<sup>236,237</sup> Nevertheless, the use of such reagents involves the addition of silver(I) oxide in stoichiometric

**Scheme 162**

metric amounts as an activator and that limits the potential application of this method (Scheme 163).

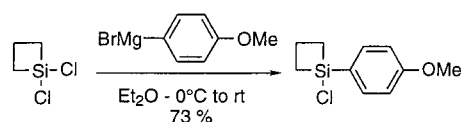
**Scheme 163**

Aryl-silacyclobutanes were also proposed as reagents for biaryl synthesis,<sup>238</sup> allowing the authors to prepare diverse unsymmetrical biaryls in good to excellent yields (Scheme 164). An excess of tri-*tert*-

**Scheme 164**

butylphosphine was nevertheless required in order to obtain the highest yields.

The authors explained that when compared to other organometallic reagents the methyl organosilacyclobutanes have several advantages: ease of synthesis, stability, and conversion to harmless byproducts despite the presence of tributylphosphine. The reagent is obtained by the reaction of a magnesium derivative with dichlorosilacyclobutane (Scheme 165).

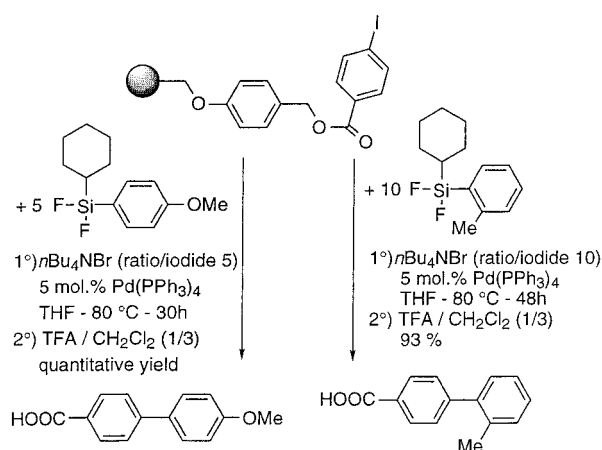
**Scheme 165**

Despite their efficiency, the interest in aryl silane cross coupling is limited by the difficulty of synthesizing such compounds. Indeed, aryl silanes are commonly generated via an organometallic intermediate such as Grignard reagents. Thus, these compounds present similar limitations to those of magnesium derivatives.

### C. Use of New Technologies in Aryl–Aryl Bond Formation Using Aryl Silanes

Recently, Hiyama et al. extended the use of aryl-(fluoro)silanes to solid-phase cross-coupling reactions.<sup>239</sup> The substrate was iodobenzoic acid tethered to the Wang resin. Optimized conditions involved a ratio of silane to iodide of 5:10 in the presence of an equivalent ratio of *n*-tetrabutylammonium bromide (Scheme 166).

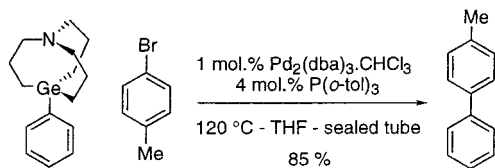
**Scheme 166**



## 5. Palladium-Catalyzed Coupling of Germanium Derivatives

Concerning other elements of the IVa group, there is only one example of palladium-catalyzed aryl cross coupling involving an organogermanium derivative,<sup>240</sup> where 4-methylbiphenyl was obtained in good yield (Scheme 167), although the synthesis of germanyl derivatives is far from easy.

**Scheme 167**



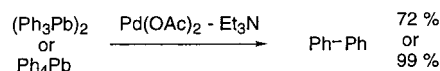
## 6. Palladium-Catalyzed Coupling of Lead Derivatives

In 1988, Barton et al. studied the reactivity of lead reagents in the presence of palladium.<sup>241</sup> They reported the preparation of biphenyl from hexaphenyldilead or tetraphenyllead in the presence of a stoichiometric amount of palladium (Scheme 168).

## 7. Palladium-Catalyzed Coupling of Bismuth Derivatives

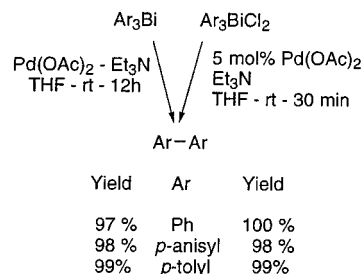
Due to their much lower reactivity, bismuth derivatives have only been used since 1988 for aryl

**Scheme 168**



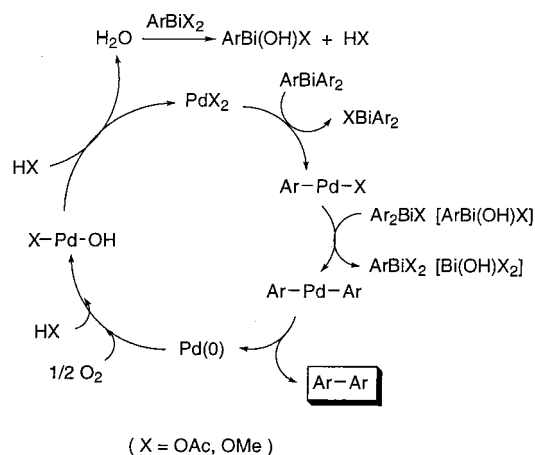
homocoupling.<sup>241</sup> The reaction with Ar<sub>3</sub>Bi required a stoichiometric amount of palladium, but the quantity of palladium needed became catalytic (5 mol %) when the authors used Ar<sub>3</sub>BiCl<sub>2</sub> (Scheme 169).

**Scheme 169**



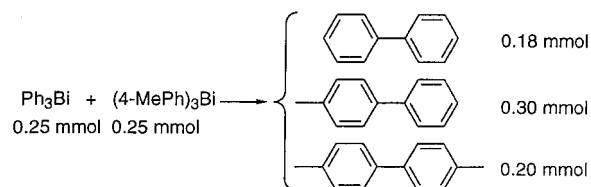
Similarly, Uemura et al. studied the use of triaryl-bismuthines for palladium(II)-catalyzed aryl homocoupling.<sup>242</sup> Treatment of Ar<sub>3</sub>Bi with a catalytic amount of Pd(OAc)<sub>2</sub> under air at room temperature produced biphenyls in high yields. The authors proposed a mechanism in which oxygen would allow palladium oxidation (Scheme 170).

**Scheme 170**



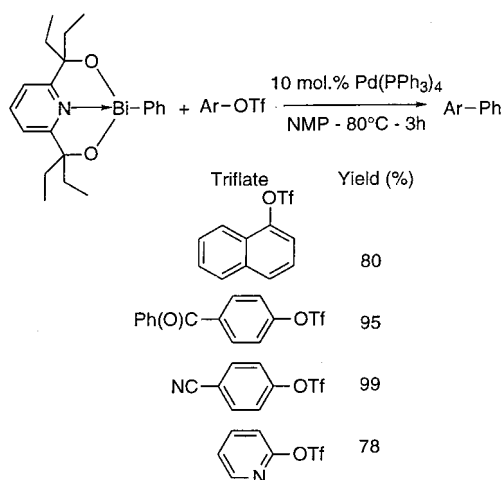
The authors also tested a mixture of two kinds of Ar<sub>3</sub>Bi under the same conditions, and they obtained a mixture of homocoupling products as well as a cross-coupling product (Scheme 171).

**Scheme 171**



Organobismuth dialkoxides have also been used for biaryl syntheses via a palladium-catalyzed cross coupling with triflates.<sup>243</sup> The different biaryls have been obtained in good to excellent yields (Scheme



**Scheme 172**

172). Synthesis of the reagent in this case appeared to be a factor limiting its use.

**8. Palladium-Catalyzed Coupling of Antimony Derivatives**

In 1988, Barton et al. performed aryl homocoupling reactions with antimony derivatives.<sup>241</sup> With triphenylantimony, the reaction needed the use of a stoichiometric amount of palladium. However, as in the case of bismuth derivatives, the reaction with triphenylantimony dichloride became catalytic. Homocoupling was observed in an 87% yield with the phenyl derivative.

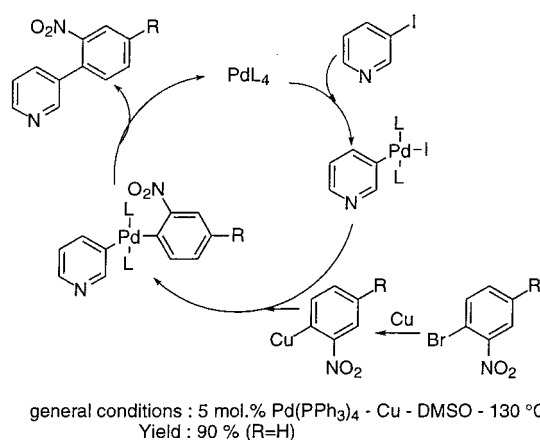
**9. Palladium-Catalyzed Coupling of Copper Derivatives**

Besides their use in Ullmann-like reactions (see section II), copper derivatives could also find an application as reagents associated with palladium catalysts. In 1993, Shimizu et al. used a mixture of copper (ratio Cu/substrate = 4) and tetrakis(triphenyl)phosphine palladium (5 mol %) for the cross coupling of halopyridines with bromo-*o*-nitroaryls.<sup>244</sup> They proposed a mechanism involving the oxidative addition of iodopyridine to Pd(PPh<sub>3</sub>)<sub>4</sub>, formation of aryl copper derivative, and subsequent reaction between these two compounds to form the arylpyridylpalladium(II) intermediate (Scheme 173). Finally, 1,1-reductive elimination would lead to arylated pyridine and regenerate a palladium(0) species. This mechanism is similar to that proposed for cross coupling of magnesium or zinc derivatives.

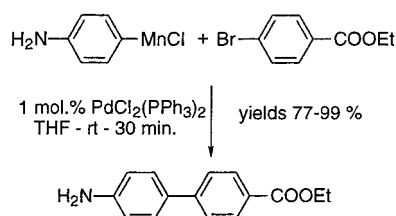
The authors also employed PdCl<sub>2</sub> as the catalyst instead of Pd(PPh<sub>3</sub>)<sub>4</sub>. This method was applied to pyridine bearing a halogen (I or Br) in the *ortho*-, *meta*-, or *para*-position.

**10. Manganese Derivatives**

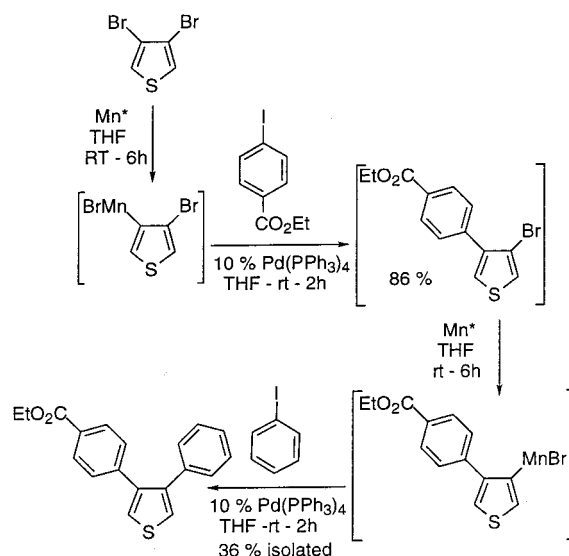
Alami and Cahiez recently demonstrated the efficiency of the palladium-catalyzed reaction of organomanganese halides with functionalized aryl halides or triflates.<sup>245</sup> Their procedure involved the use of 1 mol % of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst and allowed

**Scheme 173**

the synthesis of unsymmetrical biaryls in good to excellent yields within 30 min at room temperature (Scheme 174).

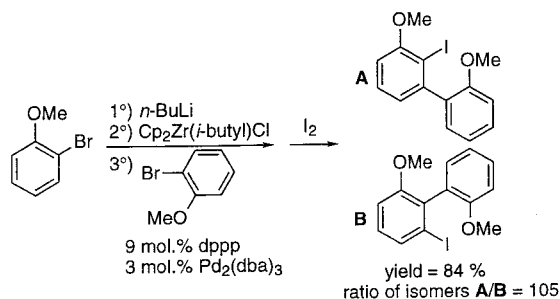
**Scheme 174**

Simultaneously, Rieke et al. performed aryl cross coupling with manganese derivatives.<sup>198</sup> Their method involved the direct addition of activated manganese and allowed the synthesis of unsymmetrical 3,4-disubstituted thiophenes (Scheme 175).

**Scheme 175****11. Palladium-Catalyzed Coupling of Zirconium Derivatives**

Buchwald et al. reported a combined zirconocene benzene-palladium cross-coupling route to substituted biphenyls and terphenyls.<sup>246</sup> The biaryl was obtained as a mixture of isomers (Scheme 176).

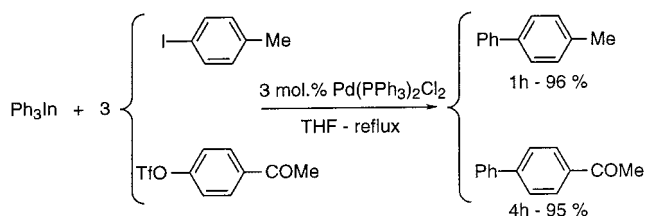
## Scheme 176



## 12. Palladium-Catalyzed Coupling of Indium Derivatives

Palladium-catalyzed aryl cross coupling has also been shown to be possible with triorganoindium.<sup>247</sup> Triphenyl indium proves to be effective for cross coupling with aryl iodide or triflate (Scheme 177).

## Scheme 177

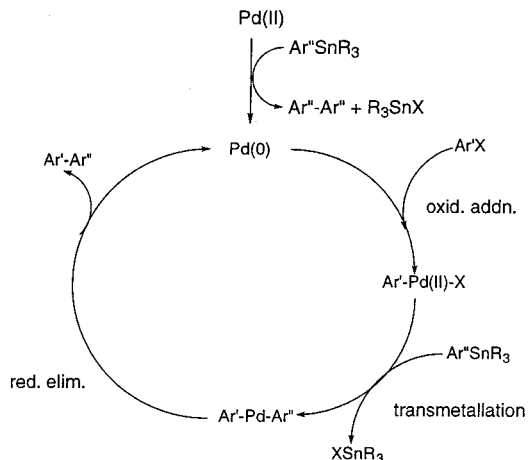


This methodology is therefore of a great interest due to the reactivity, selectivity, and low toxicity of this element. Moreover, indium allows the use of aryls bearing several types of substituents in the reaction.

## 13. Tin Derivatives and the Stille Reaction for Aromatic Carbon–Carbon Bond Formation

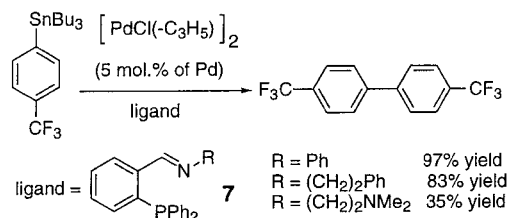
The palladium-catalyzed coupling of substituted aryl tin compounds is now in widespread use in organic synthesis and is known as the Stille reaction.<sup>248,249</sup> This is due to the growing availability of the organostannanes, their stability to moisture and air, and their compatibility with a large variety of functional groups. There is, however, a disadvantage that limits the Stille reaction: the toxicity of the organotin reagents. This drawback is limited owing to some recent results showing that tin derivatives of lower toxicity could be used.<sup>250</sup> Moreover, as described in this section, the use of supported reagent as a substrate allows an easy separation of the products from the reagent and the byproduct. It is particularly convenient in the case using the Stille reaction. The generally accepted catalytic cycle for the Stille reaction<sup>248,251–255</sup> is shown in Scheme 178. The palladium catalyst can be used either as Pd(II) or Pd(0). In the case of Pd(II), the organotin compound initially reduces the palladium(II) complex precursor to the palladium(0) species. First, an organopalladium intermediate is formed by oxidative addition of the catalyst to the aryl halide or triflate. Then transmetalation takes place to form a diarylated palladium moiety. Finally, a reductive elimination gives the biaryl product and the palladium(0) species to complete the catalytic cycle.

## Scheme 178

A. Synthesis of *C*<sub>2</sub>-Symmetric Biaryls Using the Stille Reaction

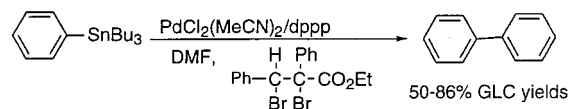
The Stille reaction requires the preparation of an organostannane compound and halide derivatives. This reaction is well suited to the preparation of unsymmetrical biaryls. There are few examples of Stille reactions for the synthesis of symmetrical biaryls and not many examples of the palladium-catalyzed homocoupling of organostannanes. An iminophosphine–palladium complex successfully catalyzed the oxidative homocoupling of aryl stannanes using air as a mild oxidant.<sup>256</sup> The iminophosphine **7** (R = Ph) appears to be the best phosphine-based ligand; a high reaction rate was observed (Scheme 179).

## Scheme 179



By using acrylate dibromides as oxidants, biaryls were obtained in good yields.<sup>257</sup> The reaction conditions revealed that the best result was obtained (biphenyl in 86% GLC yield) in the presence of the  $\delta$ -donating ligand, TMEDA, in combination with PdCl<sub>2</sub>(MeCN)<sub>2</sub> in *N,N*-dimethylimidazolidinone. The reaction was also improved in the presence of bidentate ligands (dppe, dppp, dppb) in DMF (Scheme 180).

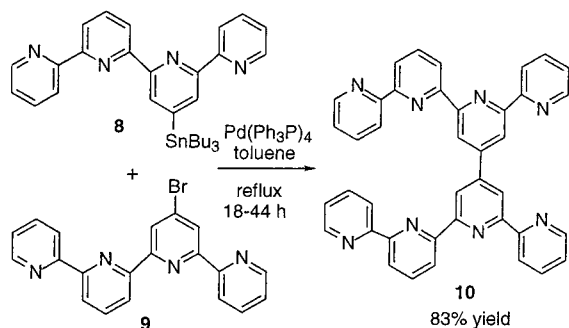
## Scheme 180



A series of symmetrical functionalized oligopyridines **10** containing 6–14 pyridine units were synthesized<sup>258</sup> by cross-coupling reactions of compounds **8** and **9**. These oligopyridines are interesting starting compounds for supramolecular chemistry. 4-Bromo-2,6-oligopyridine **9** could be easily prepared

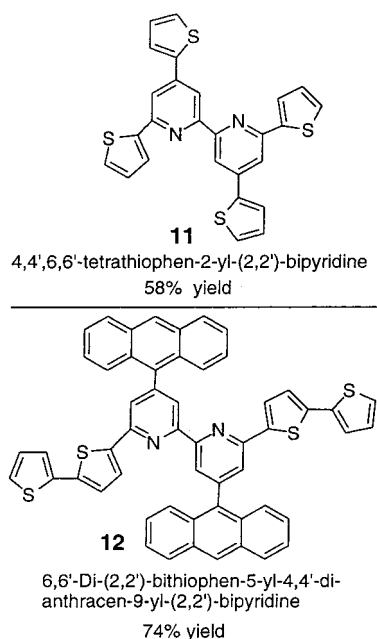
using an electrophilic reagent like Br<sub>2</sub> which cleaves rapidly the pyridine–Sn bond of tin compounds **8** (Scheme 181).

### Scheme 181



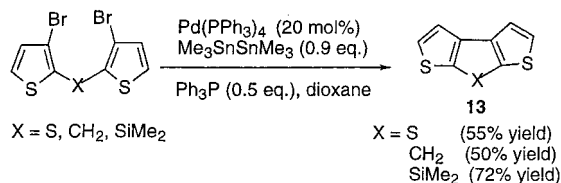
Sauer et al.<sup>259</sup> also prepared several 4-aryl-2,6-oligopyridines **12** and 4-aryl-olyl-2,6-oligopyridines **11** via the Pd-catalyzed Stille reaction. These thienyl-substituted oligopyridines have interesting pH-sensitive fluorescence properties (Scheme 182).

### Scheme 182



A number of aryl stannanes have been prepared in situ to avoid decomposition during purification.<sup>260,261</sup> The dithienothiophene **13** has also been synthesized in situ by the metal-catalyzed intramolecular cyclization reaction<sup>261</sup> (Scheme 183). After the

### Scheme 183



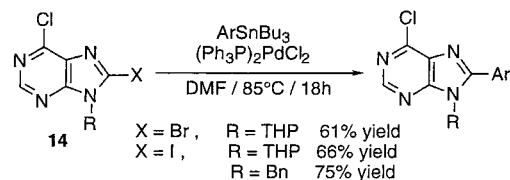
oxidative addition, transmetalation, and reductive elimination steps, monostannylated compounds give

the cyclization product by palladium-catalyzed intramolecular cross-coupling reaction.

### B. Dissymmetrical Coupling of Aromatic Rings Using the Stille Reaction

**a. Application of the Stille Reaction to the Synthesis of Di- and Triheterocycles.** The Stille reaction has enjoyed considerable success in the synthesis of large numbers of heterobiaryls.<sup>260–283</sup> The regioselectivity in Pd-catalyzed aryl coupling of 6,8-dihalopyridines **14** was examined and depends on the nature of halogens and substituents<sup>262</sup> (Scheme 184).

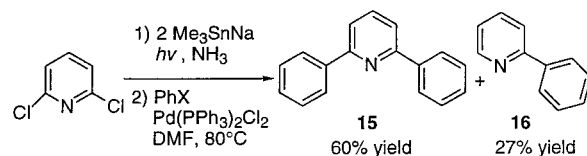
### Scheme 184



When 6,8-dichloropyridines were used, the major products were only the 6-substituted compounds; the regioisomers could not be observed.

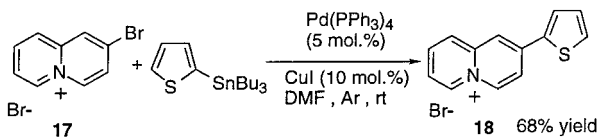
Rossi et al.<sup>282</sup> developed a procedure for the synthesis of mono-, di-, and triphenyl arenes using sequential photostimulated S<sub>RN</sub>1 and Pd(0)-catalyzed coupling reactions of aryl halides (Br, I). The authors studied the possibility of performing the synthesis of distannane and the Stille reaction in a one-pot procedure. A solution of 2,6-dichloropyridine, dry liquid ammonia, and Me<sub>3</sub>SnNa was irradiated. After the evaporation of the solvent, xylene, PhI, and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> were added, giving 2,6-diphenylpyridine **15** (60%) and 2-phenylpyridine **16** (27%) (Scheme 185).

### Scheme 185



The Stille reaction has found an application in the synthesis of different substituted quinolizinium salts.<sup>283</sup> According to the authors, the coupling reaction of bromoquinolizinium salts **17** and various aryl and heteroaryl stannanes gives the coupling products **18** with satisfactory yields. A 10 mol % amount of copper(I) iodide was used as a cocatalyst (Scheme 186).

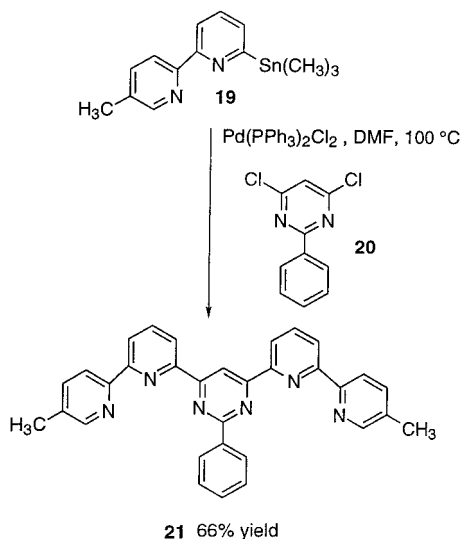
### Scheme 186



The reaction of heteroaryl halides with heterostannanes was used in the synthesis of a large number of biheteroaryls.<sup>274–276,284–293</sup> Schubert et al.<sup>284</sup> reported the synthesis of 2,2'-bipyridine, 5,5''-dimethyl-2,2':6',2''-terpyridine, and 4,6-bis(5''-methyl-2'',2'-

bipyrid-6'-yl)-2-phenylpyrimidine) **21**. The latter coupling product has been synthesized by the reaction of bipyridine **19** with 4,6-dichloro-2-phenylpyrimidine **20** in the presence of  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  as a catalyst (Scheme 187). The synthetic strategy is

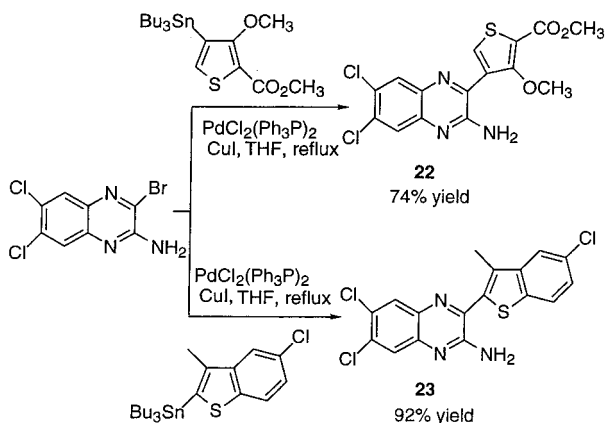
Scheme 187



valuable in supramolecular and polymer chemistry.

The synthesis of 3-aryl and 3-heterocyclic quinoxalin-2-ylamines **22**, **23** has been reported<sup>286</sup> using the Pd-catalyzed cross-coupling reaction of 3-bromo-quinoxalin-2-ylamines with various aryl and heterocyclic stannanes (Scheme 188).

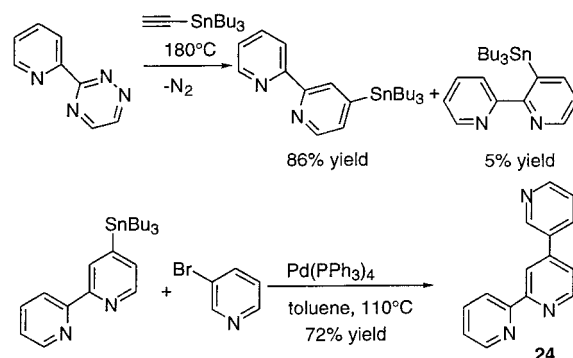
Scheme 188



Recently, an interesting method has been developed for thermally induced (4+2) cycloaddition reactions between tailor-made 1,2,4-triazines and tributyl-(ethynyl)tin, which opens up a convenient route to regioselectively stannylated 2,2'-bi- and 2,2',6',2''-terpyridines in good yields. By substitution of the stannyl group, various substituents **24** can be introduced. These compounds are building blocks for supramolecular chemistry<sup>288</sup> (Scheme 189).

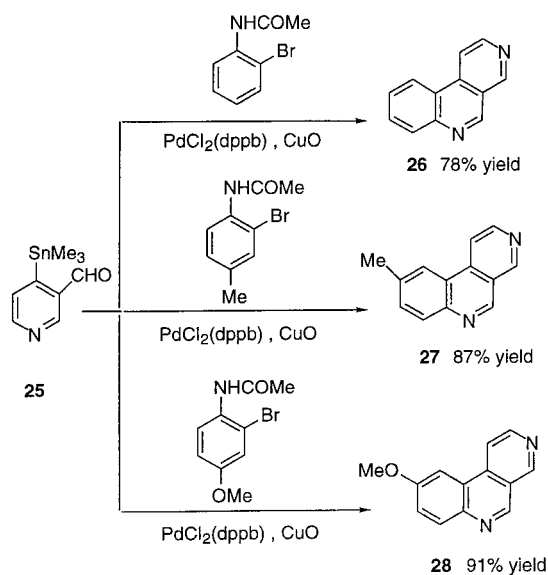
The preparation of tricyclic heterocyclic systems in one step and in good yields has been achieved based on the Pd(0)-catalyzed cross couplings of 4-trimethylstannyl-3-pyridine carboxaldehyde **25** with *ortho*-bromoacetanilides in a  $\text{PdCl}_2(\text{dppb})$ -catalyzed reaction. Benzo[*c*]-2,7-naphthyridine **26** has been syn-

Scheme 189



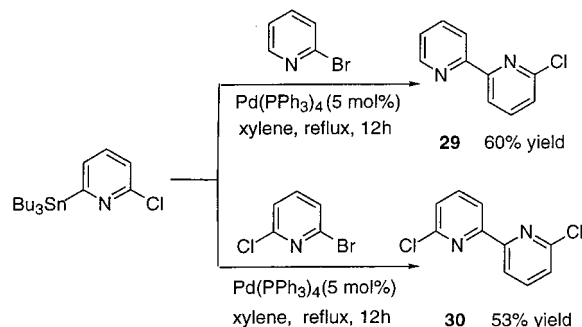
thesized from **25** and 4-bromoacetanilide. 2-Bromo-4-methylacetanilide and **25** gave 9-methoxybenzo[*c*]-2,7-naphthyridine **27**. 2-Bromo acetanilide and **25** gave 9-methoxybenzo[*c*]-2,7-naphthyridine **28**. The results were greatly improved<sup>294</sup> by the use of CuO as a co-reagent (Scheme 190).

Scheme 190



Fort et al.<sup>295</sup> reported a method for the synthesis of heteroaryl halides (I, Br) with heterostannanes (Scheme 191). The results for the synthesis of 6,6'-

Scheme 191



dichloro-2,2'-bipyridine **29** and 6-chloro-2,2'-bipyridine **30** are improved in comparison with previously reported methods.<sup>296,297</sup>

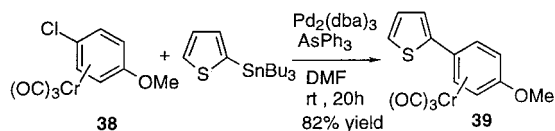
The Stille reaction has been used in the synthesis of regioisomeric bithiophenes 3,4'- and 3,3'-di-





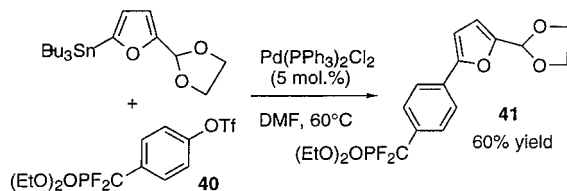
To decrease the electron density in an aromatic ring, Rose et al.<sup>317</sup> reported the use of chromium carbonyl ligand allowing an easier oxidative addition of the carbon–halogen bond to the zerovalent palladium-active species. The cross coupling of (*p*-chloroanisyl)tricarbonylchromium complex **38** with thiophene derivatives leads to the selective formation of tricarbonyl- $\eta^6$ -((2-thiophenyl) arene) **39** by slightly modifying the reaction conditions (Scheme 197).

Scheme 197



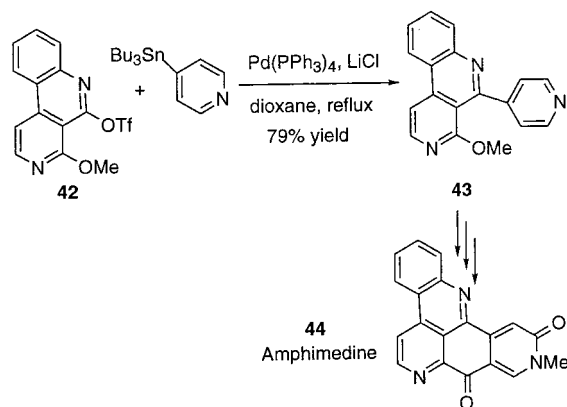
Although relatively expensive, triflates are easily prepared from phenols and have often been used for the Stille cross-coupling reaction due to their excellent leaving group properties.<sup>318–326</sup> *p*-Triflate phenylphosphonate **40** was used in a PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>-catalyzed reaction with a range of aryl- and heteroaryltributylstannanes. The coupling products were obtained in moderate to high yields<sup>318</sup> (Scheme 198).

Scheme 198



The cross-coupling reaction has found application in a total synthesis of the marine alkaloid amphimedine<sup>322</sup> **44**. By using Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst with LiCl as an additive, the cross-coupling reaction of 5-(4-methoxybenzo[*c*](2,7)naphthyridinyl) trifluoromethanesulfonate **42** with pyridylstannane leads to the 4-methoxy-5-(4-pyridyl)benzo[*c*](2,7)naphthyridine **43** in a yield of 79% (Scheme 199).

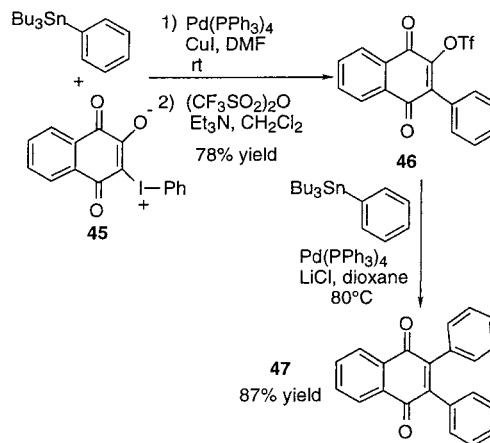
Scheme 199



In an attempt to improve the Stille cross-coupling reaction, some alternatives have been reported to carry out the reaction under mild conditions such as room temperature. It was demonstrated that both hypervalent iodines and triflates are useful electrophile components in Stille-coupling reactions.<sup>323</sup> A

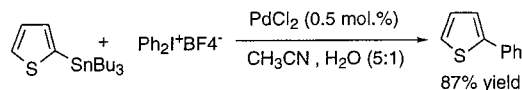
number of 2,3-diaryl-1,4-naphthoquinones have been synthesized in good yields by the reaction of aryl stannanes with 2-phenyliodonio-1,4-naphthoquinones-3-oxide **45** with Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst. The 3-aryl-2-hydroxy-1,4-naphthoquinones have been obtained and transformed to the corresponding 3-aryl-2-trifluoromethane sulfonyloxy-1,4-naphthoquinone **46**. The second coupling reaction between aryl stannane and **45** produces 2,3-diaryl-1,4-naphthoquinones **47** in good yields (Scheme 200).

Scheme 200



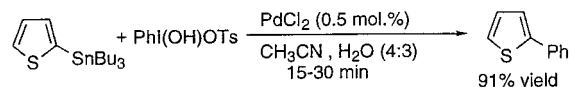
Lee et al.<sup>324</sup> reported the cross coupling of organostannanes with iodonium salts. The coupling reaction has been performed at room temperature under aqueous conditions and was presented as an alternative to aryl halides (Scheme 201).

Scheme 201



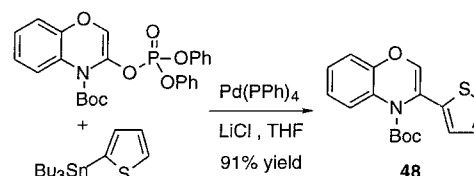
The same group<sup>325</sup> investigated the Pd-catalyzed coupling of organostannanes with iodanes (Koser's and Zefirov's reagent) at room temperature in aqueous medium (Scheme 202).

Scheme 202



A series of 3-substituted-4*H*-1,4-benzoxazines **48** possessing biological activities was obtained in high yield through palladium-catalyzed reactions between organostannanes and aryl phosphate<sup>326</sup> (Scheme 203).

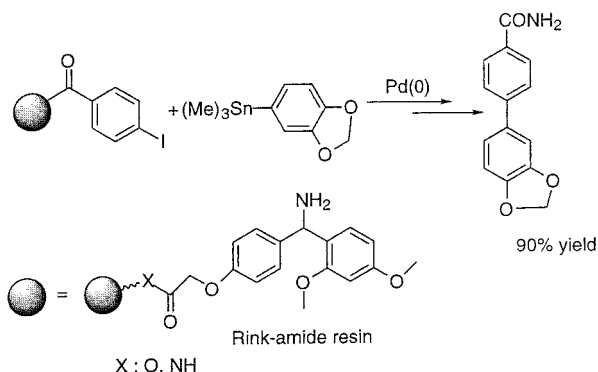
Scheme 203



**c. Use of New Technologies in the Stille Cross Coupling of Aromatic Substrates.** The solid-phase

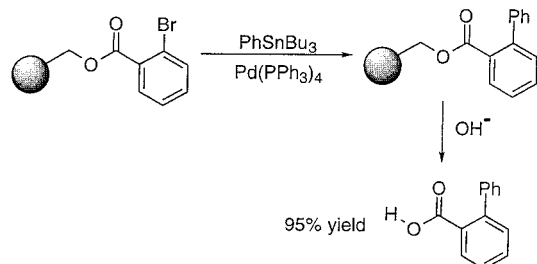
organic synthesis has emerged as an important tool in combinatorial chemistry. More important in the case of the Stille reaction is the separation of the supported substrate from the bulk of the reaction containing an excess of reagents and byproducts. The Stille reaction has enjoyed considerable success<sup>314</sup> in the synthesis of large compound libraries.<sup>304–305,307,327–333</sup> In 1994, Deshpande<sup>327</sup> reported the Stille-coupling reaction involving aryl stannanes and polymer-bound aryl iodides (Scheme 204).

Scheme 204



Sucholeiki et al.<sup>331</sup> demonstrated the high efficiency of tris(dibenzylideneacetone)palladium by comparison to triphenylphosphine and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> for the solid-phase Stille-coupling reaction. The polymer-bound aryl halides and triflates and aryl stannanes have been attached to the Rink amide resin and tested to produce biaryl products on solid support in moderate yield. Snieckus et al.<sup>329</sup> used a commercial Merrifield resin treated with various bromo- and iodobenzoic acids, and then by using the Stille Reaction they obtained biaryl-, heteroaryl-, and styrylcarboxylic acids in high yields and purities (Scheme 205). The authors also showed the synthesis

Scheme 205

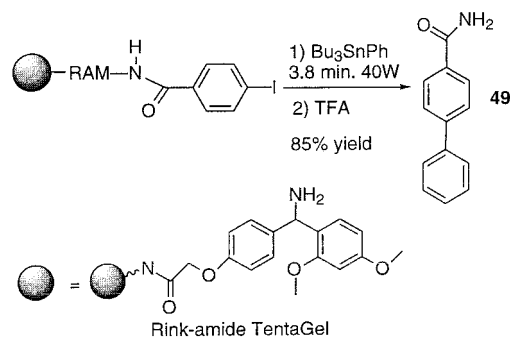


of fluorenones and dibenzopyranones by connecting this method to directed *ortho*- and remote metalation (DoM and DreM) tactics.

The ability of solid-phase organic chemistry to produce and release the desired biphenyl is a major advance in the biotechnological and pharmaceutical industries. 4-Phenylbenzamide **49** has been synthesized in excellent yield (85%) and was easily cleaved from polymer (Rink amide (RAM) TentaGel) via a microwave-assisted Stille reaction on the polymer-tethered 4-iodobenzoic acid<sup>315</sup> (Scheme 206).

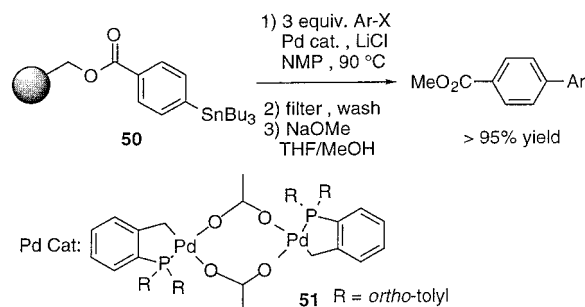
Finn et al.<sup>328</sup> reported an interesting method for the synthesis of substituted biaryls in excellent yields on the resin (1% divinylbenzene-cross-linked Merri-

Scheme 206



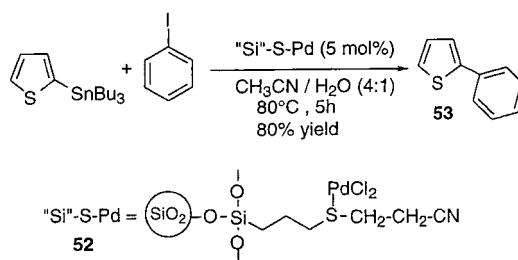
field resin), which is based on the cross coupling of aryl halides with aryl stannane **50**. Among the several catalyst systems examined, the best result was obtained using a palladacycle complex **51**. Furthermore, results in terms of yields and reaction rate were also improved by the addition of LiCl (Scheme 207).

Scheme 207



In an alternative to recover and reuse the palladium catalyst in the Stille reaction, Kang et al.<sup>333</sup> prepared silica-supported poly(3-(2-cyanoethylsulfanyl)propylsiloxanopalladium) complex **52** (Scheme 208). The cross coupling of organostannanes with aryl

Scheme 208

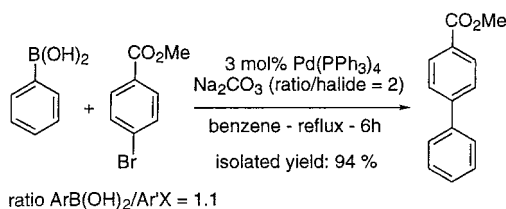


iodides was then carried out in the presence of silica-supported palladium complex and in aqueous medium. The catalyst was reused after filtration to give 2-thienylbenzene **53** in 72% yield. This second reuse of the catalyst led to a 67% yield of product.

## 14. Aromatic C–C Bond Formation Using Organoboronic Derivatives (The Suzuki Reaction)

Since the beginning of the 1980s, Suzuki initiated a major improvement in the use of palladium-catalyzed aryl-aryl bond formation by using boronic acids as the nucleophilic part of the reaction (Scheme 209).<sup>334</sup>

## Scheme 209



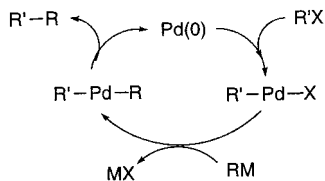
Boronic derivatives present several advantages over all the other organometallic derivatives.<sup>335</sup> First of all, they can tolerate a wide range of functional groups such as organic halides, carbonyl, etc. The original reactivity of boronic compounds is partly due to the electronegativity of boron, which is about 2.0. This value is relatively close to the value of 2.5 for carbon and is higher than the electronegativities of lithium, magnesium, or most of the transition metals which range from 0.86 to 1.75.

The second advantage is the low toxicity of the reagents and byproducts, especially compared to tin-containing compounds. Moreover, even if they are not always easy to prepare, boronic derivatives are easy to handle and present much less manipulation risk than other organometallic derivatives. The association of reagents with low reactivity, such as boronic acids or esters, with a powerful catalytic system, such as palladium catalysts, is the major improvement of the last two decades in this area. Several recent reviews described the use of Suzuki methodology, especially one by Suzuki himself—in 1995.<sup>336</sup> Thus, we limited this section to cover the most recent five years. Nevertheless, interest in the Suzuki reaction is such that many more articles have been published in this short period than for other methodologies.

The cross-coupling reaction of organoboron compounds involving the transmetalation to aryl–palladium(II) halides has been found to proceed smoothly when these are activated with suitable bases and has proven to be a good general method for a wide range of selective carbon–carbon bond formation.<sup>336</sup>

The mechanism of the Suzuki reaction is commonly depicted as a general catalytic cycle involving oxidative addition–transmetalation–reductive elimination sequences (Scheme 210).<sup>336</sup> In this case, oxidative

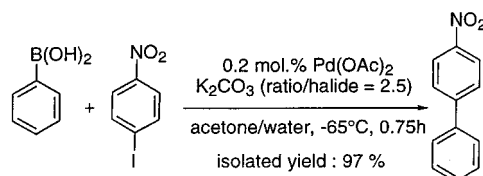
## Scheme 210



addition is often the rate-limiting step, and it is not surprising that the relative reactivity of aryl halides decreases in the order  $\text{I} > \text{Br} > \text{Cl}$ .<sup>337</sup> Of course, this reactivity is largely influenced by the proximity of electron-withdrawing or -donating groups.

In 1994, Wallow and Novak<sup>338</sup> showed that phosphine inhibition could play a key role in limiting catalytic efficiency in Suzuki aryl cross couplings. They showed that mild, efficient, and clean catalysis could occur in the absence of phosphine (Scheme 211).

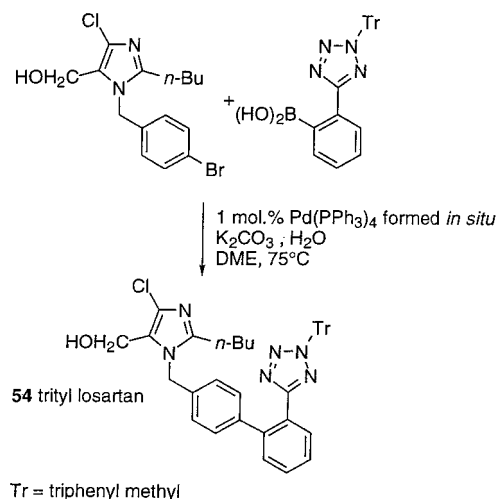
## Scheme 211



In their studies, the authors also demonstrated that the reaction rate is influenced by the pH. As an example, in some particular cases, the use of  $\text{K}_2\text{CO}_3$  instead of  $\text{KHCO}_3$  increased the rate of the reaction.

In 1994, Smith et al. performed mechanistic studies on the Suzuki cross-coupling reaction.<sup>339</sup> As their model reaction, they studied the synthesis of trityl losartan **54** (Scheme 212), which belongs to a new

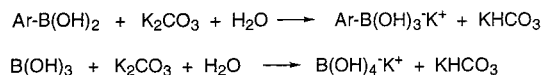
## Scheme 212



class of drugs (angiotensin II receptor antagonists) and was developed for the treatment of high blood pressure and heart failure.

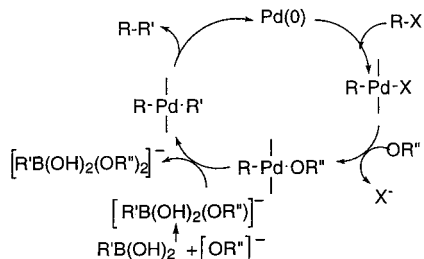
They showed that coupling was efficient when the base had a  $\text{p}K_a$  close to 10 (like alkali carbonates), whereas it failed when the base was a bicarbonate ( $\text{p}K_a$  close to 6). Considering the  $\text{p}K_a$  of phenylboronic acid (8.8), the authors explained that when the pH was superior to 9, phenylboronic acid was transformed into trihydroxyphenylborate ( $\text{PhB(OH)}_3^-$ ). The authors supposed that this anion was the reactive species rather than the neutral boronic acid. Kinetic studies also proved that water and base are required to activate the boronic acid. They assumed that one mole of water and one mole of carbonate are required initially to activate the boronic acid and then to neutralize the produced boric acid (Scheme 213).

## Scheme 213



The general features of the mechanistic cycle received further support since some of the proposed intermediates were detected by electrospray ionization mass spectrometry.<sup>340</sup>



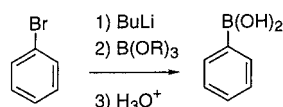
**Scheme 214**

Recently, Suzuki proposed another catalytic cycle (Scheme 214) based on his previous works on alkenyl coupling.<sup>341</sup> This mechanism involves an additional step of ligand exchange between oxidative addition and transmetalation but has not yet been validated.

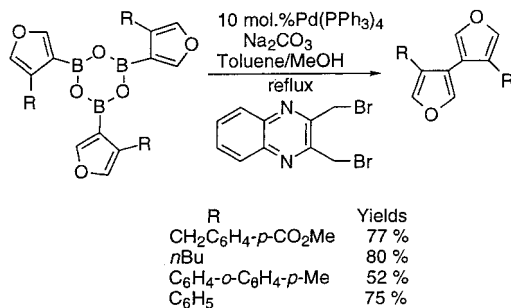
This section is organized in three parts. The first describes the use of boronic derivatives for aryl homocoupling and cross couplings. The second deals with some of the numerous examples of the classical Suzuki reaction applied in syntheses of biphenyls or heterobiaryls. The third shows recent improvements in Suzuki methodology, such as alternative boronic derivatives and/or leaving groups, the optimization of reaction conditions, new ligands for palladium, and technological improvements.

**A. Homocoupling of Aryl Boronic Acids Catalyzed by Palladium**

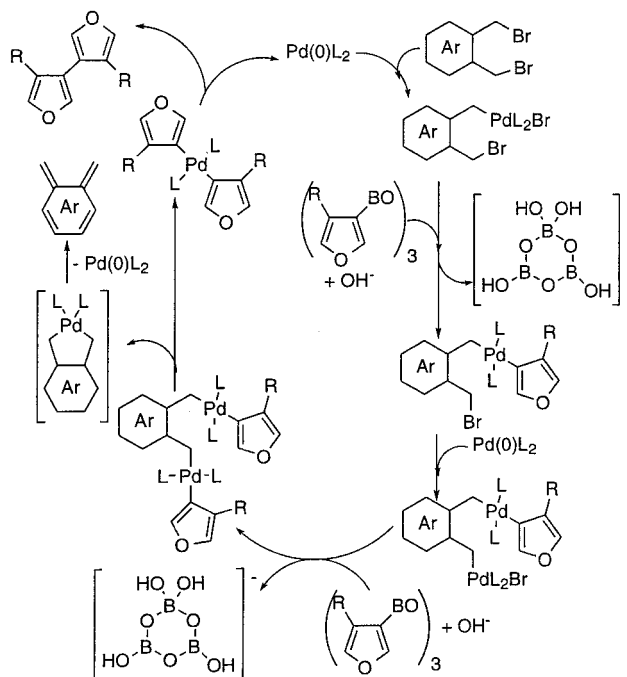
The only drawback to the use of the Suzuki reaction is the difficulty of accessing boronic derivatives. The preparation of such compounds generally requires the use of a halide derivative and a strong base, followed by careful hydrolysis (Scheme 215).<sup>335</sup>

**Scheme 215**

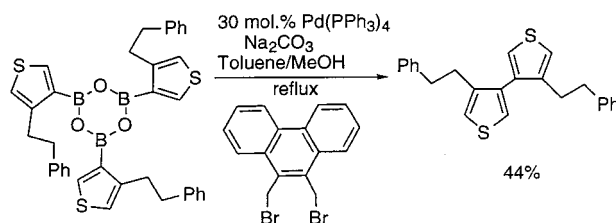
As a consequence, the Suzuki reaction is not widely used for syntheses of symmetrical biaryls, and several other methodologies are often competitive in such cases. Nevertheless, in 1994, Song and Wong turned the self-coupling into a useful synthetic method by applying it to the preparation of furan-3,4-diyl oligomers.<sup>342</sup> They performed the self-coupling of organoboroxines catalyzed by palladium (Scheme 216). In this reaction, bis(bromomethyl)-arenes were required to achieve the furan coupling.

**Scheme 216**

The authors proposed a mechanism involving a series of oxidative additions, transmetalations, and reductive eliminations in which the bromomethyl-arene acted as a hemilabile ligand and regenerated the required palladium species (Scheme 217).

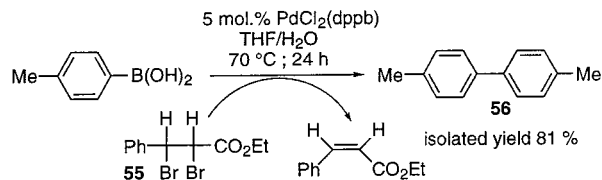
**Scheme 217**

In 1997, similar results were obtained with thiophene derivatives.<sup>343</sup> Wong et al. described the successful synthesis of thiophene 3,4-diyl dimers (Scheme 218). They also extended the method to the syntheses

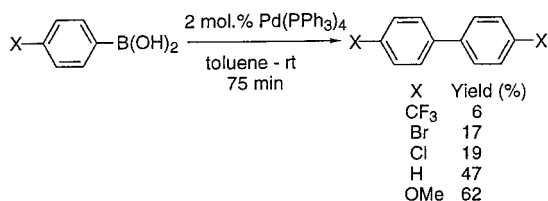
**Scheme 218**

of thiophene-3,4-diyl oligomers.

In 1997, Tamao et al. used acrylate dibromide derivatives as effective oxidants.<sup>344</sup> In the presence of phenyl acrylate dibromide **55** and a catalytic amount of PdCl<sub>2</sub>(dppb), they performed the synthesis of 4,4'-bitolyl **56** in good yield (Scheme 219).

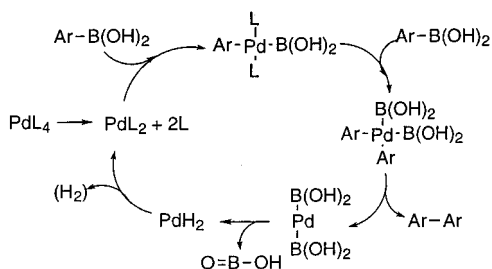
**Scheme 219**

Moreno-Mañas et al. studied the mechanism of the self-coupling of aryl boronic acids.<sup>345</sup> They reported that aryl boronic acids could be converted into symmetrical biaryls with Pd(0) catalysis (Scheme 220).

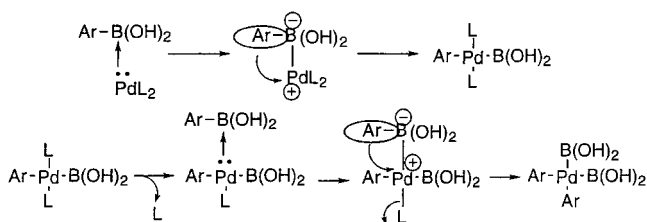
**Scheme 220**

In all cases, neither bases nor bromomethyl compounds were introduced.

Their studies also showed that the more electron-withdrawing substituent (CF<sub>3</sub>) gave lower yields and the most electron-donating group (OMe) gave higher yields. The authors observed that oxygen accelerates the reaction. The proposed mechanism is shown in Scheme 221.

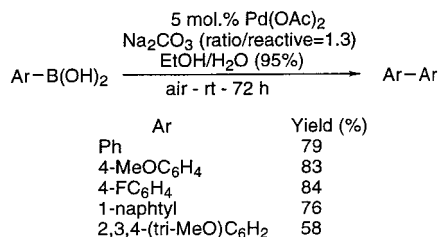
**Scheme 221**

The authors were more specific about the mechanism of the two oxidative additions (Scheme 222). In

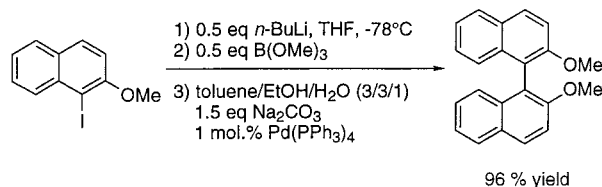
**Scheme 222**

collaboration with Aramendia's team, they completed these studies by electrospray-ionization-mass-spectrometry detection of intermediates.<sup>346</sup>

Very simple reaction conditions for palladium-catalyzed homocoupling of aryl boronic acids were reported by Jackson et al. in 1997.<sup>347</sup> The reaction occurred in aqueous ethanol (95%) containing a catalytic amount of palladium acetate (5 mol %) and a base. The better base was sodium carbonate. No addition of Cu(OAc)<sub>2</sub> or PPh<sub>3</sub> was required. Different biphenyls were obtained in moderate to good yields (Scheme 223).

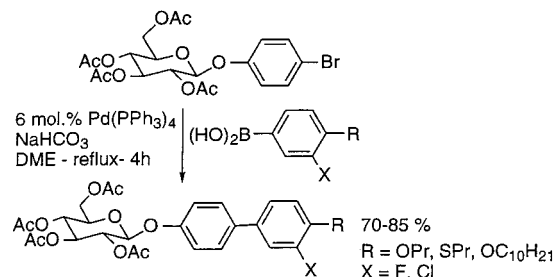
**Scheme 223**

A synthesis of binaphthyls in high yields was described by Keay et al.<sup>348</sup> in which the authors performed a modified in situ Suzuki-coupling reaction (Scheme 224).

**Scheme 224****B. Suzuki Cross Coupling of Aryl Boronic Acids with Aryl Halides**

The importance of the Suzuki reaction is mainly due to its efficiency in dissymmetrical biaryl syntheses. Since Suzuki's discovery,<sup>334</sup> numerous interesting results have been obtained by the cross coupling of aryl boronic acids with aryl halides in the presence of a base and Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst. These results fall into two major categories: biphenyls, including particular cases of binaphthyls and arene chromium complexes, and heteroatom (either N, O or S) containing biaryls. This was extended to complex structures such as porphyrines.

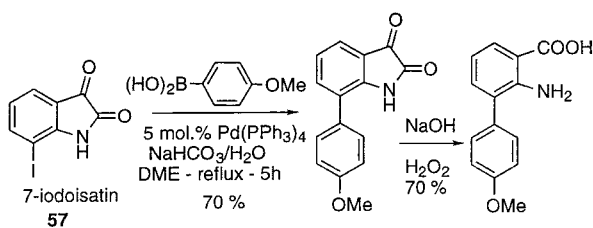
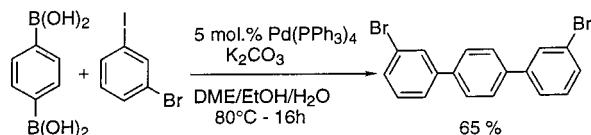
**a. Biphenyl Synthesis.** The reaction conditions described in 1981 by Suzuki<sup>334</sup> involved the use of a boronic acid with an aryl halide in the presence of a stoichiometric amount of base and Pd<sup>0</sup> as the catalyst (generally with PPh<sub>3</sub> as the ligand). These efficient initial conditions were applied to the synthesis of biphenyls bearing various functional groups. In 1995, Tschierske et al. applied this method with success to the synthesis of carbohydrate-functionalized aromatic compounds (Scheme 225).<sup>349</sup>

**Scheme 225**

The methodology was also efficient in the presence of sensitive functions such as aldehyde<sup>350</sup> or silane.<sup>351</sup>

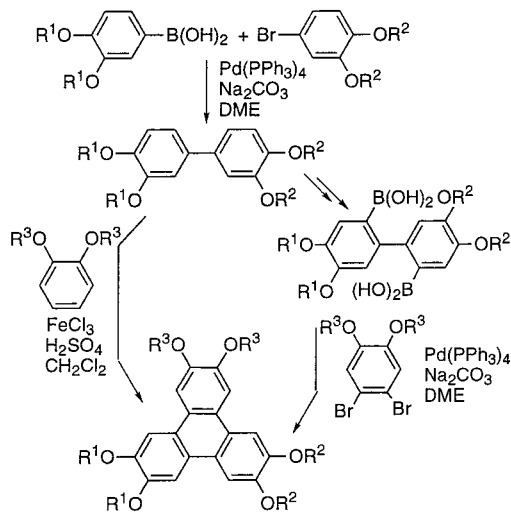
In 1995, Miura et al. applied a Suzuki cross coupling to mono-, di-, and triaminobenzenes.<sup>352</sup> Nevertheless, in the presence of amine, Hird et al. observed deamination as a side reaction.<sup>353</sup> Recently, the application of Suzuki cross coupling to 7-iodoaniline, enabled the synthesis of biaryl amino acids (Scheme 226).<sup>354</sup>

Suzuki cross coupling can also be applied to aromatic diboronic acids. In 1997, Abell et al. studied the reactivity of diboronic acids.<sup>355</sup> They obtained fairly good yields of terphenyls (Scheme 227). Such

**Scheme 226****Scheme 227**

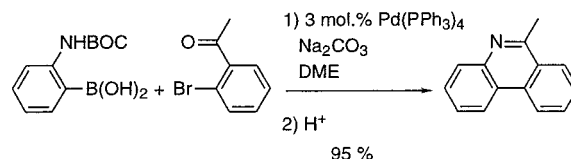
structures have recently been applied to the synthesis of reactive liquid crystals.<sup>356</sup>

The physical and electronic properties of fused polycyclic aromatics are interesting for electronic applications such as liquid crystal materials. For example, in 1995, Hird et al. developed an efficient synthetic route to unsymmetrical triphenylene mesogens.<sup>357</sup> They used Suzuki cross coupling to obtain the key intermediate and achieved the synthesis either by an oxidative coupling with iron or by another Suzuki cross coupling (Scheme 228). The

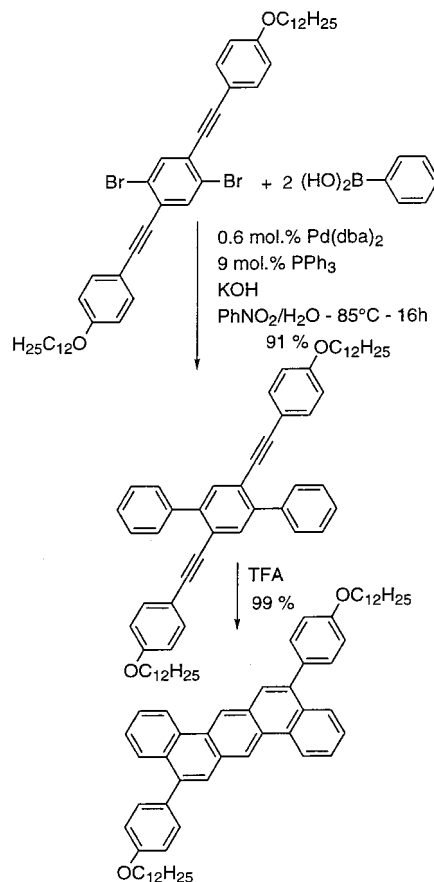
**Scheme 228**

authors explained that palladium-catalyzed cross coupling was very tolerant toward many functional groups and thus enabled a wide variation in the nature of  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$ . This method proved to be far superior to that using iron, which required activating alkoxy substituents whereas the Suzuki reaction did not.

Recently, Harvey et al. performed similar syntheses based on a naphthyl moiety.<sup>358</sup> The same year, N-containing analogues were also prepared by a boronic acid cross coupling.<sup>359</sup> The final step involved the condensation of an amine onto a ketone (Scheme 229). Similarly, the authors used an aryl dibromide to allow the synthesis of molecules bearing six-fused cycles in excellent yield (97%).

**Scheme 229**

Swager et al. developed another synthesis of such fused aromatic structures.<sup>205,360</sup> Their methodology also involved palladium-catalyzed Suzuki cross coupling for the preparation of nonfused skeletons. The final ring-forming step proceeded with the reaction of 4-alkoxyphenylethynyl groups induced by trifluoroacetic acid (Scheme 230).

**Scheme 230**

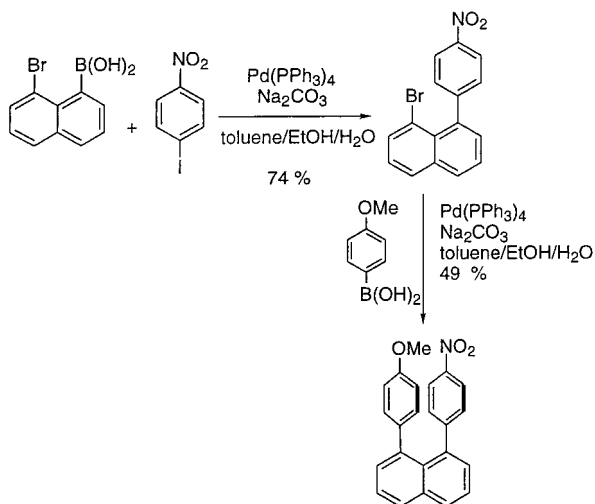
Novel blue-transparent frequency doublers were prepared by the Suzuki cross coupling of naphthyl-boronic acids with aryl halides (Scheme 231).<sup>361</sup>

Suzuki cross couplings were used early on for the modification of substituted binaphthyls. For example, in 1992, Sniekus et al. developed an efficient route to 3,3'-substituted 1,1-bi-2-naphthols (Scheme 232).<sup>362</sup>

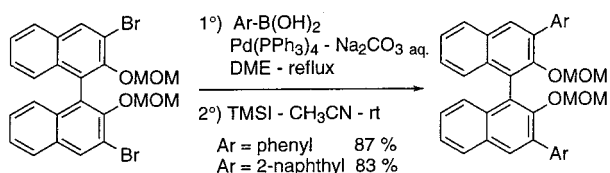
In 1998, Jørgensen et al.<sup>363</sup> synthesized the same compounds. Their methodology involved a boronic acid tethered to the binaphthol moiety and an aryl bromide. However, their yields were lower (73% with phenylbromide, 70% with 2-naphthyl bromide). Kaufmann et al.<sup>364</sup> combined both methods.

Biaryls are often included in complex structures of natural products and biologically active compounds.<sup>365-383</sup> Thus, Suzuki cross couplings were applied in the syntheses of such compounds, some-

## Scheme 231

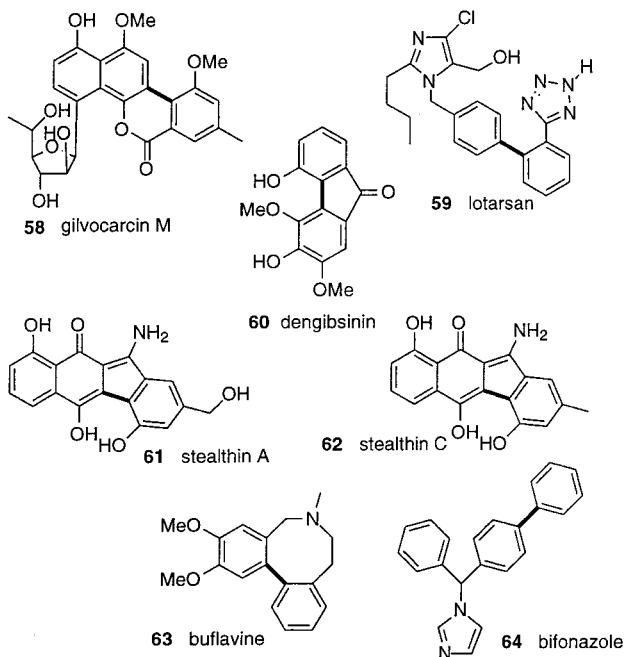


## Scheme 232



times as key steps. As examples, we can quote the studies on gilvocarcin M **58**,<sup>365–366</sup> lotarsan **59**,<sup>367–370</sup> dengibsinin **60**,<sup>371</sup> stealthins A **61** and C **62**,<sup>372</sup> buflavine **63**,<sup>373</sup> and bifonazole **64**<sup>374</sup> (Scheme 233).

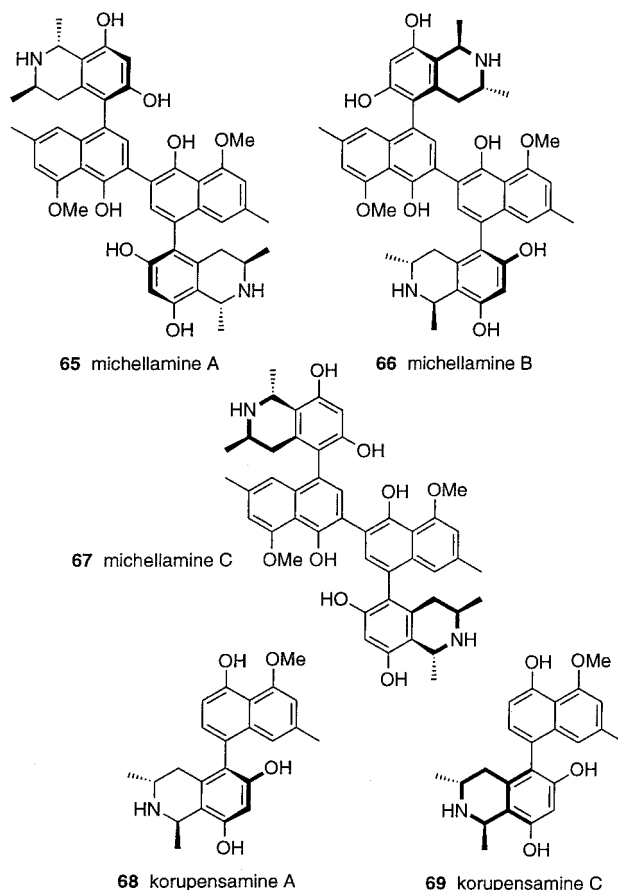
## Scheme 233



— Bond created by Suzuki cross-coupling

As a particular example, syntheses of michellamines A **65**, B **66**, and C **67** (Scheme 234) can be quoted which are novel alkaloids that showed activity against HIV.<sup>378–382</sup> All these syntheses were performed via naturally occurring atropisomers:<sup>377</sup> korupensamine A **68** or C **69**. These compounds raise two major problems: the reactivity of highly hindered

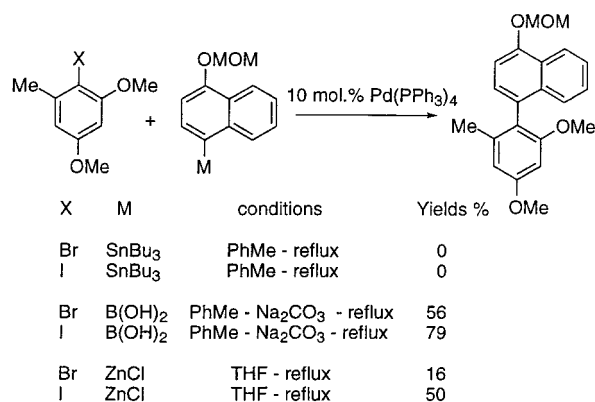
## Scheme 234



aryls and the stereoselectivity of the reaction, especially since the atropisomer A **65** exhibits weak activity.

These types of reactions were studied by Hoyer and Chen, who performed a nonstereoselective synthesis of korupensamines and michellamines.<sup>379,380</sup> They compared the reactivity of hindered aryls in different cross-coupling reactions: Stille cross coupling, palladium-catalyzed cross coupling of zinc derivatives, and Suzuki cross coupling. The authors showed the superiority of the Suzuki reaction (Scheme 235).

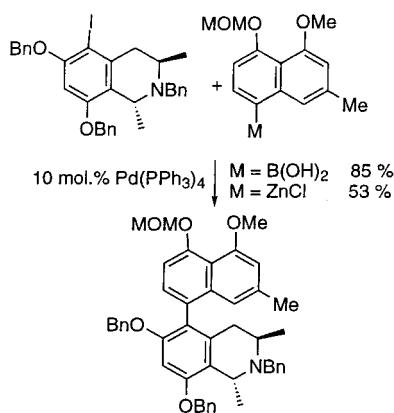
## Scheme 235



The authors applied the two superior procedures to the synthesis of korupensamines A **68** and C **69**, which are intermediates for michellamine syntheses (Scheme 236). The products were obtained as a



## Scheme 236



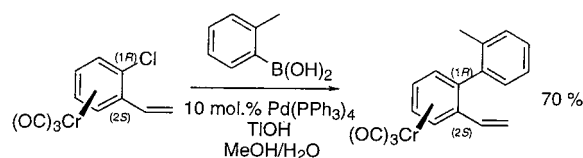
racemic mixture of atropoisomers. In this particular case, the Suzuki cross coupling gave rise to better results.

Michellamines A **65**, B **66**, and C **67** were synthesized by Dawson et al. by a stereospecific method.<sup>381,382</sup> After a nonstereoselective Suzuki cross coupling, they separated korupensamines A **68** and C **69**. Each isomer was transformed both to bromide and boronic derivatives. Then these four products enabled syntheses of each of the michellamines.

**b. Aryl–Aryl Bond Formation Applied to Tricarboxyl(arene)chromium Complexes.** Suzuki cross coupling was involved in the arylation of tricarboxyl(arene)chromium complexes by Uemura et al.<sup>384–393</sup> Oxidative addition of aryl halides to palladium(0) was shown to be accelerated by the coordination of an electron-withdrawing tricarbonylchromium group to the arene. This enables the use of chlorides for Suzuki cross coupling. Moreover, these compounds possess a planar chirality when the arene ring is substituted with different groups at the *ortho*- or *meta*-position.

The classical conditions for Suzuki cross coupling were applied with success to pure (1*R*,2*S*)-(+)-tricarbonyl(*o*-chlorostyrene)chromium (Scheme 237).<sup>384</sup>

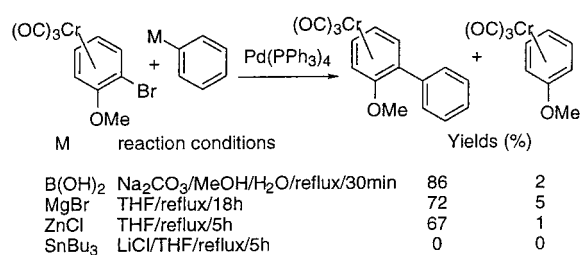
## Scheme 237



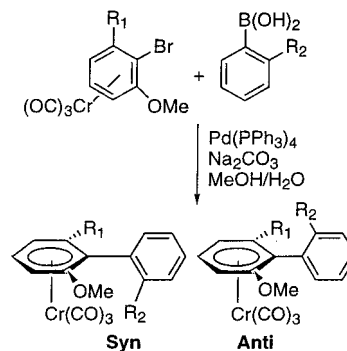
A general study of palladium-catalyzed arylation of ( $\eta^6$ -arene)chromium complexes showed that the organometallic intermediate should not be formed on the chromium species because the product becomes sensitive to reduction. On the other hand, halogeno ( $\eta^6$ -arene)chromium complexes can be involved in palladium-catalyzed cross coupling with different organometallics. However, in a general manner, Suzuki cross coupling appeared to be the most efficient methodology (Scheme 238).<sup>385</sup>

The use of disubstituted halogenoarene chromium complexes generates a stereoselective induction of axial chirality.<sup>386</sup> The stereoselectivity is controlled by the nature of the *ortho*-substituent (Scheme 239). In a general manner, *o*-alkylphenylboronic acids give

## Scheme 238



## Scheme 239

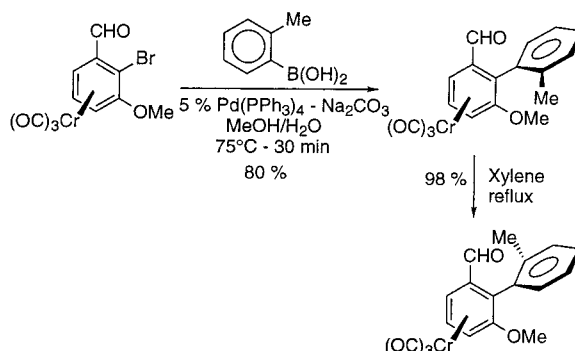


R <sub>1</sub>	R <sub>2</sub>	Yields (%)	
		Syn	Anti
Me	Me	96	-
CHO	Me	82	-
Me	CHO	-	95
CH <sub>2</sub> OH	Me	77	-
CH <sub>2</sub> OH	OMe	85	5

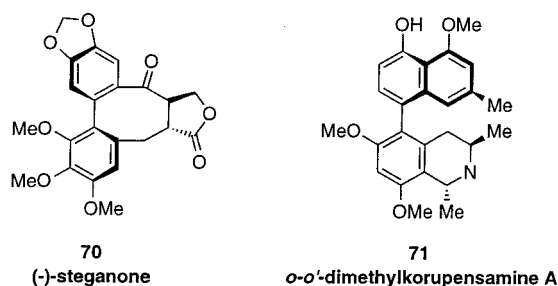
rise to the kinetically controlled tricarbonylchromium complexes of biphenyls with an axial configuration such that the *o*-alkyl substituents of the chromium-uncomplexed ring are syn to the chromium fragment. On the other hand, the cross coupling of *o*-formylphenylboronic acids affords the corresponding anti products.

The authors reported that the central bond rotation of the coupling product led to the thermodynamically more stable tricarbonylchromium complex. Then the preparation of both atropoisomeric biaryls in enantiomerically pure form became possible (Scheme 240).<sup>387–393</sup>

## Scheme 240

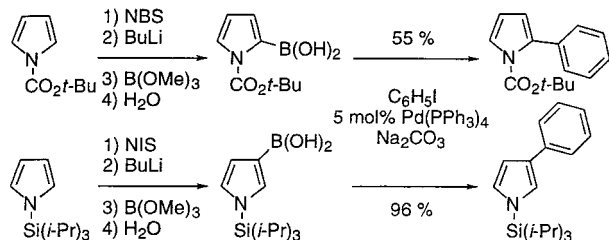


This stereoselective methodology was then applied to the synthesis of (–)-steganone **70** and *o*,*o*-dimethylkorupensamine A **71** (Scheme 241).

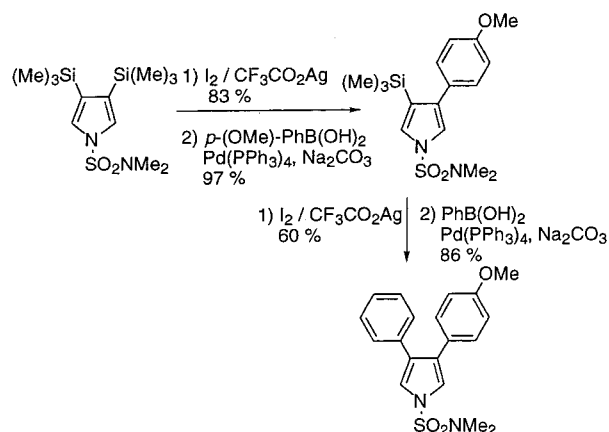
**Scheme 241****c. Heteroatom-Containing Biaryl Synthesis.**

The Suzuki reaction was largely employed for the synthesis of heteroatom-containing biaryls. These structures are of great importance because they are included in numerous biologically active substances and some ligands. This can explain the numerous studies done on nitrogen-containing aryls. However, some applications can also be found for thiophene and furane derivatives.

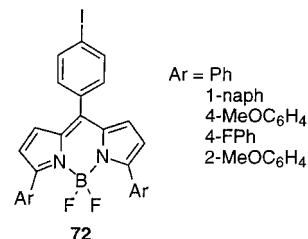
*i. Nitrogen-Containing Five-Membered Rings.* The arylation of pyrroles was performed early on by the reaction of an aryl halide with a pyrrole-boronic acid.<sup>394–396</sup> The direct synthesis of the 1-(phenylsulfonyl)pyrrole-2-boronic acid from 1-(phenylsulfonyl)pyrrole using LDA treatment has not been shown to be efficient.<sup>394</sup> Both 2-pyrrole and 3-pyrrole boronic acids can be prepared via protected pyrrole halides and arylated by aryl halides in moderate to good yields (Scheme 242).<sup>395,396</sup>

**Scheme 242**

Another method involved the cross coupling of halogeno-pyrroles with phenylboronic acid.<sup>397,398</sup> This method, developed by Wong et al., enabled highly regioselective syntheses of 3,4-disubstituted pyrroles from 3,4-bis(trimethylsilyl)pyrrole (Scheme 243).

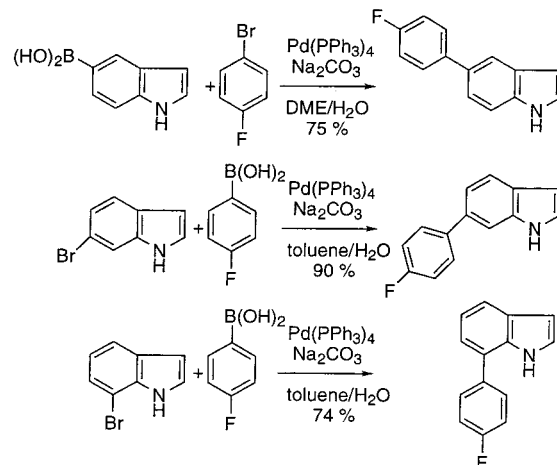
**Scheme 243**

The arylation of halogenopyrroles by aryl boronic acids allowed the synthesis of 3,5-diaryl-4,4-difluoro-4-bora-3*a*,4*a*-diazas-indacene dyes **72** (Scheme 244).<sup>399</sup>

**Scheme 244**

Recently, Lee and Chung reported a new synthesis of 3-aryl-pyrroles. Their methodology did not directly involve an aryl cross coupling. It consisted of a tandem Suzuki–dehydrogenation reaction on trifluoromethanesulfonic acid 1-benzyl-2,5-dihydro-1*H*-pyrrol-3-yl ester.<sup>400</sup>

Suzuki cross couplings were also applied for the arylation of indole moieties.<sup>401–404</sup> The reaction can involve either 5-indolylboronic acids with aryl halides<sup>401</sup> or halogenoindoles with aryl boronic acids<sup>402</sup> (Scheme 245).

**Scheme 245**

These types of indole arylation were applied as model studies toward the synthesis of diazonamide **A 73**,<sup>403</sup> chloropectin **74**, and kistamycin **75**.<sup>404</sup> (Scheme 246).

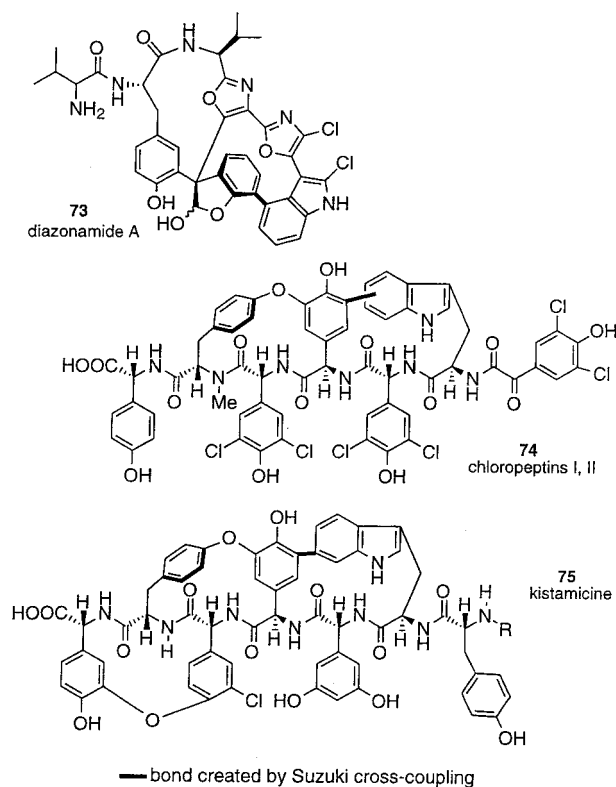
As with pyrroles, indoles can be arylated on the N-containing moiety via the formation of a boronic acid.<sup>396</sup> This procedure gave arylated compounds in moderate yields. A more efficient methodology involved the cross coupling of 2-halogenoindoles with phenylboronic acids (Scheme 247).<sup>405</sup> This latter procedure allowed the synthesis of 2,3-diaryl-indoles<sup>406</sup> and the arylation of 5- and 7-azaindoles.<sup>407</sup>

The arylation of indoles has been essentially applied to the synthesis of antagonists for the  $\eta^5$ -HT<sub>2A</sub><sup>-</sup> receptor: 2-aryl-tryptamines **76** (Scheme 248).<sup>408–410</sup>

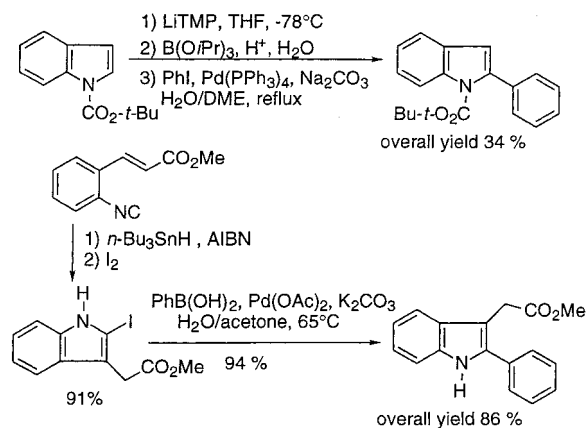
Suzuki cross couplings have also been shown to be efficient for pyrazoles,<sup>411,412</sup> arylindazoles,<sup>413</sup> imidazoles,<sup>414–416</sup> benzimidazoles,<sup>417</sup> tetrazoles,<sup>418</sup> pyrazolo[1,5-*a*]pyridines,<sup>419</sup> and imidazo[1,2-*a*]pyridines.<sup>420</sup>

*ii. Nitrogen-Containing Six-Membered Rings.* Pyridines present great interest for the synthesis of

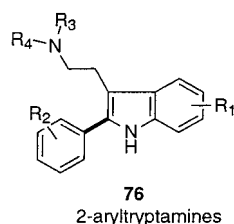
## Scheme 246



## Scheme 247



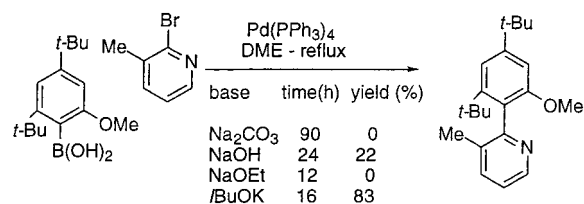
## Scheme 248



biologically active compounds or ligands. So the Suzuki cross coupling of pyridines was studied early on. The initial studies involved aryl boronic acids with bromo- or iodopyridines.<sup>421,422</sup> The base has a great influence on the cross coupling of bulky aryl boronic acids (Scheme 249).<sup>423,424</sup>

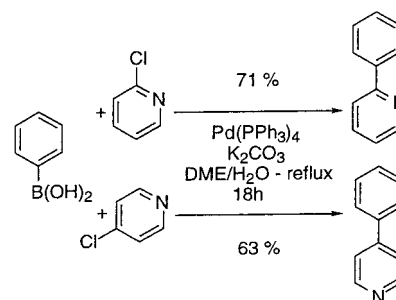
Both 2- and 4-chloropyridines have also proved to be efficient for Suzuki cross couplings.<sup>425</sup> The interest of using aryl chlorides stems from the fact that they are both the least expensive and the most widely

## Scheme 249



available aryl halides. Moreover, in the case of 2- and 4-halopyridines, chloro compounds show better stability in comparison with bromo or iodo derivatives (Scheme 250). The same procedure was applied to the

## Scheme 250



synthesis of heteroaryl benzoic acids.<sup>426</sup>

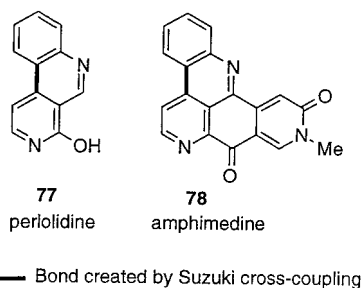
Grahn et al. developed the synthesis of new blue-transparency doublers based on the Suzuki cross coupling of pyridines.<sup>361</sup>

Suzuki cross couplings of pyridines were widely explored to prepare N-containing polycyclic alkaloids. The preparation of 1,8-naphthyridines was studied by Gronowitz.<sup>427</sup> Quéguiner et al. developed a short route to substituted benzo[*c*]-2,7-naphthyridines, and in particular, they succeeded in the synthesis of perlolidine **77** and amphimedine **78**.<sup>428–430</sup> In general, the studies performed by Quéguiner et al. largely contributed to advances in the synthesis of various N-containing polyaromatic natural and biologically active molecules using Suzuki cross couplings as the key step.<sup>431,432</sup>

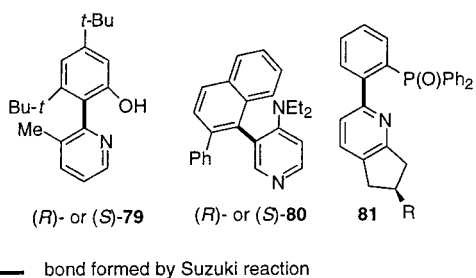
The efficiency of nitrogen-containing ligands has been documented, and recently more studies have been done on their use in asymmetric catalysis.<sup>433</sup> In 1996, Chan used a Suzuki cross coupling, followed by the resolution of the racemate, to perform the synthesis of a chiral pyridylphenol **79**.<sup>434</sup> This product was shown to catalyze the addition of diethylzinc to aromatic aldehydes with moderate to high enantioselectivities. Recently, Spivey reported the synthesis of an axially chiral analogue of DMAP, **80**.<sup>435</sup> This compound has found application in nonenzymatic enantioselective acylations. A ligand **81** with a similar structure was also prepared by Suzuki cross coupling.<sup>436</sup>

In 1992, McKillop studied the palladium-catalyzed cross-coupling reactions of aryl boronic acids with  $\pi$ -deficient heteroaryl chlorides.<sup>437</sup> He reported that tetrakis(triphenylphosphine)palladium(0) is an excellent catalyst for the reaction of a wide range of chloroquinolines (Scheme 253). The results established that this reaction is an excellent method for the synthesis of functionalized arylated quinolines,

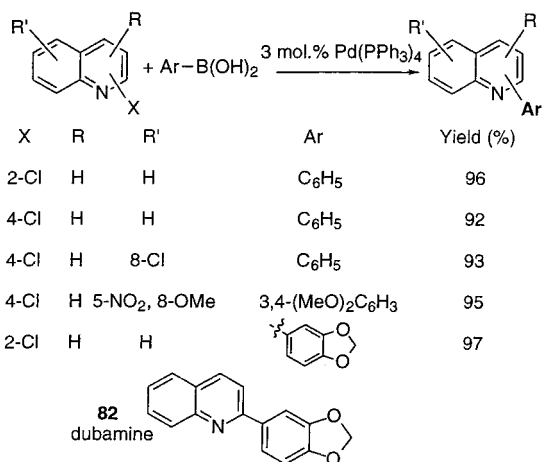
## Scheme 251



## Scheme 252



## Scheme 253

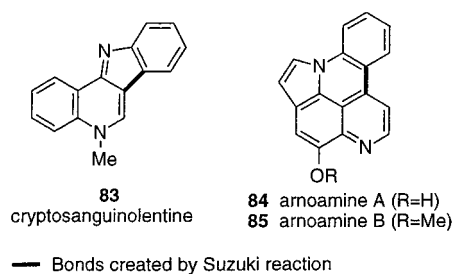


and generally, chloro derivatives can be used as the substrate instead of the more expensive iodo and bromo counterparts. The experimental procedure was simple and conditions were mild. The authors illustrated the efficiency of this reaction by the high-yield synthesis of a simple alkaloid: dubamine **82**. This result (97% yield) was better than that obtained by a Stille reaction (79% yield). Later, Ciufolini et al. obtained similar results for the cross coupling of commercially available phenylboronic acid with Pd(PPh<sub>3</sub>)<sub>4</sub> generated in situ.<sup>438</sup>

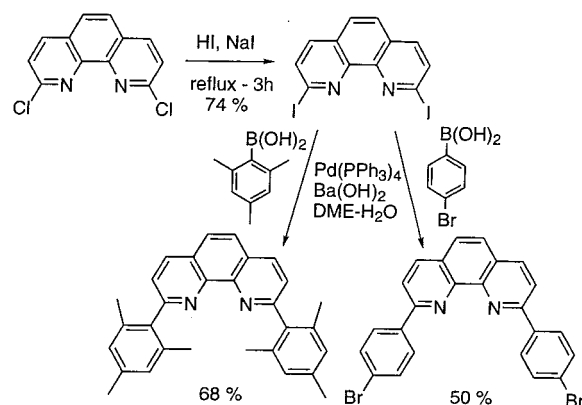
The cross coupling of halogenoquinolines finds application in the synthesis of new synthetic drugs<sup>439</sup> or naturally occurring alkaloids, such as cryptosanguinolentine **83**<sup>440</sup> and arnoamines A **84** and B **85**.<sup>441</sup>

The extension of Suzuki cross coupling to phenanthrolines has for a long time been limited by the control of the regioselectivity of halogenation around the phenanthroline nucleus. Recently, Siegel developed a general method for the preparation of unsymmetrical 2,8- and 2,9-dihalophenanthrolines and involved these compounds in Suzuki cross couplings (Scheme 255).<sup>442</sup> Thus, he obtained key building

## Scheme 254



## Scheme 255

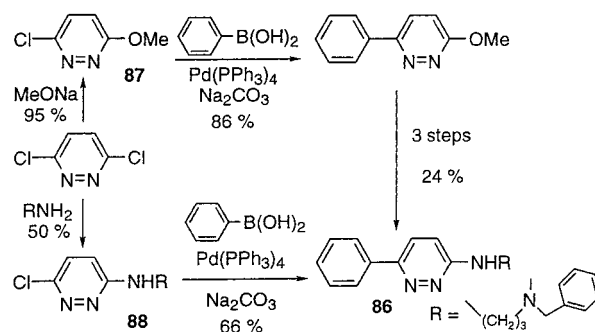


blocks for the design and construction of topologically complex polynuclear metal-coordination complexes.

In 1995, Grivas and Lindström synthesized analogues of purine by the arylation of imidazo[4,5-*b*]pyridines.<sup>443</sup>

Wermuth reported the synthesis of a series of 3-amino-6-aryl pyridazines, such as **86** in Scheme 256, which showed acetylcholinesterase-inhibiting

## Scheme 256



activities.<sup>444</sup> The Suzuki cross coupling of 3-chloro-6-methoxy-pyridazine **87** was efficient (yields up to 90%), but the transformation of the methoxy group into an amino substituent required three additional steps and the overall yield (from 3,6-dichloropyridazine) fell from 82% to 20%. Then the authors studied the arylation of previously amino-substituted chloropyridazines **36**, which was less efficient (35–65% yield), but the overall yield reached 30% (Scheme 256). Recently, Lemièr<sup>445</sup> and Rival<sup>446</sup> reported the Suzuki cross coupling of 3-amino-6-halogenopyridazines.

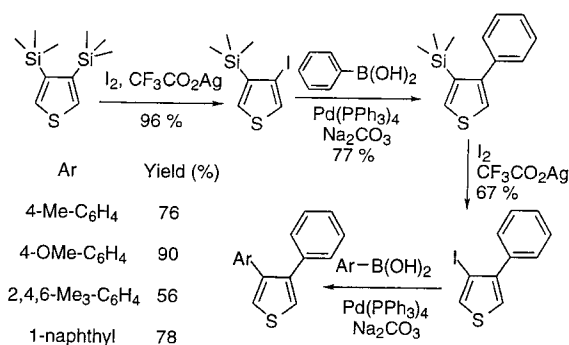
Generally, the Suzuki reaction is an efficient method for the arylation of various N-containing



aryls including pyrimidines<sup>447,448</sup> and quinazolines.<sup>449,450</sup>

**c. Arylation of Sulfur- or Oxygen-Containing Aryls.** Because of their potent biological activity and their use as ligands, the reactivity of N-containing aryls has been widely studied. Nevertheless, some S- or O-containing aryls are also worthy of interest. No particular studies have been performed concerning the reactivity of these aromatic compounds except for the synthesis of 3-substituted and 3,4-disubstituted thiophenes. These compounds are difficult to prepare due to the inclination of thiophenes to endure both metalation and electrophilic substitution preferentially at the  $\alpha$ -position. In 1997, Wong and Ye used 3,4-bis(trimethylsilyl)thiophene to enable the synthesis of 3-substituted and 3,4-disubstituted thiophenes (Scheme 257).<sup>343</sup>

Scheme 257



Suzuki cross coupling of thiophenes was used to perform syntheses of various thieno[*c*]isoquinolines **89** and thieno[*c*]quinolines **90**,<sup>451</sup> new peptide analogue **91**,<sup>376</sup> 5-thienylninhydrins **92**,<sup>452</sup> novel bithiophenes with pendant fullerenes<sup>453</sup> or substituted with anthracene and pyridine,<sup>454</sup> 3-(thien-2-yl)anthranilic acid **93**.<sup>354</sup> Benzothiophenes<sup>455</sup> and dibenzothiophenes<sup>205</sup> can also undergo Suzuki cross couplings.

Furanes and benzofuranes are the least studied heteroaryls. Few examples can be found regarding their use in Suzuki cross couplings.<sup>354,376,456</sup> In conclusion, we can affirm that Suzuki-cross coupling is an efficient method for the synthesis of complex poly-aromatic structures which can bear various and numerous heteroatoms.<sup>396,401,403,409,410,413–415,421,427,445,448,457</sup>

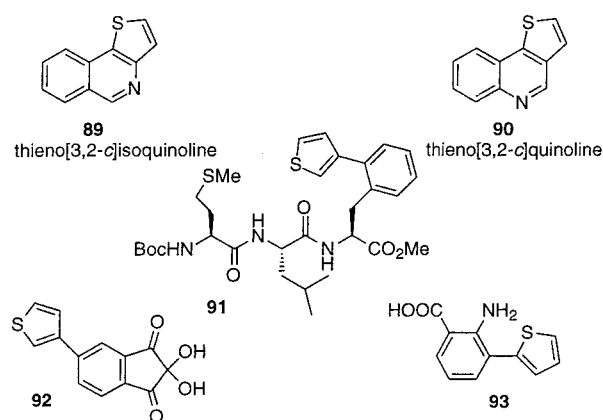
**d. Application to the Synthesis of Porphyrins and Phthalocyanines.** The biological importance of porphyrin-like compounds, such as hemin and chlorophyll, coupled with their unusual and striking physical and chemical properties makes them both interesting and important objects for researchers.<sup>458</sup>

Substituents at the  $\beta$ -positions of porphyrins exert important steric and electronic effects on the porphyrin ring that can confer some unusual optical properties, enhanced electrochemical redox stability, and increased catalytic efficiency to metal complexes.<sup>459,460</sup>

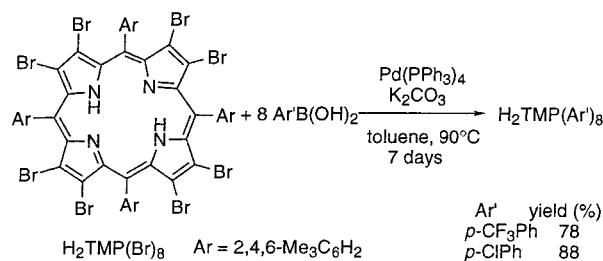
Chan in particular studied the synthesis of  $\beta$ -aryl-substituted porphyrins by palladium-catalyzed cross-coupling reactions of aryl boronic acids on brominated porphyrins.<sup>461–464</sup>

Similar compounds were prepared by the phenylation of pyrroles followed by classical cyclization via the 5-acetoxymethyl derivative.<sup>465</sup> This methodology

Scheme 258



Scheme 259



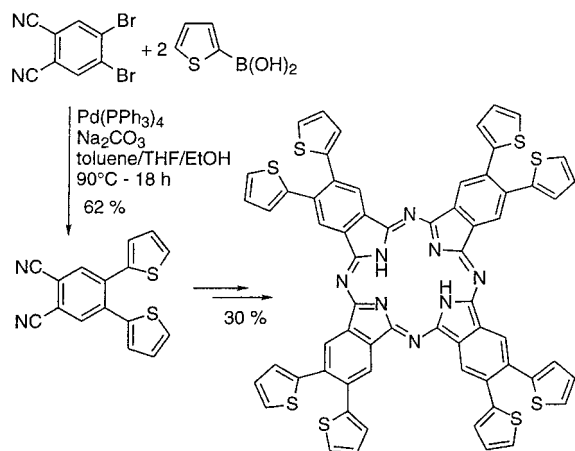
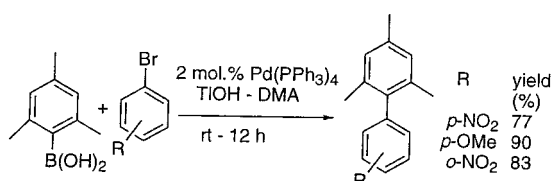
also enabled the synthesis of phthalocyanine derivatives having peripheral 2-thienyl substituents.<sup>466</sup>

### C. Recent Improvements in the Suzuki Reaction for Aryl–Aryl Bond Formation

As shown in the previous section, the Suzuki reaction has led to numerous spectacular results. It represents a major improvement in the aryl–aryl bond formation even when compared to other efficient and selective methods (i.e., Stille, Kumada). These initial successes have, on the other hand, induced new research in order to improve its usefulness. Indeed, much new research has dealt with the extension of the scope and the amelioration of the economical and ecological parameters of the Suzuki reaction. New reaction conditions have been perfected in order to obtain satisfying results in the case of both *ortho*-substituted aryl substrates and substrates bearing other nucleophilic or leaving groups.

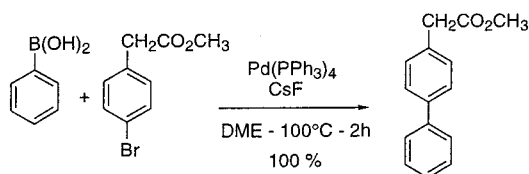
**a. Improvement of Suzuki Cross Coupling of Aromatic Substrates by Modification of Experimental Conditions.** The modifications of Suzuki reaction conditions have always elicited great interest, especially when these improve the cross coupling of sterically hindered aryl species.<sup>467–469</sup> Many parameters have been studied such as the base, the solvent, and the ionic additives.

Anderson et al. developed an ambient-temperature methodology.<sup>470,471</sup> They used various bases including carbonates, hydroxides, and phosphate and found that thallium hydroxide gave the best results. Their studies also included the impact of the solvent. The best conditions involved 2 mol % of Pd(PPh<sub>3</sub>)<sub>4</sub> and TIOH in DMA, and the results for the coupling of mesityl boronic acid with various aromatic halides (Scheme 261) were comparable to procedures involving heat (100 °C).<sup>468</sup> Recently, Chaumeil did similar

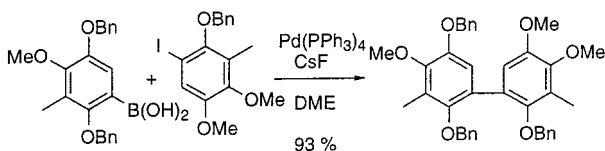
**Scheme 260****Scheme 261**

studies with mesityl boronate and he found that, in this case, thallium carbonate should be used as the base.<sup>472</sup> It is important to note that the influence of these parameters depends on the nature of the substrate. Indeed, Snieckus had good results with  $\text{Na}_2\text{CO}_3$  in DME or  $\text{K}_3\text{PO}_4$  in DMF for the syntheses of chlorodihydroxybiphenyls.<sup>473</sup>

Another improvement in the Suzuki reaction consisted of the addition of fluoride ions. Indeed, in 1994, Wright et al. discovered that the addition of cesium fluoride enables the reaction to occur rapidly with good yields (Scheme 262).<sup>474</sup>

**Scheme 262**

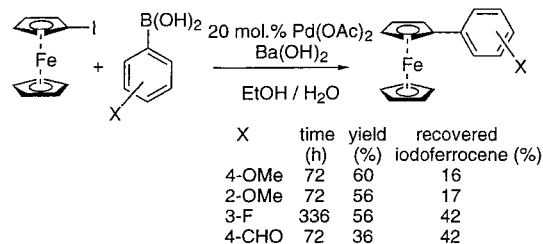
In 1996, Benbow et al. used similar conditions.<sup>475</sup> For the reaction of highly oxygenated aryl boronic acids (Scheme 263), they observed that the fluoride-

**Scheme 263**

assisted procedure provided superior results with a good reproducibility when compared with standard alkaline conditions.

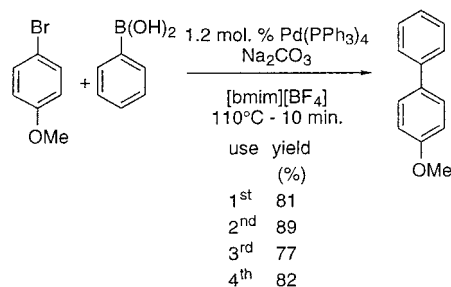
Suzuki cross coupling has also been improved by the use of palladium acetate without phosphine ligand.<sup>475-478</sup> These methodologies have enabled simple purification procedures and limited aryl-aryl ex-

change side reactions. In a general manner, the reaction has occurred in protic media such as ethanol<sup>475</sup> or acetone/water<sup>476,477</sup> and has led to biaryls with good to excellent yields. These conditions have been applied to the synthesis of monoarylferrocenes<sup>479</sup> (Scheme 264).

**Scheme 264**

Recently, Dupont used  $\text{Pd}(\text{OAc})_2$  or  $\text{PdCl}_2(\text{SEt})_2$  in an aprotic medium (DMF).<sup>480</sup> With  $\text{Pd}(\text{OAc})_2$  as the catalyst, a quaternary ammonium was also used as a salt additive. They proposed that the beneficial effect of the salt was probably due to the stabilization of the anionic palladium species.<sup>481</sup>

The use of ionic liquids has enabled fast effective cross couplings.<sup>482</sup> The reactions have been conducted in 1-butyl-3-methylimidazolium tetrafluoroborate ( $[\text{bmim}][\text{BF}_4]$ ) and have led to easy product isolation and catalyst recycling. The catalytic solution has been reused three times without loss of activity (Scheme 265).

**Scheme 265**

**b. New Boron Derivatives as Nucleophiles for Aromatic Coupling.** The specific advantages of the Suzuki reaction are related to the use of boron derivatives. These compounds are highly electrophilic and weakly nucleophilic. Fair aromatic cross coupling can be obtained in the presence of a palladium catalyst with aryl iodides, triflates, bromides, and even in some cases chlorides. The low nucleophilicity of the boronic derivatives are partly responsible for the widespread applications of the Suzuki reaction, since boronic derivatives remain unreactive with most functional groups. This selectivity associated with the low toxicity of the boronic-salt byproducts and the stability of the reagent are the main advantages which explain the success of the reaction.

Synthesis of boronic acids generally requires the use of organometallic derivatives and trialkyl borate. The procedure presents the advantage of aryl-organometallic chemistry and directed *ortho*-metalation could, for example, be used.<sup>429</sup> Introduction of the boronate should be followed by hydrolysis of the boronic ester groups due to the lack of reactivity of

the former reagent. Boronic acids are not always easy to purify, especially when a reagent with high purity is required, in the case of reagents for polymerization, for example. Several other derivatives were tested in order to avoid these limitations. Chan recently used a 1,3-propanediol ester of boronic derivatives in the synthesis of  $\beta$ -linked diporphyrins.<sup>483</sup> The same type of boron derivative was also used in the approach to the synthesis of korupensamine by Lipshutz.<sup>484</sup>

2,2-Dimethyl-1,3-propanediol and pinacol esters of boronic acids also proved to be of major interest in the synthesis of conjugated oligomers<sup>359,485,486</sup> and in the synthesis of part of the streptonigrin CD moiety.<sup>487</sup>

These compounds are easily prepared using a palladium(0)-catalyzed coupling reaction of dialkoxyborane with aryl halides.<sup>488</sup> Using a tetraalkoxydiborane, Giroux developed a one-pot biaryl synthesis via an in situ boronate formation.<sup>489</sup>

Tour et al. also proposed the use of a derivative of diethanolamine for the same purpose. The very high stability of the boronic ester of this diol allowed its easy separation and storage but required specific activation using acetyl chloride.<sup>359</sup>

One of the most popular types of boronic derivative is the boroxine derivative. Formally, these reagents are anhydrides of boronic acid. They are relatively easy to synthesize and often easier to handle than the boronic acid itself.<sup>490,491</sup>

Boroxine was used for the synthesis of furan<sup>492</sup> and thiophene derivatives<sup>493</sup> including oligomers.<sup>494</sup> Although there are fewer examples, borane derivatives were also used in Suzuki-type cross coupling of aromatics. Quéguiner and Snieckus used pyridylborane in the formal synthesis of amphimedine.<sup>429</sup>

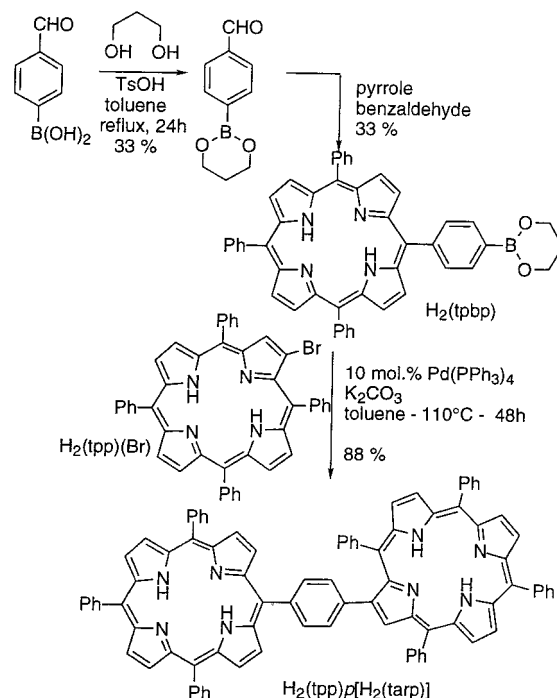
The arylation of indole derivatives using a borane derivative in Suzuki conditions was successfully performed by Ishikura,<sup>492</sup> and the synthesis of substituted bipyridines was achieved with diethyl borane pyridine as reagent.<sup>493,494</sup> Sonesson used the same commercially available reagent for the synthesis of a biologically active chiral piperidine.<sup>495</sup>

The diversity of easily available boron reagents is also one of the present advantages of the Suzuki reaction. As part of the synthesis of vancomycin, Nicolaou used a cyclic boronic derivative as the reagent.<sup>496</sup>

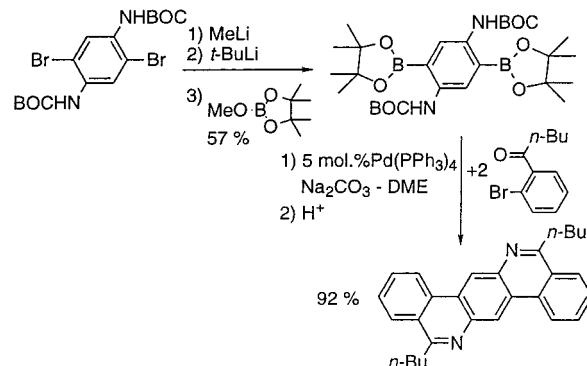
**c. Extension of the Suzuki Reaction to New Leaving Groups.** We showed the great importance of Suzuki cross coupling due to its efficiency and the variety of boron derivatives which can be used. The use of aromatic halides can be limited by their access, cost, and stability, in particular for iodides. To avoid these drawbacks, research has been done to develop the use of new leaving groups. Indeed, the access to triflate or diazonium derivatives is easier due to both the variety of commercially available phenols or anilines and their low cost.

*i. Uses of Aryl Triflates and Nonaflates.* The trifluoromethanesulfonate group presents excellent leaving group properties. The scope in application of aryl triflates is considerable.<sup>497</sup> For cross-coupling reactions with organometallics, aryl triflates can be

### Scheme 266



### Scheme 267



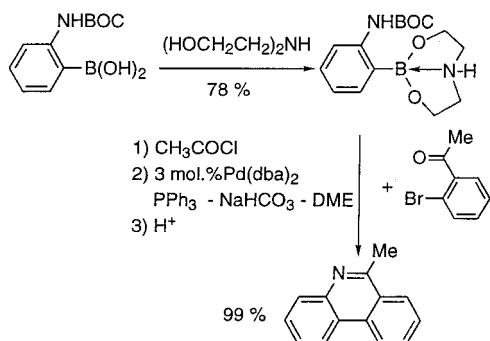
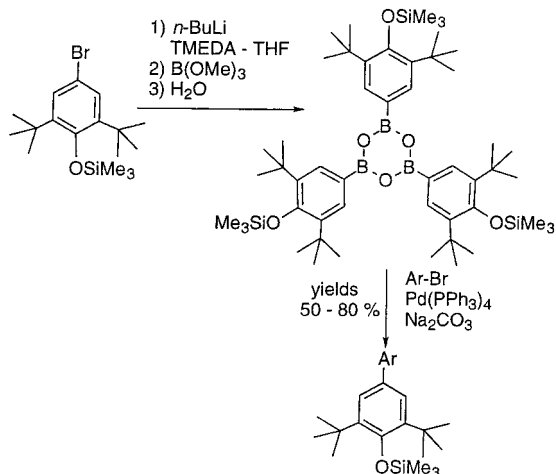
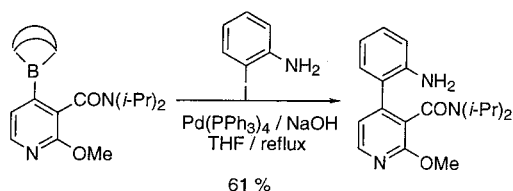
compared with aryl bromides. The order of reactivity for these compounds allows selective transformations:  $\text{Ar-I} > \text{Ar-Br} \sim \text{Ar-OTf} > \text{Ar-Cl}$ .

The use of aryl triflates for Suzuki cross coupling with aryl boronic acids was reported in the early 1990s by Huth, Snieckus, and Suzuki.<sup>498–500</sup>

This reaction was widely applied in the synthesis of naturally occurring or biologically active molecules.<sup>436,501–505</sup> Other particular syntheses also needed the palladium-catalyzed cross coupling of an aryl triflate with aryl boronic acid, e.g., (benzoquinonylphenyl)porphyrins<sup>464</sup> or arylated arene–tricarbonyl complexes.<sup>506</sup>

Like aryl halides, aryl triflates can undergo palladium-catalyzed cross coupling with various boron derivatives. Different studies were done on the cross coupling of aryl boronates with aryl triflates.<sup>507–509</sup> Miyaura et al. prepared aryl boronates with good yields (Scheme 273).<sup>508</sup> They developed conditions that enabled cross coupling in the presence of a wide range of functional groups including nitro, cyano, ester, and carbonyl groups.

The direct preparation of the aryl boronic ester from an aryl triflate enabled a one-pot procedure for

**Scheme 268****Scheme 269****Scheme 270**

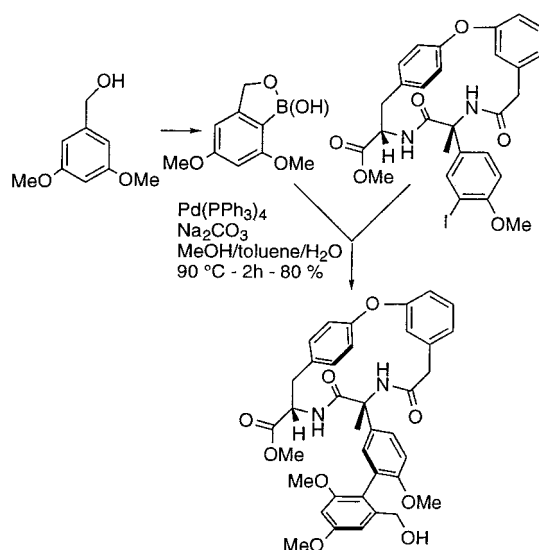
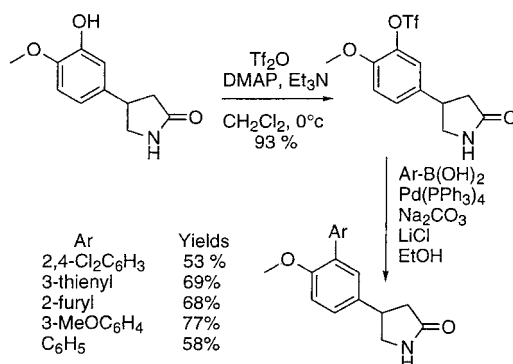
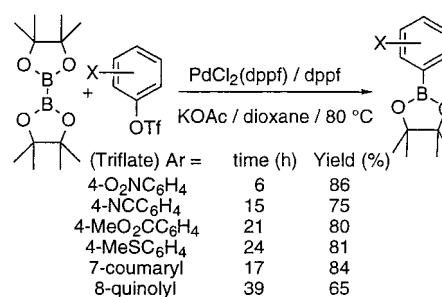
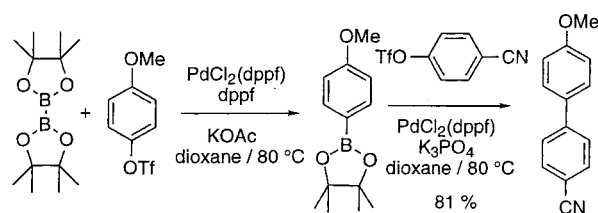
the synthesis of unsymmetrical biaryls (Scheme 274).<sup>508</sup>

Coudret et al. applied the palladium-catalyzed cross coupling of aryl boronates with aryl triflates to the synthesis of polyaromatic bridging ligands (Scheme 275), whereas the Stille reaction with 4-trimethylstannyl-pyridine was ineffective.<sup>509</sup>

Tetraaryl borates were also successfully involved in cross couplings with triflates.<sup>510</sup> Ortar et al. used commercially available sodium tetraphenylborate as the phenyl-transfer agent (Scheme 276).

A perfluorated analogue of triflate, the nonaflate was also used as an efficient leaving group (Scheme 277).<sup>511</sup>

*ii. Uses of Arenediazonium Salts and Other Leaving Groups.* Arenediazonium tetrafluoroborates were easily prepared from the corresponding anilines. They proved to be highly reactive for cross coupling with aryl boronic acids.<sup>512,513</sup> The reaction was selective and could tolerate the presence of triflate or bromide substituents. Conditions were mild at room temperature, and no base was needed (Scheme 278). In 1997, Sengupta et al. described a similar method where

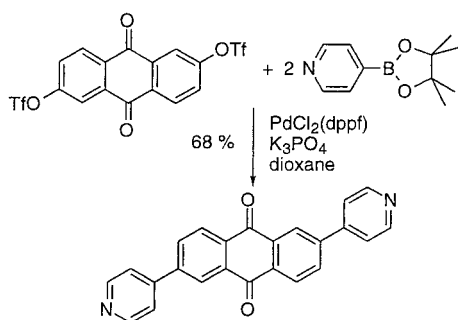
**Scheme 271****Scheme 272****Scheme 273****Scheme 274**

methanol replaced dioxane as the solvent, but under these conditions the reaction occurred at reflux temperature.<sup>514</sup>

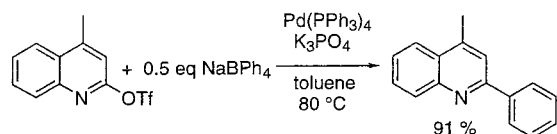
The arenediazonium tetrafluoroborates were involved in palladium-catalyzed cross coupling with various boron derivatives such as boronic esters<sup>515</sup> and aryl trifluoroborates.<sup>516,517</sup> For the synthesis of



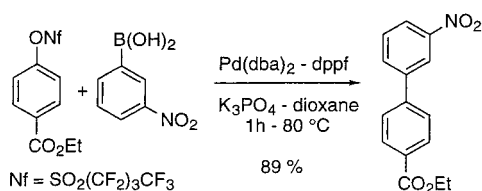
## Scheme 275



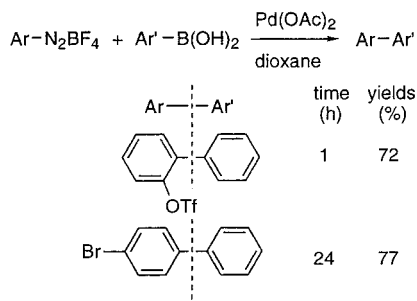
## Scheme 276



## Scheme 277



## Scheme 278



this last boronic group, Genêt et al. used the conversion of aryl boronic acids into potassium trifluoroborates described by Vedejs.<sup>518</sup> These compounds were very stable, water resistant, and easily isolated. Genêt et al. showed not only that arenetrifluoroborates could undergo aryl cross coupling, but also that they were more efficient than the corresponding boronic acids (Scheme 279).

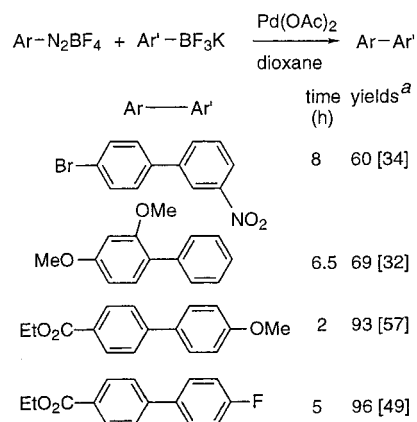
*iii. Uses of Other Leaving Groups.* In 1996, Kang et al. showed the efficiency of the palladium-catalyzed cross coupling of organoboron compounds with iodonium salts and iodanes.<sup>519</sup> The reaction occurred in very mild conditions at room temperature and in a DME/ $\text{H}_2\text{O}$  mixture (Scheme 280).

Recently, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one was used in cross couplings with aryl boronic acids or aryl borates to prepare biaryl-2-carboxylic acids in good yields.<sup>520</sup>

Coudert et al. used another leaving group: phosphate.<sup>521</sup> The authors obtained unusual substituted nitrogen-containing heterocycles (Scheme 282).

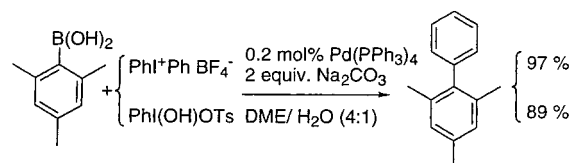
The last type of leaving group discussed for aryl-aryl cross coupling with boronic acids is sulfonium

## Scheme 279

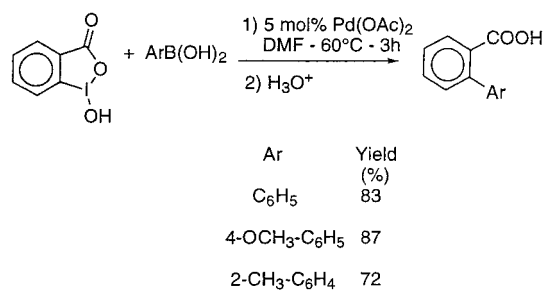


<sup>a</sup>: yields in brackets are obtained with corresponding boronic acid.

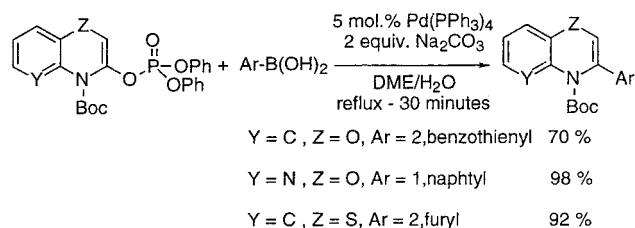
## Scheme 280



## Scheme 281



## Scheme 282



salts.<sup>522</sup> These compounds are easily and economically prepared using various methodologies. Moreover, they present good solubility and stability in both aprotic and protic solvents.

**d. New Ligands for the Suzuki Reaction.** Despite the broad synthetic utility of  $\text{Pd}(\text{PPh}_3)_4$  in the Suzuki cross-coupling reaction, its air- and light-sensitivity and the formation of a number of byproducts<sup>523</sup> led research teams to develop a wide range of palladium catalysts for the synthesis of biaryls. Moreover, catalyst loadings in such reactions were generally high (1–10 mol %), which imposed financial constraints on scaling-up reactions and problems associated with catalyst removal. Therefore, the synthesis of high-activity catalysts which can be used in low concentrations has also become a major goal.

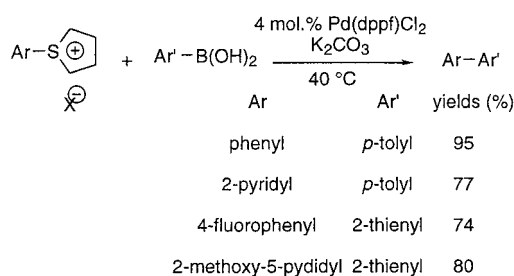
Table 1

Categories	Ligands
bis(diphenylphosphino)alkyl	
trialkylphosphine	P( <i>t</i> -Bu) <sub>3</sub> PCy <sub>3</sub>
aryl-dialkylphosphine	
palladacycle	
N-heterocyclic carbene	

Suzuki cross couplings of aryl bromides and iodides have been extensively studied in organic syntheses. Apart from further expanding the scope of this reaction, current interest focuses on the use of economically more attractive aryl chlorides as substrates. The decreased reactivity of aryl chlorides is usually attributed to their reluctance to oxidative addition to Pd(0).<sup>524</sup> Since 1998, several research groups have described electron-rich ligands for palladium that overcome this limitation. Fu,<sup>525</sup> Herrmann,<sup>526</sup> and especially Buchwald<sup>527</sup> comprehensively reviewed these electron-rich ligands, which can be classified in five categories: bis(diphenylphosphino)alkyl (Shen<sup>528</sup>), trialkylphosphine (Fu,<sup>529</sup> Shen,<sup>528</sup> Firooznia<sup>530</sup>), aryl-dialkylphosphine (Buchwald,<sup>531–533</sup> Bei and Guram<sup>534,535</sup>), N-heterocyclic carbene ligands (Herrmann<sup>526,536</sup>), and palladacycle (Herrmann,<sup>526,537–539</sup> Trudell and Nolan<sup>540,541</sup>) (Table 1).

It is generally agreed that these in situ 'Pd'-L catalysts, consisting of a Pd(II) source and sterically hindered basic ligands, are reduced under the reaction conditions<sup>542</sup> to generate coordinatively unsaturated complexes such as 16e<sup>-</sup> PdL<sub>3</sub>, 14e<sup>-</sup> PdL<sub>2</sub>, and

Scheme 283



12e<sup>-</sup> PdL, which may constitute the "real" catalysts.

Thus, since the advent of these catalyst systems, the Suzuki coupling can be conducted with "nonactivated" aryl chlorides, under mild reaction conditions, and using low catalyst concentrations.

In this section, we will focus first on recent improvements performed in the categories of ligands mentioned above and then on developments of new ligands that do not belong to those categories.

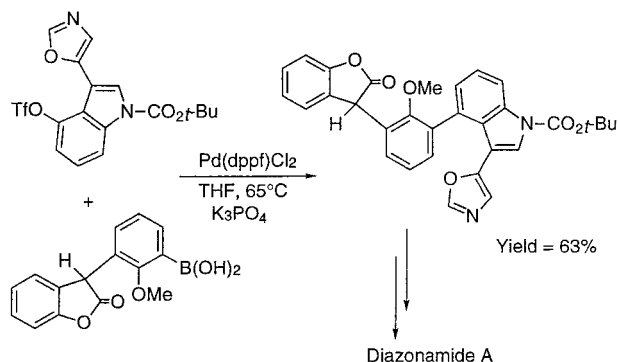
*i. Bis(diphenylphosphino)alkyl Ligands.* To replace the traditional (tetrakis(diphenylphosphino)palladium) catalyst, a wide range of Pd catalysts have been developed. Binuclear catalysts such as bis(diphenylphosphino)alkyl-ligated palladium, formed in situ, were found to be generally more efficient in promoting the Suzuki-coupling reaction.

(a) 1,1'-Bis(diphenylphosphino)ferrocene (dppf). In 1988, Thompson et al.<sup>543</sup> used [1,1'-bis(diphenylphosphino)ferrocene]palladium, Pd(dppf), to perform the coupling of chloro- or bromopyrazines and -pyridines with areneboronic acids in good yields. One explanation to account for the remarkable efficiency of Pd(dppf)<sub>2</sub>(OAc)<sub>2</sub> as a catalyst might be the decreased steric hindrance enforced by the rigid ferrocene backbone which acts to "stretch" the Pd-P bond distance past its usual length.<sup>544</sup> This bidentate ligand is still used nowadays. Satoh et al.<sup>545</sup> carried out the synthesis of 4-substituted phenylalanine derivatives by cross-coupling reactions of *p*-boronophenylalanines with aryl halides (I, Br) and triflates using PdCl<sub>2</sub>(dppf) as the catalyst and potassium phosphate as the base. Having obtained biarylalanines in moderate to good yields, the authors turned their attention to the asymmetric version of the cross coupling through a homochiral boronophenylalanine derivative. Compounds of high diastereomeric purity were produced in most cases. With the same catalyst, Franc et al.<sup>546</sup> developed a general synthesis of 2-formyl-3-arylpyrroles by cross coupling of 2-formyl-3-iodo-1-tosylpyrrole with aryl boronic acids in high yields.

More recently, Vedejs et al.<sup>547</sup> performed the Suzuki cross coupling depicted in Scheme 284, using dppf as the ligand, to synthesize an intermediate for the total synthesis of diazonamide A.

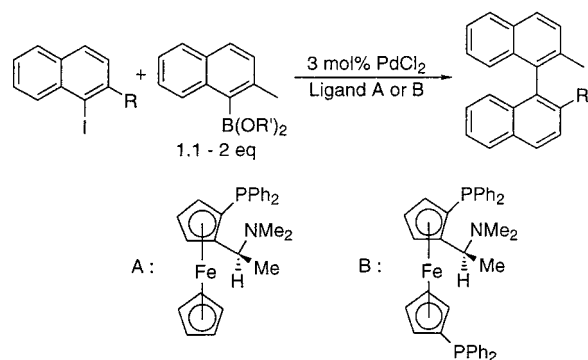
Working on the same kind of ligands, Cammidge et al.<sup>548</sup> achieved what was probably the first example of an asymmetric Suzuki-coupling reaction for the construction of binaphthalenes. Racemic couplings were first performed to optimize the reaction conditions (base-solvent combinations, heterogeneous vs

## Scheme 284



homogeneous conditions, boronic derivatives, etc.). The authors then extended their best conditions to investigating the asymmetric Suzuki reaction using chiral ligands (Scheme 285). The highest selectivity

## Scheme 285



Halide	Boronate	Base Solvent Time	Ligand <sup>a</sup>	ee% (yield%) Product
R = CH <sub>3</sub> R' = -CH <sub>2</sub> -CH <sub>2</sub> -		CsF DME 6-9 days	A	85 (50) R(-)
			B	17 (13) S(+)
R = H R' = H		Ba(OH) <sub>2</sub> DME-H <sub>2</sub> O 19 h	A	63 (44) R(-)
			B	4 (73) S(+)

(a) carried out using 6 mol% monophosphine A ligand or 3 mol% bidentate B ligand

was observed for ligand A, i.e., when a monophosphine ligand was used. Replacing the tertiary amine with a methoxide in ligand A led to a decrease in observed selectivity. The high ee obtained with tertiary amine phosphine ligand A (85% ee) suggests that precomplexation is arising between nitrogen and boron prior to transmetalation.

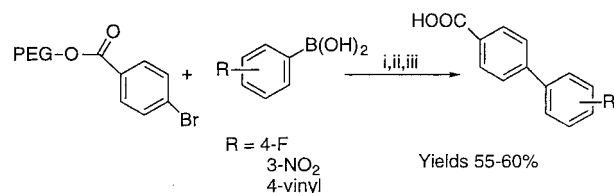
(b) Other Bis(diphenylphosphino)alkyls. Even though dppf is the most used ligand in the family of bis(diphenylphosphino)alkyls, it is not the only one. 1,4-Bis(diphenylphosphino)butane (dppb)<sup>549-551</sup> has also been used for the coupling of heteroaryl chlorides or bromides with aryl boronic acids in good yields.

Using 1,3-bis(diphenylphosphino)propane (dppp), Shen<sup>528</sup> achieved the coupling of various aryl chlorides bearing electron-withdrawing groups with aryl boronic acids.

More recently, using a derivative of 1,2-bis(diphenylphosphino)ethane (dppe), De et al.<sup>552</sup> showed that bis[1,2-bis(diphenylphosphino)ethane]palladium(0),

[Pd(DIPHOS)<sub>2</sub>], catalyzed cross-coupling reactions of free or polymer-bound aryl halides with organoboron compounds to produce biaryls in good yields. The authors first performed Pd(DIPHOS)<sub>2</sub>-catalyzed (1 mol %) coupling reactions of aryl boronic acids with various aryl halides bearing electron-withdrawing or -donating groups with good to excellent yields (60–96%). Polar solvents such as DMF and THF-MeOH and bases such as K<sub>2</sub>CO<sub>3</sub> and Et<sub>3</sub>N were suitable for this reaction. Furthermore, the presence or absence of an inert atmosphere (N<sub>2</sub>) had little effect on the catalytic activity of Pd(DIPHOS)<sub>2</sub>. The reaction was next extended to the synthesis of several biaryl carboxylic acids using polymer-bound aryl bromides with aryl boronic acids (Scheme 286).

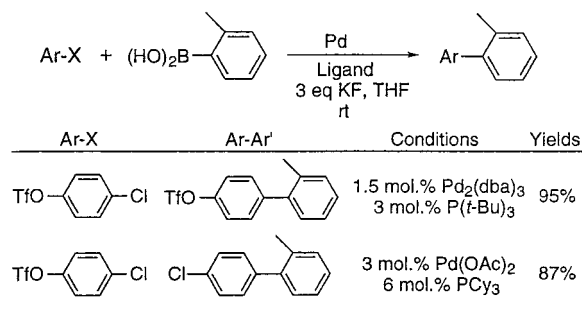
## Scheme 286



i) Pd(DIPHOS)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, DMF, 70-80°C, 3-4h; ii) NaOH, 90°C, 1h; iii) HCl.

ii. *Trialkylphosphine Ligands.* Looking for a general protocol that could reliably result in cross couplings independently of the structure of the reactants, Fu et al.<sup>525</sup> used trialkylphosphines, P(*t*-Bu)<sub>3</sub> and PCy<sub>3</sub>, as ligands of palladium. The authors have been particularly interested in the ability of substrates that bear more than one halide/triflate to achieve selective monofunctionalization through Suzuki cross couplings. As already mentioned in Section IV.14, for palladium catalysts the general order of reactivity is the following:<sup>336</sup> I > Br = OTf ≫ Cl. Using Pd<sub>2</sub>(dba)<sub>3</sub>/P(*t*-Bu)<sub>3</sub> as the catalyst, a wide range of aryl halides (I, Br, Cl), including electron-rich aryl halides, underwent Suzuki cross couplings with electron-poor, -neutral, and -rich aryl boronic acids in very good yields, typically at room temperature. However, this catalytic system was not efficient for aryl triflates. Through the use of Pd(OAc)<sub>2</sub>/PCy<sub>3</sub> as the catalyst, several aryl triflates reacted properly at room temperature. In view of the low reactivity of aryl triflates and of the high reactivity of aryl chlorides toward the Pd<sub>2</sub>(dba)<sub>3</sub>/P(*t*-Bu)<sub>3</sub> catalyst system, the authors achieved a selective Suzuki coupling of a chloride in the presence of a triflate (Scheme 287).

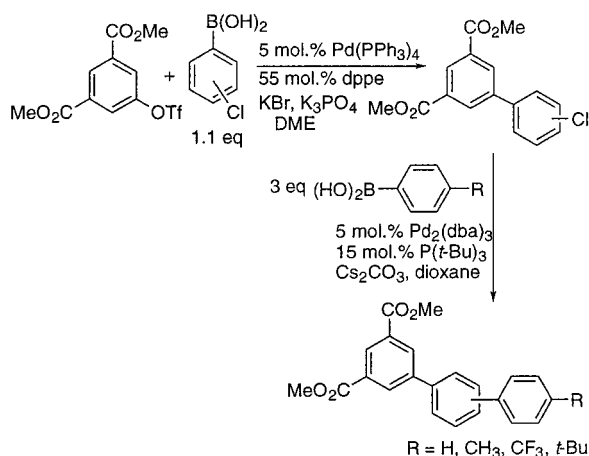
## Scheme 287



To the knowledge of the authors, this is the first example of a Pd-catalyzed cross-coupling process showing a greater reactivity toward an aryl chloride than an aryl triflate. Thus, their catalyst systems cover a broad spectrum of commonly encountered substrates for Suzuki couplings and can be used at low loading, even for reactions of aryl chlorides (with a turnover number of nearly  $10^4$ ). Preliminary mechanistic works, with the  $\text{Pd}_2(\text{dba})_3/\text{P}(t\text{-Bu})_3$  catalyst system, indicated that a palladium monophosphine adduct might be the active catalyst in the Suzuki couplings and that phosphine-free palladium complexes, which are present in the reaction mixture, might serve an important role by increasing the concentration of the active catalyst. The unusual cross-coupling activity furnished by  $\text{P}(t\text{-Bu})_3$  might thus be attributable both to its size and to its electron richness: the steric demand favors dissociation (relative to less bulky phosphines) to a monophosphine complex that, due to the donating ability of  $\text{P}(t\text{-Bu})_3$ , readily undergoes oxidative addition.

Sutton et al.<sup>553</sup> used the catalyst system of Fu,<sup>525</sup>  $\text{Pd}_2(\text{dba})_3/\text{P}(t\text{-Bu})_3$ , to synthesize a series of terphenyl systems chosen as potentially selective inhibitors of dihydroorotate dehydrogenase. Indeed, the difference in reactivity between an aryl triflate and an aryl chloride allowed the terphenyl system to be synthesized directly via chemoselective Suzuki cross couplings (Scheme 288). The addition of 1,2-bis(diphe-

Scheme 288



nylphosphino)ethane (dppe) proved necessary to stabilize the palladium catalyst in the first step and perform the cross coupling with a 75% yield. In the second step, the desired terphenyls were synthesized in good yields ranging from 67% to 91%.

Shen<sup>528</sup> used tricyclohexylphosphine,  $\text{PCy}_3$ , as the palladium ligand to efficiently activate aryl chlorides in the Suzuki reaction. The electron-donating and steric demand of this ligand gave rise to the coupling of phenylboronic acid and aryl chlorides with *ortho* or *para* electron-withdrawing substituents in very good yields (89–98%).

Wilhelm et al.<sup>554,555</sup> achieved the Suzuki cross coupling of (fluoroarene)tricarbonylchromium(0) complexes with aryl boronic acids using 5 mol % of  $\text{Pd}_2(\text{dba})_3$ , trimethylphosphine, and  $\text{PMe}_3$  as the ligand and  $\text{Cs}_2\text{CO}_3$  as the base. The authors demonstrated

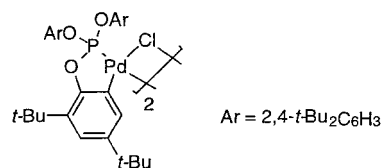
that the fluoroarene complex participates directly in the coupling process with the implication of an unprecedented oxidative addition of the C–F bond to the palladium(0) intermediate. The (fluoroarene)–chromium complex was coupled with a series of electron-rich aryl boronic acids in good yields (61–87%).

To achieve the total synthesis of the vancomycin aglycon, Boger et al.<sup>556</sup> performed an intermolecular Suzuki biaryl coupling following the protocol introduced by Hartwig,<sup>557</sup> i.e., using  $\text{P}(o\text{-tolyl})_3$  as the ligand. The success of this coupling step (90% yield) was largely dependent on the use of this ligand.

*iii. Palladacycle Ligands.* Palladacycles have emerged during the past few years as promising catalysts to achieve Suzuki cross-coupling reactions of aryl bromides and chlorides and aryl boronic acids.<sup>526</sup> Indeed, the carbometalated Pd(II) complexes exhibit higher air and thermal stability than palladium(0) complexes and can operate through a Pd(II)–Pd(IV) cycle instead of the traditional Pd(0)–Pd(II) mechanism.<sup>558</sup>

Orthopalladation of inexpensive, commercially available tris(2,4-di-*tert*-butylphenyl)phosphite gave a dimeric complex that Albisson et al.<sup>559</sup> tested for the Suzuki reaction (Scheme 289).

Scheme 289



The catalyst proved to be extremely active, giving unprecedented turnover numbers of up to  $10^6$  [mol of product (mol of Pd)<sup>-1</sup>] and turnover frequencies of nearly  $9 \times 10^5$  [mol of product (mol of Pd)<sup>-1</sup> h<sup>-1</sup>] when tested at 110 °C in toluene with 4-bromoacetophenone, phenylboronic acid, and  $\text{K}_2\text{CO}_3$  as a base. Obviously, lowering the temperature led to a reduction in activity, but even at 20 °C, high levels of activity were observed. As expected, activity decreased with increasing electron density. However, with 4-bromoanisole, even if TOFs are lower by about 2 orders of magnitude than with 4-bromoacetophenone, the TONs reach  $3 \times 10^4$ .

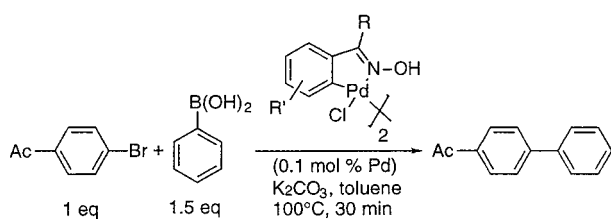
Alonso et al.<sup>560</sup> used phosphine-free complexes to catalyze the Suzuki reaction. The authors synthesized several oxime palladacycles in high yields and investigated the coupling of 4-bromoacetophenone and phenylboronic acid (Scheme 290). The easy synthetic accessibility and structural versatility of the complexes make them very promising catalysts.

Weissman et al.<sup>561</sup> and Zim et al.<sup>562</sup> obtained similar good results also using cyclopalladated phosphine-free complexes: imine **94** and sulfur-containing **95** palladacycles (Scheme 291).

Interested in making high-activity catalysts derived from inexpensive and easily synthesized ligands, Bedford et al.<sup>563</sup> synthesized bis(phosphinite) 'PCP'-pincer complexes in good overall yields (64–76%) (Scheme 292). These complexes showed moderate to good activity at low concentrations in the coupling

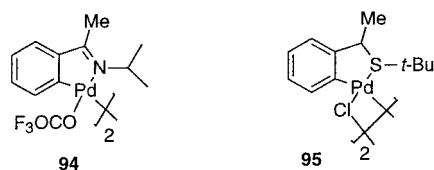


## Scheme 290

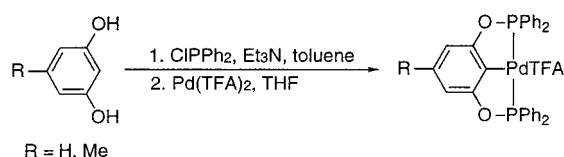


R	R'	Yield (%)	TON
Ph	H	93	930
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Cl	97	970
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	MeO	94	940
Me	H	95	950
fluorenone		97	970

## Scheme 291



## Scheme 292

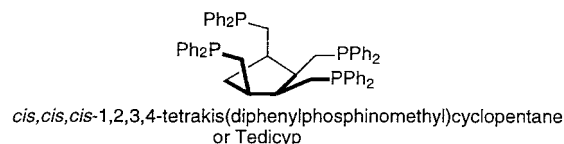


of the sterically hindered, electronically deactivated substrates 2-bromo-*o*-toluene, 2-bromo-*p*-xylene, 2-bromo-*m*-xylene. Good conversions were also observed with the electronically deactivated 4-bromoanisole.

*iv. Other Unusual Ligands.* The molecules described above represent the main types of Pd ligands studied nowadays for the Suzuki cross-coupling reaction. However, we have noticed the development of new efficient ligands that do not correspond to the categories already mentioned. We will deal with them in this section.

Noting that if bulky monodentate ligands had been successfully used for the Suzuki reaction the efficiency of bulky polydentate ligands had not yet been demonstrated, Santelli et al.<sup>564</sup> prepared a new tetrapodal phosphine ligand: Tedicyp (Scheme 293).

## Scheme 293

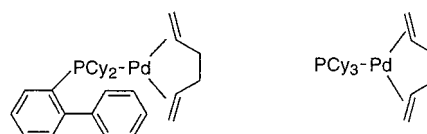


In this ligand, since the four phosphines, which are bound stereospecifically to the same face of the cyclopentane ring, are both close to the metal and increase the coordination of the ligand to the metal center, they therefore improve the stability of the catalyst. This system catalyzed the cross coupling of aryl bromides and aryl boronic acids with very high substrate–catalyst ratios in good yields. A turnover

number of  $28 \times 10^6$  was obtained when 4-bromobenzophenone was added to benzenboronic acid in the presence of this catalyst.

To avoid side reactions which may parallel the preformation of coordinatively unsaturated complexes (which constitute the “real” catalyst) and which often lead to the loss of catalyst activity, Andreu et al.<sup>565</sup> used defined Pd(0) monophosphine complexes as catalysts. The authors prepared various 1,6-diene-stabilized Pd(0)–PR<sub>3</sub> complexes for the Suzuki cross coupling of aryl chlorides (Scheme 294).

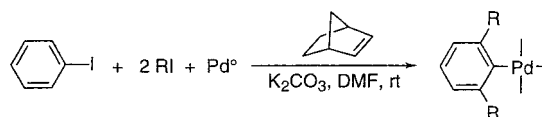
## Scheme 294



The best results were achieved with the 1,6-diene complex containing the so-called “Buchwald’s ligand” *o*-biphenylcyclohexylphosphine. With only 0.05 mol % of this catalyst, good to excellent yields of biaryls were obtained from activated, nonactivated, and deactivated aryl chlorides.

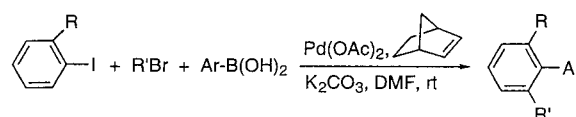
Last but not least, Catellani et al.<sup>566</sup> synthesized symmetrical and unsymmetrical 2,6-dialkyl-1,1'-biaryls by the combined catalysis of aromatic alkylation via palladacycles and Suzuki-type coupling. The main feature of this original methodology is the aromatic *ortho*-alkylation based on the formation of palladium(II) and palladium(IV) metallacycles<sup>567</sup> (Scheme 295).

## Scheme 295



A Suzuki-type coupling reaction could then be initiated directly in the reaction mixture, leading to symmetrically and unsymmetrically *ortho*-dialkylated biaryls (Scheme 296). The procedure appeared

## Scheme 296



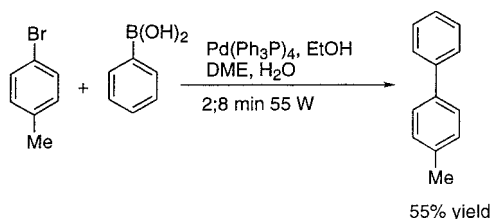
to be tolerant of various substituents but was sensitive to the bulkiness of the reagents. Thus, it appears to offer a simple, original, and direct tool to gain access to 2,6-dialkyl-substituted 1,1'-biaryls.

## D. Use of New Technologies in Suzuki Cross Coupling of Aromatic Substrates

**a. Microwave-Assisted Suzuki Reaction.** The use of microwave irradiations in organic chemistry is now one of the classical methods of activation. Among the numerous applications of such technology in organic synthesis, some are devoted to aryl–aryl bond formation. Halleberg et al.<sup>568</sup> showed that microwave irradiations allow the activation of homo-

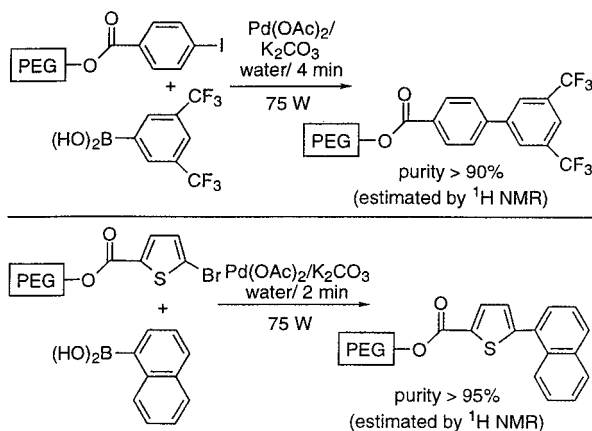
geneous palladium-catalyzed reactions. The authors demonstrated that the rate of the reaction is accelerated affording faster and cleaner chemical conversions (Scheme 297).

Scheme 297



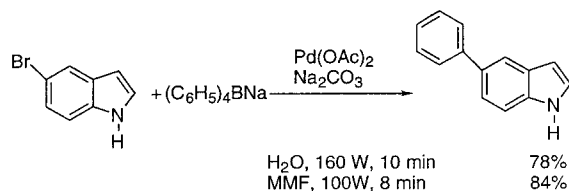
Schotten et al.<sup>569</sup> reported the liquid-phase “ligandless” palladium-acetate-catalyzed Suzuki reaction in water with poly(ethylene glycol) as the soluble support and phase-transfer catalyst. By using microwave irradiations, the reaction time shortened from 2 h to 2–4 min. Under these conditions, the linkage to the polymer and the polymer itself remained stable. The poly(ethylene glycol) ester of bromo, iodo, and triflated *para*-substituted benzoates are smoothly coupled with aryl boronic acids (Scheme 298).

Scheme 298



Very recently, Villemin et al.<sup>570</sup> showed the efficiency of microwave irradiations in the phenylation of heteroaromatics in water or methylformamide. The commercially available and nontoxic sodium tetraphenylborate has been used for the rapid and efficient phenylation of heteroaromatic halide in a palladium-catalyzed Suzuki reaction (Scheme 299).

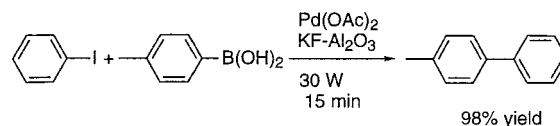
Scheme 299



The monomethylformamide (MMF) has been used because of its high boiling point (183 °C) and polarity ( $\epsilon = 182.5$ ). This type of solvent is very efficient at dissolving heterocycles and increasing microwaves.

On the other hand, Villemin et al.<sup>571</sup> showed the possibility of using  $\text{KF-Al}_2\text{O}_3$  as a base without any solvent under mono-mode microwave irradiation. The Suzuki reaction has been carried out in air, in the presence of palladium acetate. To obtain a good yield, grinding of the palladium catalyst with  $\text{KF-Al}_2\text{O}_3$  before the reaction allows a good dispersion of palladium(II) complex on  $\text{KF-Al}_2\text{O}_3$ . Moderate yields were obtained with both bromide and chloride compounds (Scheme 300).

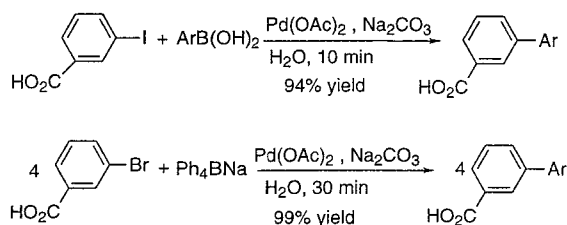
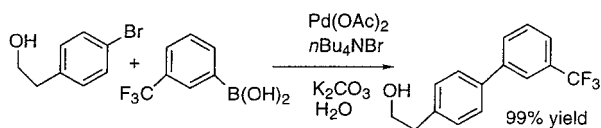
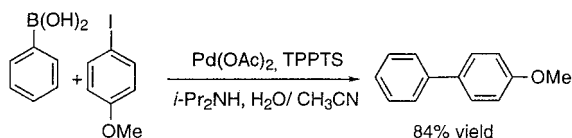
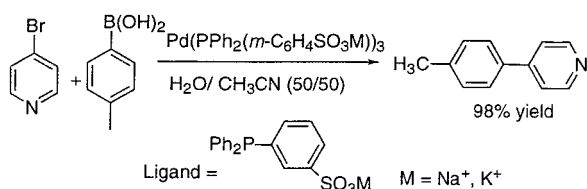
Scheme 300



**b. Suzuki Cross-Coupling Reaction in Aqueous Media.** In recent years, many methods have been developed that involve the use of water to synthesize biaryls; often these processes are more economically and ecologically acceptable. The use of water facilitates the catalyst–product separation. Bumagine et al.<sup>572,573</sup> reported the palladium-catalyzed Suzuki cross-coupling reaction between aryl boronic acids or sodium tetraphenylborate and aryl halides (I, Br, Cl) in aqueous solvent. The effect of bases ( $\text{Na}_2\text{CO}_3$ ,  $\text{NaOH}$ ) and catalysts on the cross-coupling reaction has been largely studied. The addition of phosphine increases the reaction rate. The yields range generally from good to excellent at 25 °C. However, *o*-iodo- and bromobenzoic acids led to low to moderate yields. In the case of tetraphenylborate, all four phenyl groups are coupled with halophenyls. At 100 °C, the amount of catalyst can be significantly decreased from 1 to 0.0004 mol %. On the other hand, the best results were obtained for aryl halides insoluble in water. The coupling reaction between aryl chlorides and  $\text{Ph}_4\text{BNa}$  led to polyfunctional biaryls in moderate to good yields in the presence of  $\text{PdCl}_2$  and  $\text{NaOH}$  at 100 °C. The palladium salts probably play the role of both catalysts and phase-transfer agents.

Badone et al.<sup>574</sup> demonstrated the effect of tetrabutylammonium bromide on the Suzuki-coupling reaction in aqueous media. The substrate played the role of an organic solvent. The presence of a stoichiometric amount of tetrabutylammonium bromide accelerated the coupling reaction of aryl bromides with aryl boronic acids, due to the formation of an  $\text{ArB(OH)}_3^- \text{Bu}_4\text{N}^+$ . Under these conditions, the steric hindrance decreased the yield in the case of 1-bromo-2-(trifluoromethyl)phenyl. Moreover, aryl iodides did not give satisfactory results, probably due to the reduction reaction.

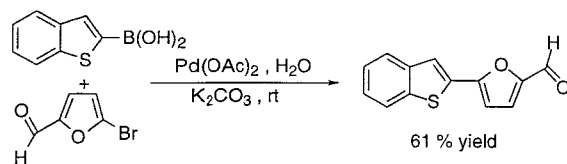
Genêt et al.<sup>575</sup> used organic bases and a water-soluble catalyst in the synthesis of functionalized dienes by the Suzuki cross-coupling reaction. It is interesting to note that the catalyst  $\text{Pd/TPPTS}$  was prepared in situ. *p*-Iodoanisole has been also successfully coupled with phenylboronic acid by using organic bases such as diisopropylamine. It is noteworthy that inorganic bases are inefficient. The same group had previously shown that the palladium

**Scheme 301****Scheme 302****Scheme 303****Scheme 304**

water-soluble catalyst formed in situ from palladium(II) acetate and TPPTS is a useful and practical catalyst system for various cross-coupling reactions.<sup>576–581</sup>

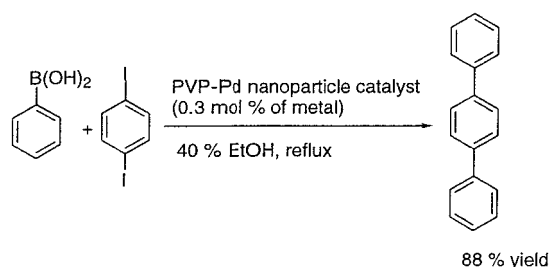
A water-soluble Pd(0) catalyst  $\text{Pd}(\text{PPh}_2(m\text{-C}_6\text{H}_4\text{SO}_3\text{M}))_3$  ( $\text{M} = \text{Na}^+, \text{K}^+$ ) has been synthesized and used in the Suzuki cross-coupling reaction of aryl and vinyl boronic acids with aryl halides.<sup>582</sup> The reaction proceeded in single and biphasic systems with complete conversion within several hours at 80 °C. It is possible to easily recover the products in good yields and recycle the catalyst due to the solubility characteristics of the catalyst.

Bussolari et al.<sup>583</sup> synthesized a series of 5-aryl-furfurals and aryl-thiophen-2-carboxaldehydes in moderate to good yields by using  $\text{Pd}(\text{OAc})_2$  as the catalyst in aqueous media (Scheme 305). These mild

**Scheme 305**

reaction conditions allow the cross-coupling reaction to occur in the presence of electrophilic functional groups.

Recently, El-Sayed et al.<sup>584</sup> demonstrated that a colloidal solution of palladium nanoparticles stabilized by poly(*N*-vinyl-2-pyrrolidone) PVP is an efficient catalyst for Suzuki reactions in aqueous

**Scheme 306**

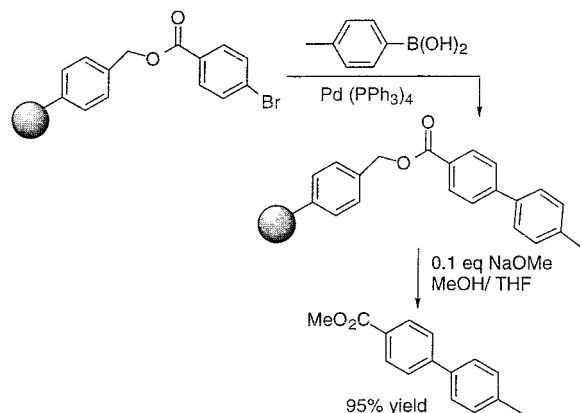
solution (Scheme 306). The colloidal solution has been easily prepared and separated from reaction products.

**c. Solid-Phase-Supported Biaryl Synthesis in the Suzuki Cross-Coupling Reaction.** High yields, fair selectivity, and large scope of applications have made the Suzuki reaction a method of choice for solid-phase synthesis. The halide substrates, the boronic derivatives, and the catalyst have been bound to the solid support. On the other hand, almost all types of organic and inorganic supports and spacers were tested and used with the Suzuki reaction. Nowadays, the solid-phase-supported Suzuki cross-coupling reaction is a powerful tool in organic synthesis. Biaryls bearing many functional groups have been synthesized, generally with good to excellent yields. With the evolution of combinatorial chemistry, the formation of biaryl systems by solid-phase-supported synthesis is a demanding target, in view of their numerous applications in medical chemistry. Recently, Kurth and Lorbach<sup>585</sup> published a detailed review on carbon–carbon bond-forming solid-phase reactions. This review summarized the literature for the period 1990–1997.

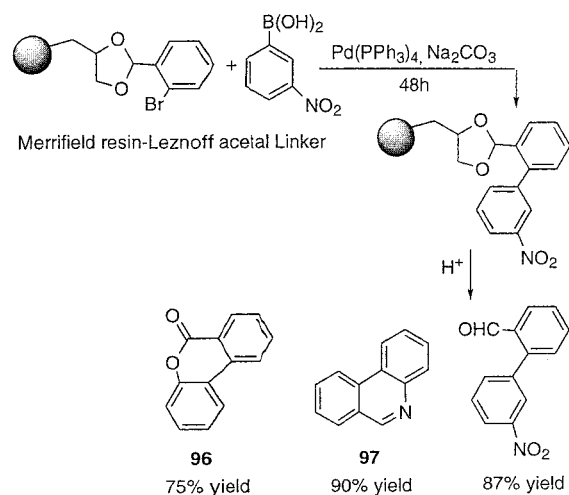
*i. Aryl Halides Bound to a Solid Support.* In recent years, many Suzuki reactions involving aryl halides bound to a solid support have been described. From these experiments, we see that aryl halides are typically more readily available than the aryl boronic acids. In most cases, upon cleavage from the solid support biaryl products were obtained in good to excellent yields. However, it is important to note that only aryl iodides and bromides have been tested. Aryl chlorides seem to be unreactive in solid-phase synthesis. We mention the Suzuki-supported coupling reaction, reported by Friesen et al.<sup>586</sup> of aryl iodides and bromides linked to a Merrifield resin, with a variety of aryl boronic acids. The efficiency of this method was illustrated by testing both functionalized aryl bromides (in *ortho*-, *meta*-, and *para*-positions) and aryl boronic acids having electron-deficient or electron-rich groups. The biaryl products were obtained in excellent yields (Scheme 307).

The solid-supported Suzuki–Miyaura coupling reactions of aryl and heteroaryl boronic acids with bromo benzaldehyde on Merrifield resin–Leznoff acetal linker has been performed in a  $\text{Pd}(\text{Ph}_3\text{P})_4$ -catalyzed reaction<sup>587</sup> (Scheme 308). The steric effects have been minimized by doubling the reaction times from 24 to 48 h. The coupling product was then cleaved from the solid support and cyclized to phenanthridine **96** in excellent yield upon treatment with  $\text{LiAlH}_4$  and Jones oxidation. A similar procedure has been used to synthesize dibenzo(*b,d*) pyranone **97**.

## Scheme 307

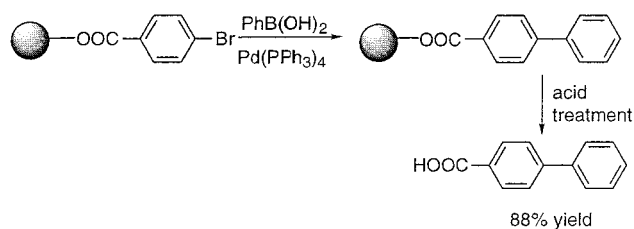


## Scheme 308



Bleicher et al.<sup>588</sup> described the synthesis of a new 9-phenylfluoren-9-yl-modified polystyrene resin. The authors compared its acid stability with trityl resins; 4-bromobenzoic acid was immobilized on the activated 9-phenylfluoren-9-yl resin. The corresponding biphenyl product was synthesized by the Suzuki cross-coupling reaction (Scheme 309). Five different

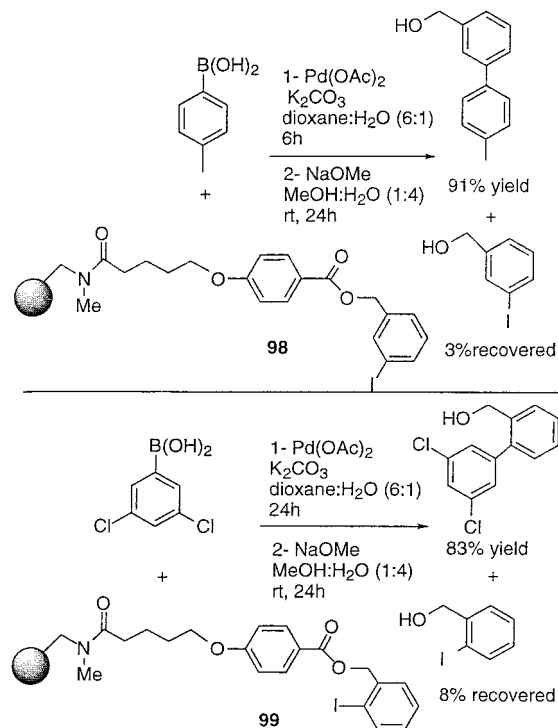
## Scheme 309



acidic conditions were then tested to cleave the biphenyl product from the resin; the coupling yield was 88% after acid treatment of the resin by using 20% TFA in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (9:1) in 2 h. This method has found several applications; the immobilized and modified compounds such as phenols and anilines have been assayed. The corresponding biphenyl products were obtained in moderate to excellent yields.

Mesmaeker et al.<sup>589</sup> used three linkers for the connection of aromatic iodides to polystyrene. Base-

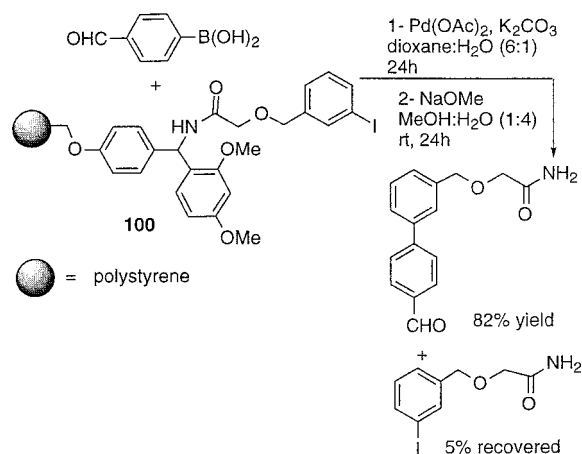
## Scheme 310



labile linkers **98**, **99** which are resistant to conditions of the Suzuki reaction (Scheme 310) lead to biaryl products with excellent yields by using either  $\text{Pd}(\text{OAc})_2$ - or  $\text{Pd}(\text{PPh}_3)_4$ -catalyzed reactions. The reaction rate was low when unactivated aryl bromides were used, and only iodide derivatives lead to a good yield. In addition, incomplete conversion has been observed in the case of *ortho*-substituents on the phenylboronic acids due to steric hindrance.

By using the acid-labile Rink resin **100** (Scheme 311), the Stille-coupling reaction has also been evalu-

## Scheme 311



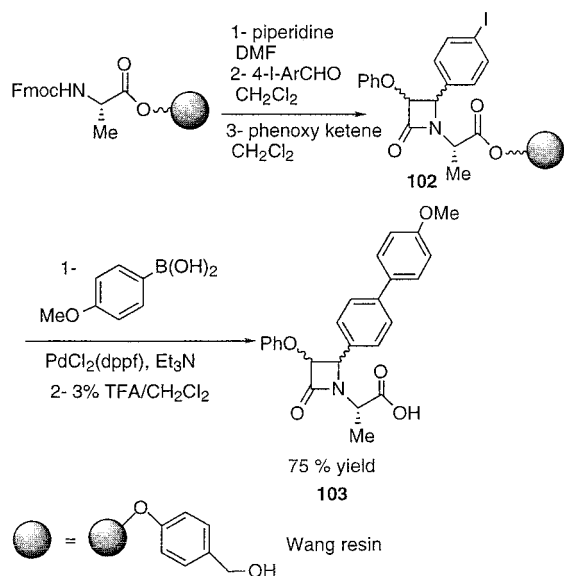
ated in a  $\text{Pd}_2(\text{dba})_3$ -catalyzed reaction. Generally, results were inferior to those obtained with the corresponding boronic acids.

Lago et al. reported the synthesis of 1,3,5-trisubstituted pyridinium salt **101** in 33% yield by Suzuki  $\text{Pd}(0)$ -catalyzed coupling of 5-bromonicotinic acid linked to a Rink amide resin and boronic acid derivatives<sup>590</sup> (Scheme 312). The alkylation of the

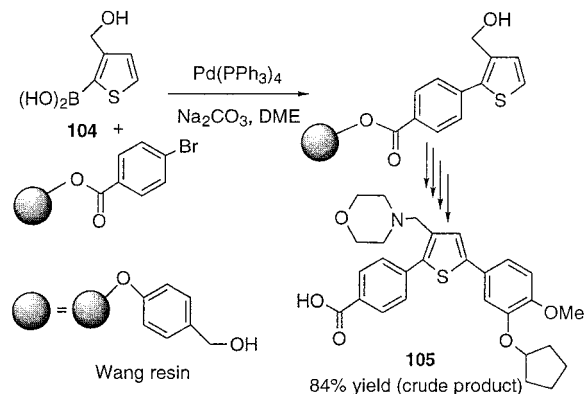




## Scheme 316



## Scheme 317

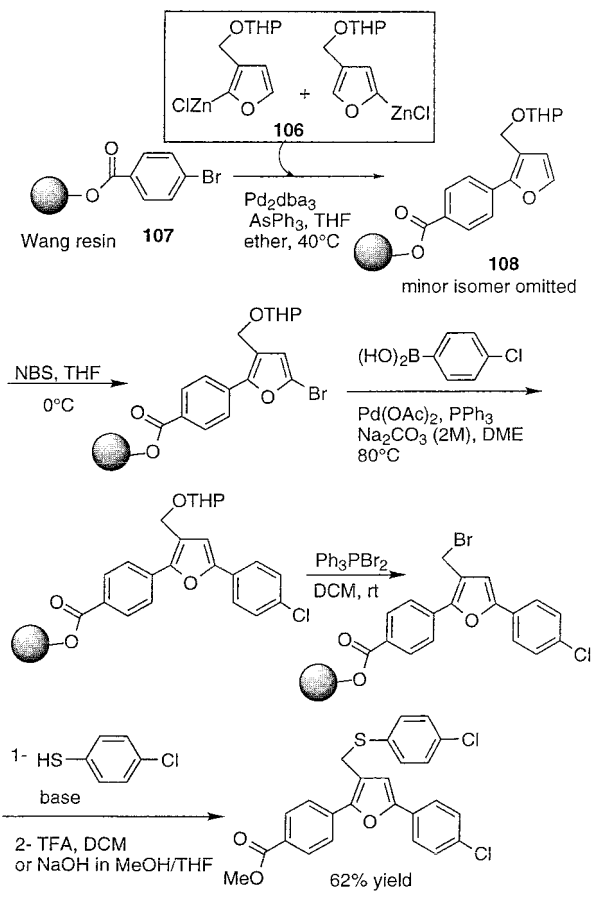


Recently, the same group<sup>596</sup> developed a general solid-phase protocol for the synthesis of highly substituted furan derivatives. The first step is the use of zincate **106** which reacts with polymer-bound aryl bromide **107** or iodide (on Wang resin) giving the resin intermediate **108**; then the Suzuki type reaction was performed. Structurally diverse furane derivatives were synthesized in a good overall yield using this methodology (Scheme 318).

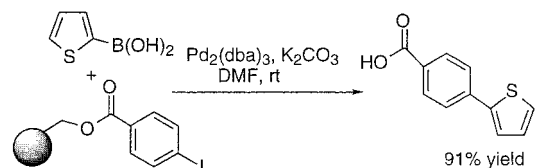
In an attempt to perform the solid-phase synthesis, commercial resins SASRIN<sup>597</sup> or Wang have been coupled with iodobenzoic acid and aryl boronic acids, respectively.<sup>598</sup> Biaryls have been synthesized in good yields by using Pd<sub>2</sub>(dba)<sub>3</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> catalysts at ambient temperature and at 70 °C, depending on the substrate nature. Under these conditions, aryl bromides were unreactive and *o*-iodobenzoate led to a moderate yield due to steric hindrance. There was no reaction in the case of Pd(II) or Ni(II) catalysts.

In many cases, the solid-phase synthesis occurs with difficulties and requires large quantities of solid support, low reaction rate, and relatively low loading of the material. Schotten et al.<sup>599</sup> proposed the use of different poly(ethylene glycol) supports to synthesize biaryls with good to excellent yields. In the presence of soluble PEG supports, the reaction has been carried out in homogeneous phase and moni-

## Scheme 318



## Scheme 319

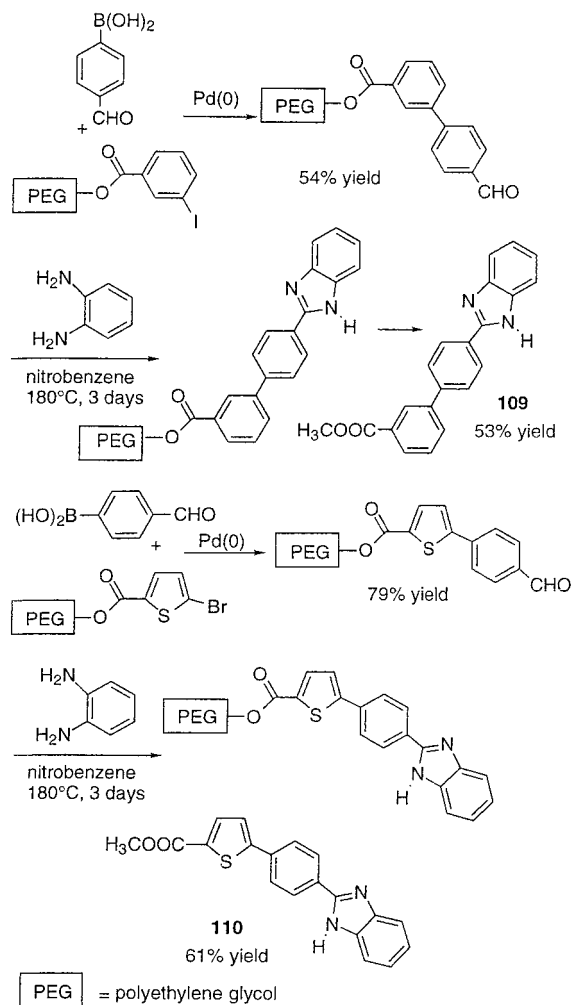


tored by conventional spectroscopy. The same team<sup>600</sup> also described the synthesis of biaryl benzimidazoles and imidazol pyridines **109**, **110** on soluble PEG support in a Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed reaction (Scheme 320). The coupling reaction between polymer-bound aryl halides and *o*-, *m*-, or *p*-formyl benzene boronic acid gives biaryl aldehydes with good to excellent yields. In some cases, the cleavage of the ester bond of the polymeric support has been observed as a side reaction.

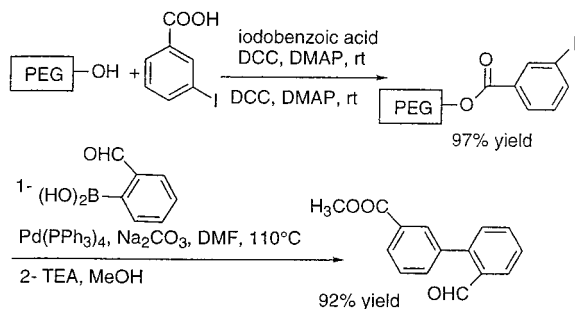
Schotten et al.<sup>601</sup> reported the liquid-phase synthesis of biaryls via the Suzuki-coupling reaction on poly(ethylene glycol) supports. Four different PEGs have been tested in order to generate a library of biaryls. The reaction of polymer-bound aryl iodides with boronic acids gives rise to biaryl products with moderate to good yield (Scheme 321).

De et al.<sup>602</sup> showed the efficiency of bis(1,2-bis(diphenylphosphino)ethane) palladium(0) (Pd(dppe)<sub>2</sub>) for the Suzuki-coupling reaction with free or polymer-bound aryl halides and organoboron compounds (Scheme 322). The polymer-bound aryl bromide **111** reacts with substituted aryl boronic acid to give the biaryl product with acceptable yields (55–60%).

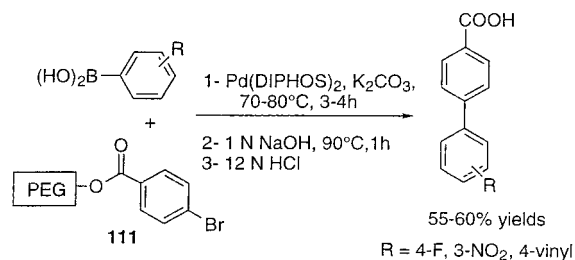
## Scheme 320



## Scheme 321



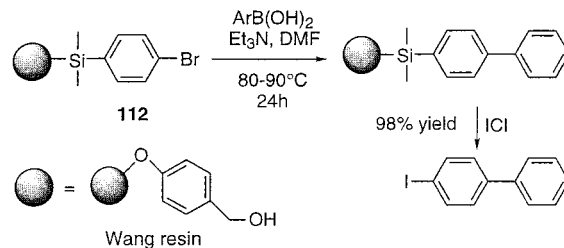
## Scheme 322



Han et al.<sup>603</sup> reported the utility of novel bromoarylsilane linkers for solid-phase synthesis. An efficient procedure for attaching aryl silanes to solid support has also been described. Using haloarylsilanes linked

to Wang resin **112**, the Suzuki cross coupling was carried out between the polymer-bound aryl halides and a variety of aryl boronic acids with moderate to good yields (Scheme 323). This methodology shows

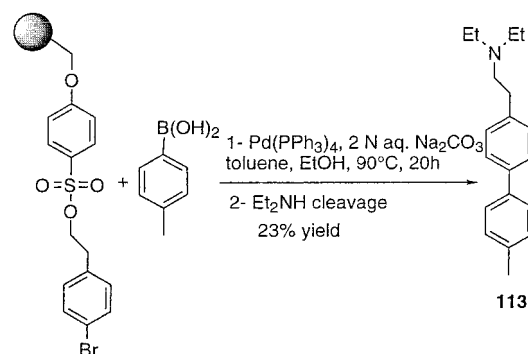
## Scheme 323



another specific interest due to the introduction of an iodo substituent during the cleavage. Only this iodoaryl product can undergo further chemical transformation including other aryl–aryl bond formation.

Reitz et al.<sup>604</sup> showed the compatibility of resin-bound aryl sulfate esters under several reaction conditions including Suzuki coupling (Scheme 324).

## Scheme 324

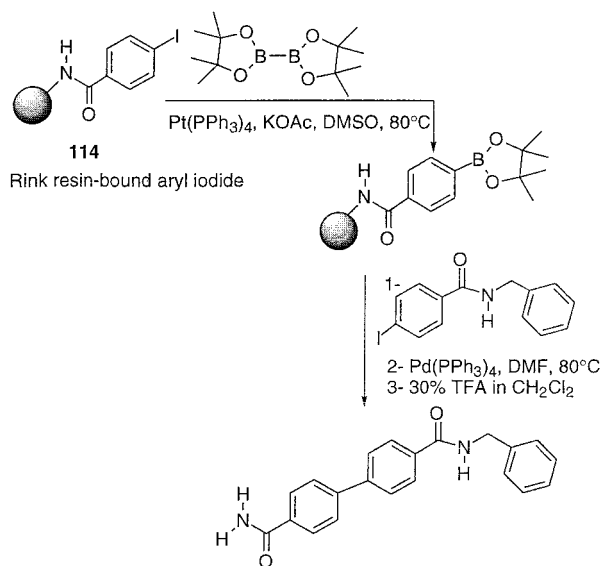


Nevertheless, the coupling product **113** was obtained in relatively low yield (23%).

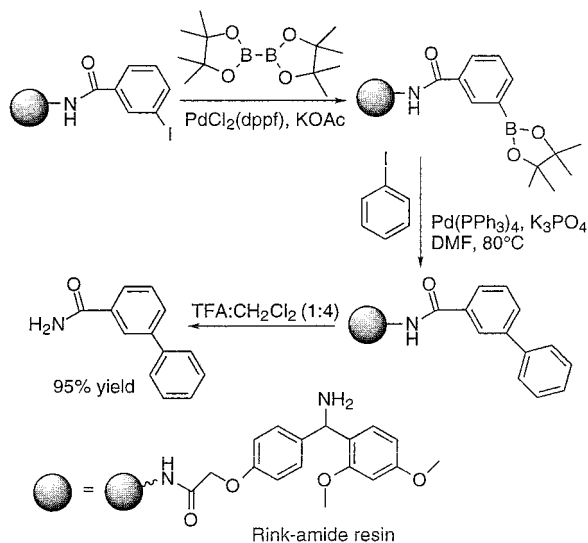
*ii. Aryl Boronic Acids Bound to the Solid Support.* In most Suzuki reactions, the most difficult reagent to obtain or the most expensive when it is commercially available is the boronic derivative. Some examples describe the use of boronic reagent bound to the resin in order to obtain a solid–liquid Suzuki reagent. Armstrong et al.<sup>605</sup> reported the biaryl synthesis in a Pt-catalyzed reaction. The Rink resin-bound aryl iodide **114** reacted with the bis-boronate to give the Rink resin-bound aryl boronic ester which could be coupled, in a Pd-catalyzed reaction, to *N*-benzyl-4-iodobenzamide with 95% yield (Scheme 325).

Piettre et al.<sup>606</sup> reported a new approach to the solid-phase-supported Suzuki-coupling reaction. This approach consists of the in situ synthesis of polymer-bound boronate by the reaction of polymer-bound aryl halides with pinacol ester of diboron (Scheme 326). The Suzuki-coupling reaction was then carried out in a palladium-catalyzed reaction, using a variety of aryl iodides and bromides bearing different functional groups. In the case of *para* and *meta* polymer-bound boronate, isolated yields in biaryl products range from good to excellent. However, steric hindrance in the case of *ortho* polymer-bound boronates led to a

## Scheme 325



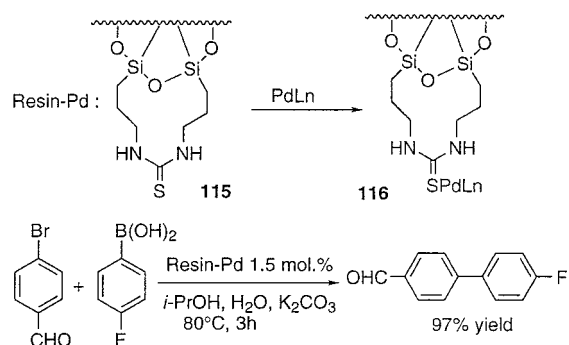
## Scheme 326



moderate yield. This method offers an advantage over previous methods, with the use of polymer-bound boronates instead of commercially limited boronic acids.

*iii. Catalyst Bound to the Solid Support.* It has to be noticed that all reported methods demonstrate the ability of solid-phase synthesis in which a reactant is linked to a polymer support. In an attempt to perform a palladium-catalyzed process, Zhang et al.<sup>607</sup> reported the use of a polymer-supported palladium catalyst from the commercially available thiourea resin Deloxan THP **115**. This resin has a cross-linked macroporous polysiloxane backbone and is stable in moisture and air. The resin-bound catalyst **116** has been synthesized by the reaction between the thiourea resin Deloxan and a solution of Pd(OAc)<sub>2</sub> in methanol (Scheme 327). The Suzuki cross-coupling reaction of aryl halides with aryl boronic acid has been carried out to give biphenyls with good to excellent yields. It seems that the catalyst is efficient with iodo- or bromoaryls activated by electron-withdrawing groups such as carbonyl or cyano groups. This protocol offers some advantages

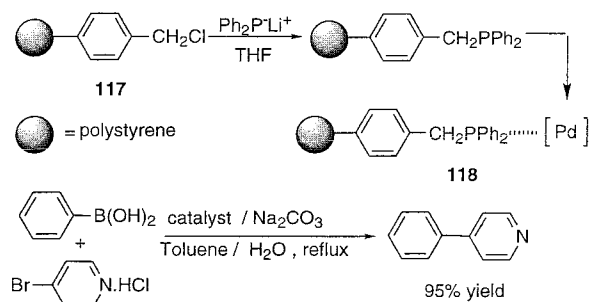
## Scheme 327



over several solid-supported palladium catalysts, requiring the addition of free ligands to stabilize the resin-bound systems.

A number of polymer-supported palladium catalysts have been prepared such as **118** (Scheme 328)

## Scheme 328



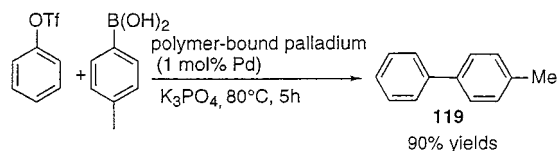
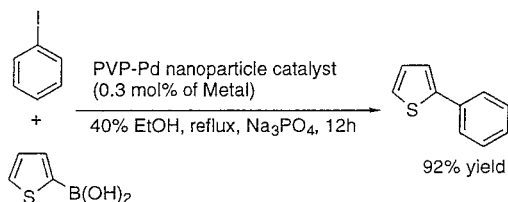
in two steps from commercially available chloromethylated polystyrene **117**.<sup>608</sup> These catalysts have been tested in the Suzuki cross-coupling reaction between phenylboronic acid and 4-bromo aromatics. Nevertheless, best results were obtained by using Pd(PPh<sub>3</sub>)<sub>4</sub>. Other palladium complexes led to biaryls with moderate to good yields. In all these cases, the catalyst was easily recovered and reused.

Another polymer-bound palladium catalyst has been prepared<sup>608</sup> by this method. An example of an aromatic Suzuki-coupling reaction was reported concerning *p*-methylbiphenyl synthesis **119** with 90% yield from *p*-toluylboronic acid and phenyltriflate. It seems that the catalyst remains active even after several uses and recycling.

Kabalka et al.<sup>610</sup> investigated the use of a potassium fluoride/alumina mixture, KF/Al<sub>2</sub>O<sub>3</sub>, doped with a ligandless Pd<sup>0</sup> catalyst. The coupling reaction of *p*-methylphenyl boronic acid with iodobenzene gives rise to 4-methylbiphenyl with 86% yield. This reaction was chosen in order to optimize the reaction conditions. Both potassium phosphate and potassium fluoride were effective in the solid-phase Suzuki-coupling reaction. The reagent can be easily recycled by simple filtration.

Recently, El-Sayed et al.<sup>584</sup> showed the efficiency of a colloidal solution of Pd nanoparticles as a catalyst for the Suzuki cross-coupling reaction in aqueous solution. The authors suggest that the catalytic reaction takes place on the surface of the Pd nanoparticles stabilized by poly(*N*-vinyl-2-pyrrolidone) (PVP). The reaction product is more easily separated



**Scheme 329****Scheme 330**

from the colloidal solution, more so than water-soluble complexes.

## 15. Aryl–Aryl Bond Formation Using Palladium Catalyst without Additional Organometallic

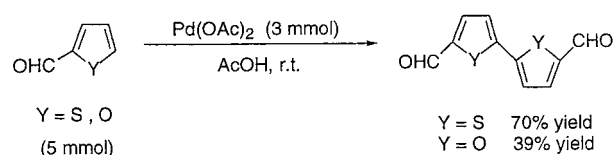
In the past decade the interest for environmentally friendly synthetic methods, i.e., giving rise to less toxic or dangerous waste, has been growing. Trost<sup>611</sup> and then Sheldon<sup>612</sup> defined the so-called atom economy concept. In the previous section we described the success of using both a transition-metal catalyst and organometallic reagent simultaneously, the latter acting as the reducing agent of the catalyst during the catalytic cycle but giving rise to a stoichiometric (often over-stoichiometric) amount of inorganic salt as a byproduct. Conversely, methods have recently appeared showing palladium catalysis without organometallic reagents. Three types of reactions were shown to lead to aryl–aryl bond formation without prior formation of an organometallic intermediate: oxidative coupling of electron-rich-aromatic rings, reductive coupling using harmless mild catalysis associated with an organic reducing agent, and the extension of a Heck-type reaction onto aromatic rings.

### A. Oxidative Coupling of Aromatic Rings Using Palladium

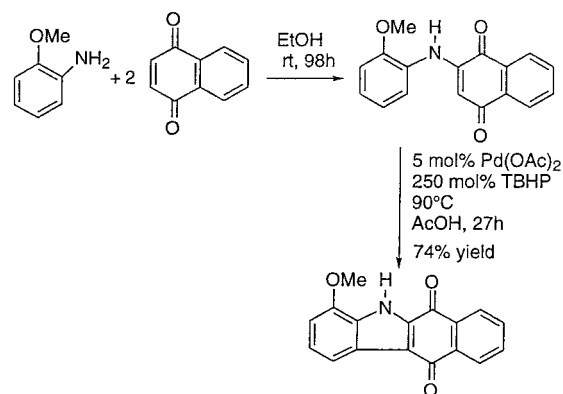
The coupling of aromatic substrates is made possible thanks to the oxidative properties of palladium(II) and/or the reversibility of the reduction by molecular hydrogen in the presence of palladium(0). Both stoichiometric amounts of palladium or a catalytic amount of palladium associated with an oxidizing reagent were used in the oxidative coupling of aromatic rings. Only a few examples of catalytic oxidative methods were described. Moreover, these methods can be applied only to relatively electron-rich aromatic rings. These methods do have an advantage in terms of atom economy since they produce only water or hydrogen as byproducts.

The 2,2'-bithienyls and 2,2'-bifuryls were synthesized<sup>613</sup> in moderate to good yields by oxidative coupling of thiophenes and furans bearing electron-withdrawing substituents in the presence of an over-stoichiometric amount of palladium acetate (Scheme 331).

Recently, palladium acetate as a catalyst and an excess of *tert*-butyl hydroperoxide (TBHP) as an

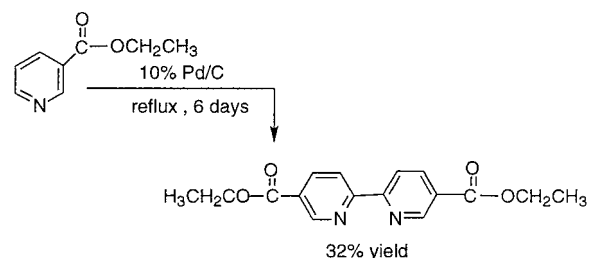
**Scheme 331**

oxidant have been used in intramolecular carbon–carbon bond formation of 2-aryl-amino-1,4-quinones<sup>614</sup> (Scheme 332). According to the authors, the

**Scheme 332**

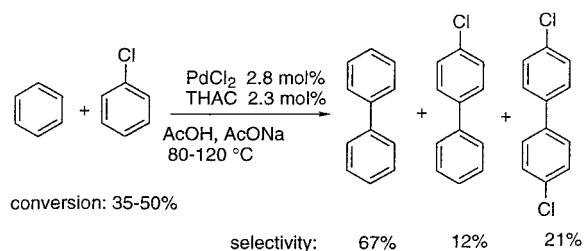
reoxidation of palladium is necessary and the cyclization reaction strongly depends on the quality of both palladium acetate and *tert*-butyl hydroperoxide.

Elsewhere, palladium on charcoal has been used in the synthesis of diethyl-2,2'-bipyridine-dicarboxylate from ethyl nicotinate<sup>615</sup> (Scheme 333). This

**Scheme 333**

reaction occurred probably by dehydrogenation processes, and the regeneration of Pd<sup>0</sup> should be performed by the release of molecular hydrogen.

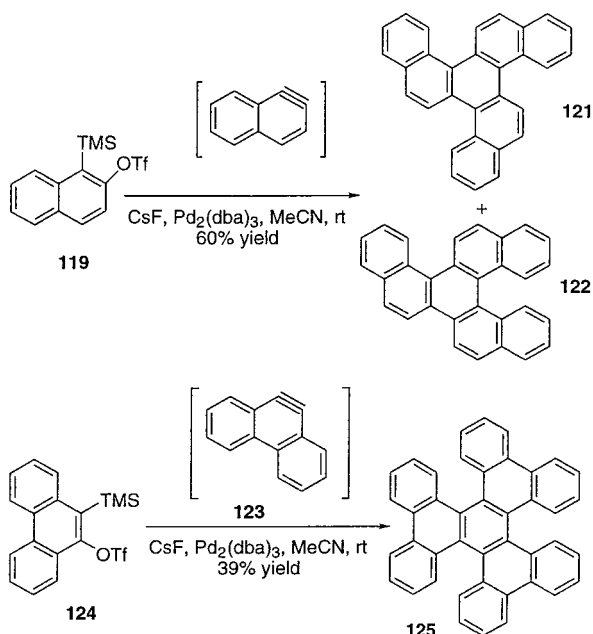
Very recently, Sasson et al.<sup>616</sup> demonstrated the homogeneous tandem-oxidative coupling of benzene to biphenyl using PdCl<sub>2</sub> and in situ reductive coupling of chlorobenzene to biphenyl using Pd<sup>0</sup> (Scheme 334). An equimolar mixture of benzene and chlorobenzene gives biphenyl as the major product with some

**Scheme 334**

dichlorobiphenyl and some of the cross-coupling product 4-chlorobiphenyl. According to the authors, there are two catalytic cycles. In each cycle, the reductive process regenerates the catalyst for the oxidative process and vice versa. The Pd<sup>0</sup> becomes an active catalyst of the reductive coupling of chlorobenzene despite its aggregation and precipitation.

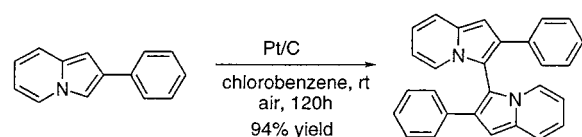
The trimerization of arynes for the synthesis of strained polycyclic hydrocarbons was recently reported.<sup>617</sup> 1-Trimethylsilylnaphthyl-2-trifluoromethanesulfonate **119** and 1,2-didehydronaphthalene were transformed into a mixture of tribenzo (*a,g,o*) triphenylene **121** and tribenzo (*a,g,m*) triphenylene **122**. The 9,10-didehydrophenanthrene **123** with the 10-trimethylsilylphenanthryl-9-trifluoromethanesulfonate **124** were transformed into hexabenz (*a,c,g,i,m,o*) triphenylene **125** giving 39% yield. The trimerization reaction was carried out with CsF in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> as the catalyst at room temperature (Scheme 335).

Scheme 335



Sonnenschien et al.<sup>618</sup> showed the efficiency of palladium on carbon for the oxidative dimerization of 3-unsubstituted indolizines (Scheme 336). Biindolizines were obtained in quantitative yields on bubbling air through the refluxing mixture in chlorobenzene. In the absence of oxygen, a drastic decrease in the rate of reaction was observed. The oxidative coupling on palladium on carbon (Pd/C) under refluxing conditions has also been carried out.

Scheme 336

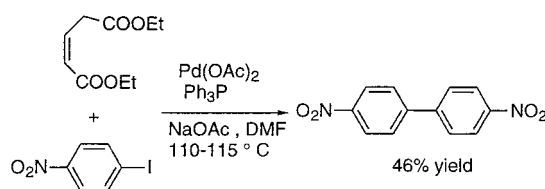


dolizines were obtained in quantitative yields on bubbling air through the refluxing mixture in chlorobenzene. In the absence of oxygen, a drastic decrease in the rate of reaction was observed. The oxidative coupling on palladium on carbon (Pd/C) under refluxing conditions has also been carried out.

### B. Reductive Coupling of Aromatic Rings Using Palladium

It is important to note that biaryl formation was originally observed in the Heck reaction<sup>619,620</sup> (Scheme

Scheme 337

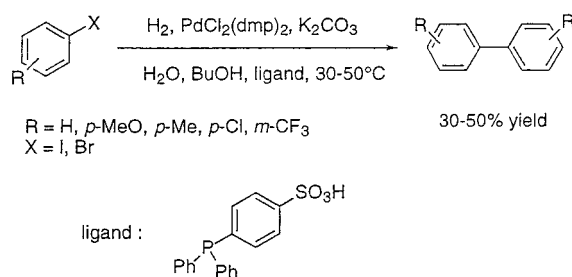


337). This symmetrical biaryl was considered as an unwanted byproduct by the authors who were looking for the Heck coupling of aromatic substrate and the ethylenic substrate. Nevertheless, 46% of the symmetrical product was obtained with only 5 mol % of palladium acetate and 10 mol % of triphenyl phosphine.

Very recently, some new methods appeared in the literature which are able to form aryl-aryl bonds without the use of additional stoichiometric amounts of organometallic reagent. These observations have been applied to aromatic carbon-carbon formation. Such methods, using catalytic amounts of palladium, are different from those applied in the original Ullmann-type reaction using stoichiometric amounts of copper, although the carbon-carbon bond step formation is also a reductive elimination. In these methods, regeneration of palladium(0) is obtained by an organic-reducing agent such as formic acid derivatives, 2-propanol, and even other organic solvents.

Nowadays, there are relatively few reported palladium-catalyzed coupling reactions. The use of catalytic amounts of palladium complexes to produce biaryls was first reported by Norman,<sup>621</sup> and Bamfield<sup>622,623</sup> used the Pd/formiate under phase-transfer catalysis conditions. A catalytic amount of palladium leads to moderate yields, and this method is not compatible with many functional groups such as aldehyde or nitro which were reduced under similar conditions. Davydov et al.<sup>624</sup> studied the reductive coupling of aryl halides insoluble in water. The reaction was performed in microemulsions with PdCl<sub>2</sub>(dmp)<sub>2</sub> and water-soluble triphenylphosphine. A reducing agent-catalyst combination, H<sub>2</sub> and PdCl<sub>2</sub>(dmp)<sub>2</sub>, has been used containing water-soluble monosulfonate triphenylphosphine in the coordination sphere of the palladium complex. The conversion of aryl halides is low under these conditions (30–50%) (Scheme 338), and only iodo and bromo deriva-

Scheme 338

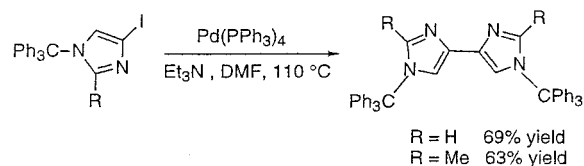


tives could be used as substrate.

The 4,4'-biimidazoles can be used as meta-ion chelators or as precursors for the synthesis of new heterocyclic compounds.<sup>625</sup> This synthesis has been

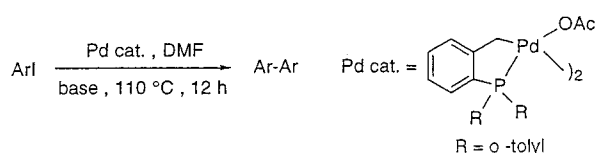
performed by the Pd(0)-catalyzed coupling reaction of 4-iodo-1-triphenylimidazol or its 2-methyl analogue (Scheme 339).

### Scheme 339



Biaryls have been synthesized<sup>626</sup> via monoiodoarenes in high yields in the presence of less than 0.1 mol % of a palladacycle catalyst and *N,N*-diisopropylethylamine as a base in DMF at 100 °C (Scheme 340). The base effect has been studied, and *i*-Pr<sub>2</sub>NEt

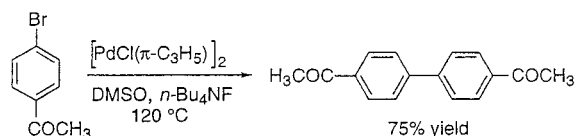
### Scheme 340



appears to be the most efficient and selective base. Under similar reaction conditions, the coupling reaction of 1,4-diiodobenzene leads to poly-*p*-phenylene with an 85% isolated yield.

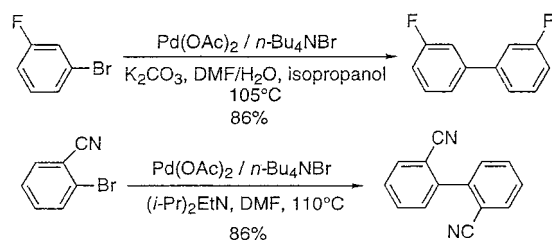
The use of 2.5 mol % of allylpalladium chloride dimer (PdCl( $\pi$ -C<sub>3</sub>H<sub>5</sub>))<sub>2</sub> and tetrabutylammonium fluoride leads to biaryl products in moderate to good yields<sup>627</sup> (Scheme 341).

### Scheme 341



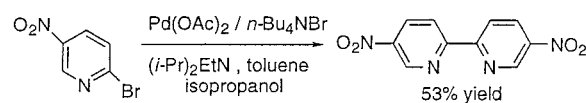
Lemaire et al.<sup>628,629</sup> reported the ability of Pd(OAc)<sub>2</sub> as a catalyst for the homocoupling Ullmann-type reaction and compared it with reported methods. A great variety of substrates bearing different groups (electron-withdrawing and -donating groups) in the *para*-, *meta*-, and *ortho*-positions were successfully coupled (Scheme 342).

### Scheme 342



By using this catalytic system, biheterocycles were synthesized. The synthesis of dinitrobipyridine was also improved compared to the previously reported methods<sup>630</sup> (Scheme 343). In most cases described above, the reducing agent, although not fully determined, is probably the solvent itself (DMF), but in

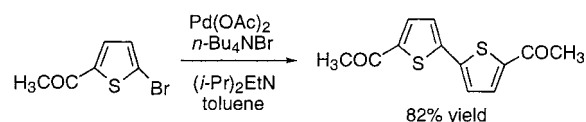
### Scheme 343



the case of the pyridine substrate, the addition of a hydride donor such as 2-propanol is needed in order to obtain maximum yields.

The coupling reaction of 2-bromopyridine (92%), 2-bromo-3-methylpyridine (95%), and 3-bromoquinoline (79%) was carried out with a good yield. Only a few chlorinated substrates could be coupled using this method (2-chloroquinoline (62%)). A series of symmetrical functionalized bithiophenes has also been synthesized in good to excellent yields<sup>631</sup> (Scheme 344).

### Scheme 344

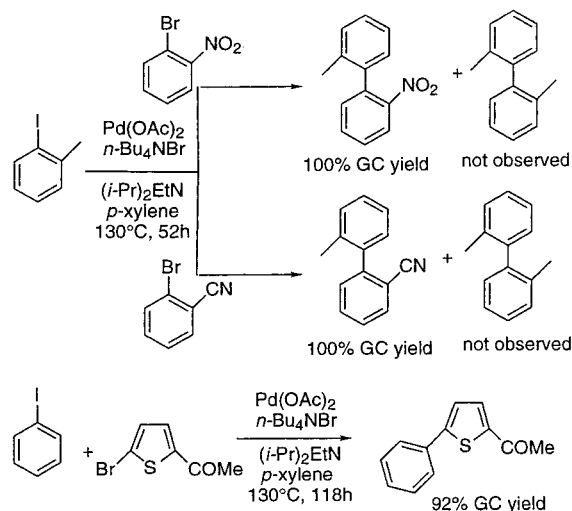


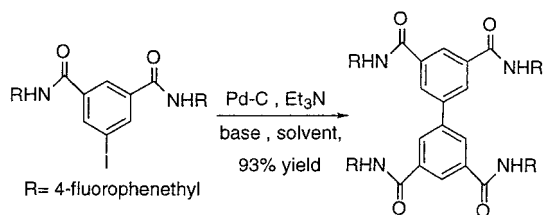
Furthermore, the effectiveness of Pd(OAc)<sub>2</sub> as a catalyst for the direct preparation of unsymmetrical biaryls was also described.<sup>632,633</sup> Aryl bromides react with aryl iodides to form unsymmetrical biaryls with marked selectivity. This procedure is efficient even with substituents in the *ortho*-position, but the use of an excess of bromo derivatives (iodo/bromo ratio: 1/4) is required and limits the practical interest in these cross couplings.

Modifications to this work were examined by Andersson et al.<sup>634</sup> Heterogeneous catalysts were used; Pd(OAc)<sub>2</sub> was replaced by Pd on carbon (10% Pd/C). Consequently, the product isolation and purification have been improved. Biaryl libraries via iodoarenes were synthesized in high yield (Scheme 346).

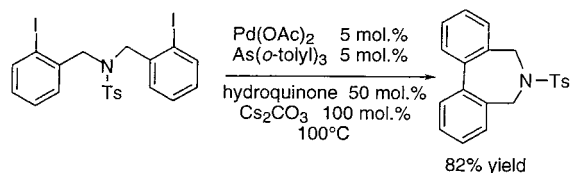
The inter- and intramolecular homocoupling of aryl halides (I, Br) have been carried out<sup>635</sup> using a 1:1 molar ratio of Pd(OAc)<sub>2</sub> and As(*o*-tolyl)<sub>3</sub> in catalytic amounts under basic conditions and hydroquinone as a reductant in a stoichiometric amount. The rates

### Scheme 345



**Scheme 346**

of conversion were slower than expected for intramolecular processes, probably due to the steric hindrance of the *ortho*-substituents (Scheme 347). More-

**Scheme 347**

over, the coupling reaction is even slower in the case of aryl bromides.

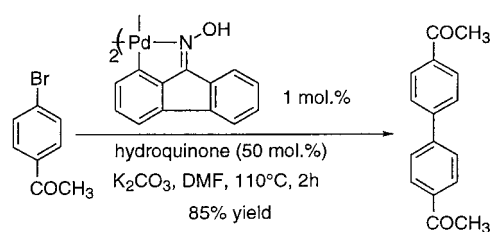
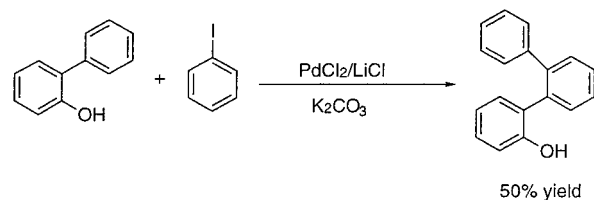
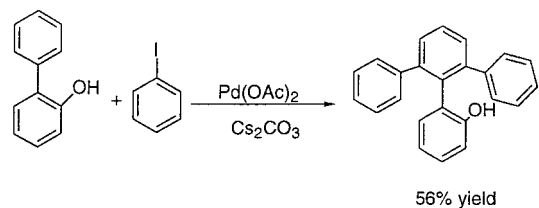
Different carbon–carbon bond-forming reactions have been carried out using oxime palladacycles.<sup>636</sup> These catalysts are thermally stable and not sensitive to air or moisture. The coupling reaction of *p*-bromoacetophenone was carried out with a 85% isolated yield.

### C. Coupling of Aryl Halide onto Nonfunctionalized Aromatic Position Catalyzed by Palladium

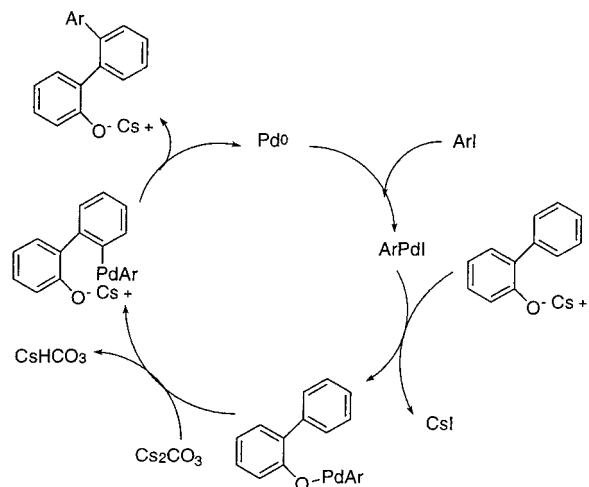
The Heck reaction is one of the most significant tools for carbon–carbon bond formation. This reaction enjoys widespread success in making bonds between aromatic rings and alkenes. The extension of this reaction to the formation of aryl–aryl bonds was considered impossible. Indeed, some mechanistic consideration could discourage research in this field. First of all, a Heck-type reaction onto aromatic rings should induce the breaking of aromaticity in the early step of the chemical pathway. Second, the *cis* elimination required in the last step of the reaction is impossible in the case of aromatic substrates. Nevertheless, some recent results describe the substitution of the hydrogen in the arene by aryl halide catalyzed by palladium in the presence of a base. Although still limited, these “Heck-like” reactions are observed in the *ortho*-position of phenol or amide groups or onto a few membered heterocycles and/or via an intramolecular process. A Heck-type reaction has been extended to biaryl synthesis. Activated and nonactivated substrates have been used. The Heck-type reaction has been performed intra- and intermolecularly.

Miura et al.<sup>637</sup> observed the reaction between aryl iodide and an activated 2-phenylphenol (Scheme 349) in the course of their study of palladium-catalyzed reactions with phenolic substrate.

Then they showed regioselective monoarylation and diarylation of 2-phenylphenols in the presence of Cs<sub>2</sub>CO<sub>3</sub> as a base and Pd(OAc)<sub>2</sub> as a catalyst<sup>638</sup> (Scheme 350).

**Scheme 348****Scheme 349****Scheme 350**

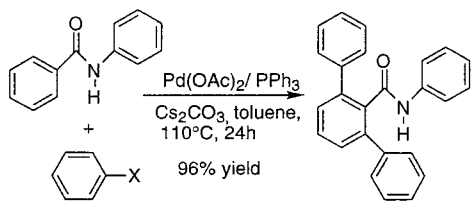
The diarylated product was obtained when the amounts of both aryl iodide and base were increased. The monoarylated product was also observed as a minor product. The authors suggested a possible mechanism for the reaction (Scheme 351). After an

**Scheme 351**

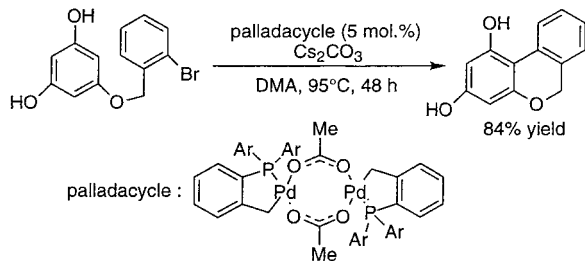
oxidative addition of aryl iodide to the palladium(0) species, an aryl(aryloxy)palladium intermediate was formed after a ligand exchange. This intermediate was then transformed into a diarylpalladium species. A reductive elimination led to the monoarylated product. The mechanism may be the same for the second arylation.

Very recently, the authors<sup>639</sup> tested other functional groups than enolate oxygen. Benzanilides can efficiently lead to diarylation products after treatment with aryl triflates or bromides (Scheme 352).



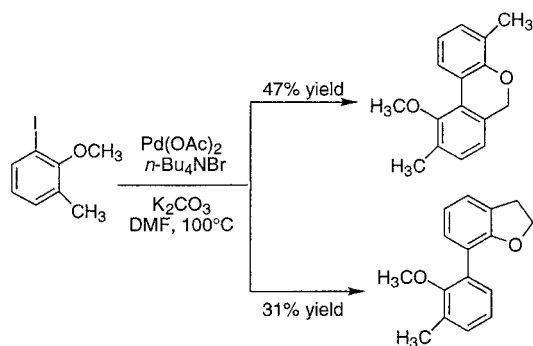
**Scheme 352**

Rawal et al.<sup>640</sup> reported the intramolecular coupling of phenols with aryl halides under basic conditions with palladium catalyst. Herrmann's catalyst was particularly useful due to its efficiency compared with other palladium catalysts such as  $\text{Pd}(\text{OAc})_2$ ,  $\text{Pd}(\text{PPh}_3)_4$ , and  $\text{Pd}_2(\text{dba})_3$  (Scheme 353). Herrmann's

**Scheme 353**

catalyst can be stored without any special precautions.

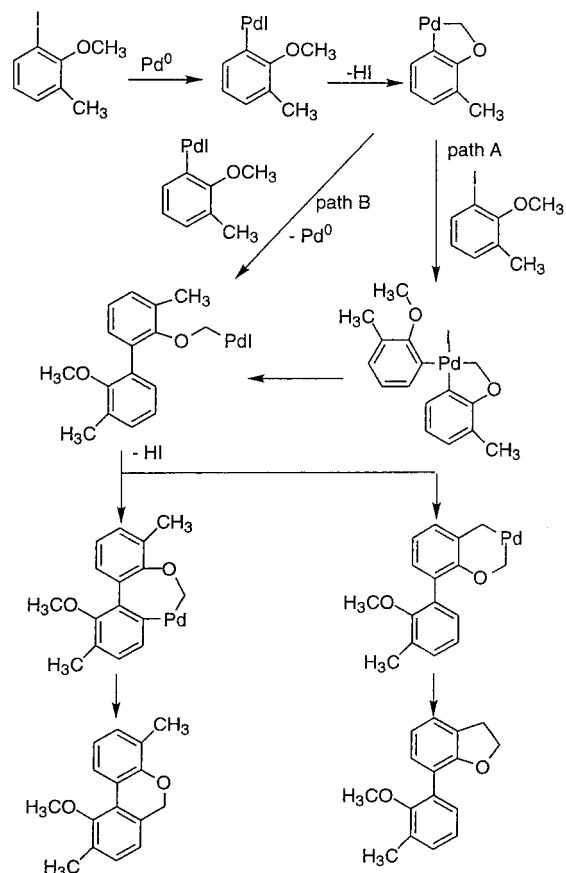
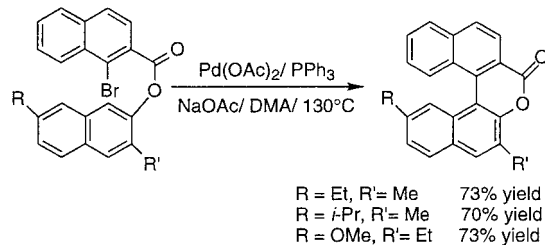
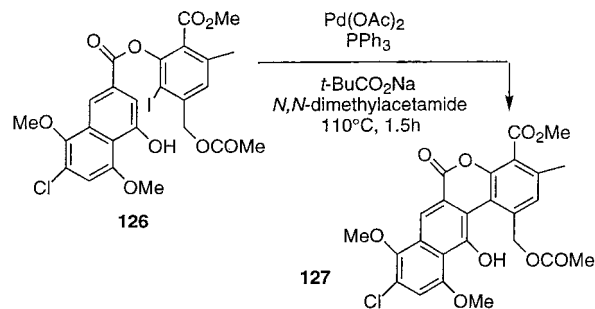
Dyker<sup>641,642</sup> reported a palladium-catalyzed C–H activation of methoxy groups of substituted *ortho*-iodoanisoles. Pyran or furan derivatives were obtained depending on the reactivity of additional substituents (Scheme 354).

**Scheme 354**

Concerning the reaction mechanism, the authors developed a mechanistic rationale for the regiochemistry of the studied domino-coupling process. This mechanism involved catalytic  $\text{Pd}^{\text{II}}\text{--Pd}^{\text{IV}}$  cycles and  $\text{Pd}^0\text{--Pd}^{\text{II}}$  cycles (Scheme 355). The main step was suggested to be the five-membered ring compound involving an intramolecular C–H activation by the neighboring methoxy group.

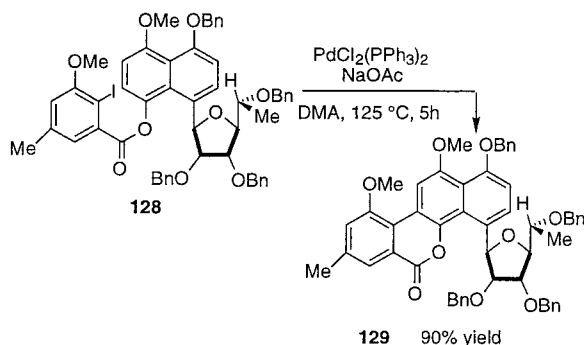
Bringmann et al.<sup>643,644</sup> synthesized various biaryl lactones in a palladium-catalyzed reaction (Scheme 356). The variation of the *ortho*-substituent R allowed a stepwise enhancement of the steric hindrance at the biaryl axis.

Suzuki et al.<sup>645</sup> reported a total synthesis of pradimicinol, a compound that has biological activities such

**Scheme 355****Scheme 356****Scheme 357**

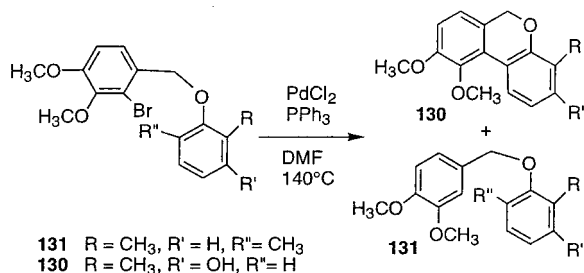
as anti-HIV (Scheme 357). The Pd-catalyzed internal cyclization of ester **126** proceeded smoothly and regioselectively in the presence of sodium pivaloate to give the tetracycle **127**.

The authors<sup>646</sup> already used the Heck-type reaction in the total synthesis of the C-glycoside antibiotic gilvocarcin. For example, C–C bond formation with iodide **128** gave the tetracycle **129** in a 90% yield (Scheme 358). The coupling reaction with triflate was

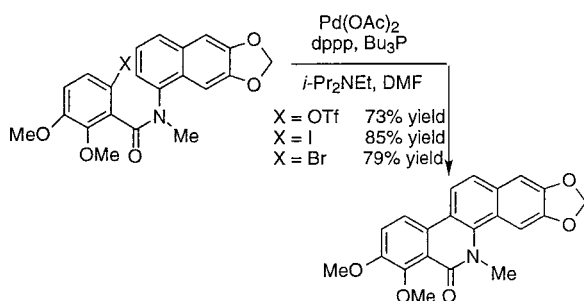
**Scheme 358**

also reported using sodium pivalate in place of sodium acetate.

Schäfer et al.<sup>647</sup> reported a regioselective C-4a–C-2' coupling of 2'-bromoeticulines by means of a palladium(0)-catalyzed reaction. The influence of substituents was studied. The phenolic function of **130** enables a successful cyclization. However, in **131** where the coupling site was substituted by a methyl group, the reduced compound was the only observed product (Scheme 359).

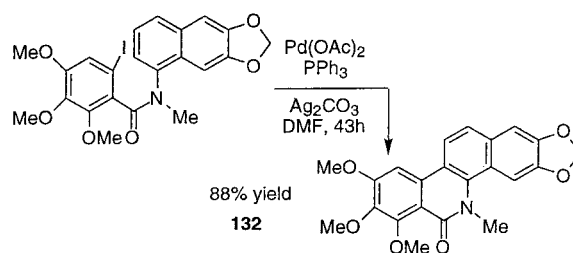
**Scheme 359**

In view of their potent pharmacological and biological activities, Harayama et al.<sup>648–650</sup> developed the synthesis of chelerythrine and nitidine **132** via the aryl–aryl cyclization reaction. The authors investigated a biaryl-cyclization reaction of amides possessing a triflate instead of a halogen as a leaving group. A novel palladium reagent system was prepared from Pd(OAc)<sub>2</sub>, dppp, and Bu<sub>3</sub>P (Scheme 360). The ef-

**Scheme 360**

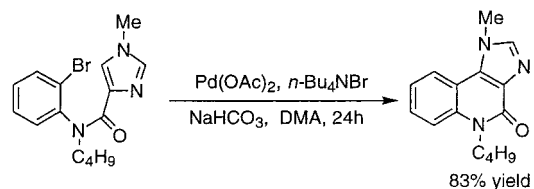
iciency of this method has been shown not only for the triflate group but also for the halogen group.

Recently, Harayama et al.<sup>651</sup> demonstrated the efficiency of the palladium-assisted cyclization reaction for the synthesis of not only the chelerythrine

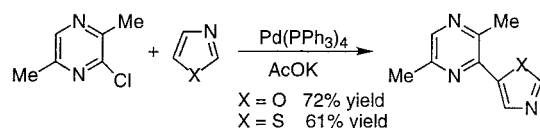
**Scheme 361**

class but also the nitidine class of alkaloid. High yields of oxynitidine have been observed using an equimolar amount of Pd(OAc)<sub>2</sub> (Scheme 361).

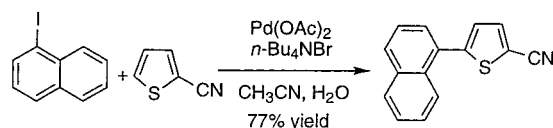
A tricyclic heterocycle 5-butyl-1-methyl-1*H*-imidazo(4,5-*c*)quinolin-4(5*H*)-one was synthesized in 60% yield. The yield of the cyclization was improved by changing base, additive, and reaction temperature<sup>652</sup> (Scheme 362).

**Scheme 362**

Ohta et al.<sup>653</sup> reported the palladium-catalyzed cross-coupling reactions of chloropyrazines with aromatic heterocycles such as furan, thiophene, pyrrole, *N*-substituted pyrroles, benzo(*b*)thiophenes, oxazole, thiazole, *N*-methylimidazoles, benzo(*b*)oxazole, and benzo(*b*)thiazole. Cross-coupling products were obtained in moderate to good yields. An excess of aromatic heterocycles was used in the presence of tetrakis(triphenylphosphine)palladium at 150 °C in a sealed tube, in consideration of the volatility of furan and thiophene (Scheme 363).

**Scheme 363**

Lemaire et al.<sup>654–656</sup> used substituted thiophene as a substrate. The arylation of a thiophenes substituted in position 2 or 3 was accomplished in the presence of a combination of tetra-*n*-butylammonium bromide, potassium carbonate, and catalytic amounts of palladium (Scheme 364). The authors demonstrated that

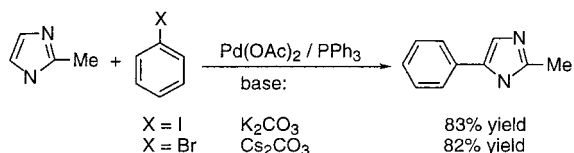
**Scheme 364**

the nature and position of the substituent influence the cross coupling. The reaction conditions were improved in order to favor a thiophene arylation rather than a symmetrical coupling product. Indeed, an overstoichiometric amount of tetrabutylammo-

nium bromide or a stoichiometric amount of tetraacetylammonium bromide with potassium carbonate as a base inhibits the competitive formation of biaryl.

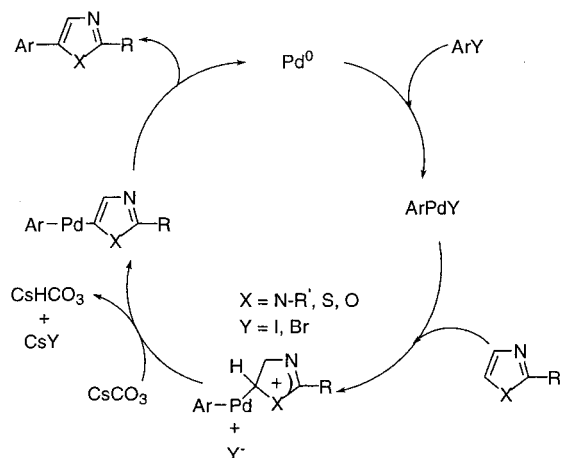
Miura et al.<sup>657</sup> reported the arylation of azole compounds with aryl halides in a palladium-catalyzed reaction. In the presence of Pd(OAc)<sub>2</sub> as a catalyst and PPh<sub>3</sub> and CsCO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub> as a base, the coupling products 5-aryl-azoles could be selectively obtained in good yields (Scheme 365).

Scheme 365



The authors found that the reactions of thiazoles as well as those of thiophene derivatives were promoted by using a stoichiometric amount of CuI. On the other hand, CuI may mediate the arylation of 2-unsubstituted azole to some extent. Concerning the mechanism, the authors suggested an electrophilic attack by addition of aryl halides to the palladium(0) species generated from aryl palladium(II). The deprotonation led to the aryl(heteroaryl)palladium(II) intermediate. A reductive elimination gave the corresponding arylation product. The authors ruled out a *syn*-elimination of HPdY after the reduction (Scheme 366).

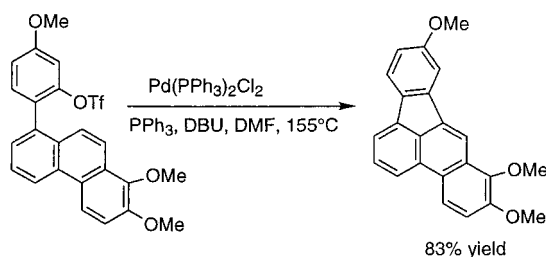
Scheme 366



This type of reaction has not been limited to activated substrates. Rice et al.<sup>658–660</sup> developed a palladium-catalyzed triflate-arene cyclization procedure allowing the synthesis of benzo[*b*]fluoranthene (BbF) in a regiocontrolled manner. The key step is an intramolecular Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>-catalyzed coupling of aryl triflate with an aromatic carbon. Contrary to their previous results, the addition of LiCl seemed to decrease the yield (Scheme 367).

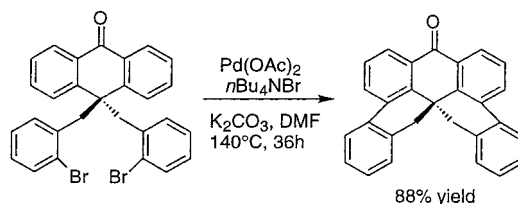
The synthesis of spiro-polycyclic aromatic hydrocarbons and planar-polycyclic aromatic hydrocarbons has also been performed by a palladium-catalyzed intramolecular arylation.<sup>661</sup> The presence of electron-withdrawing groups facilitated the coupling reaction.

Scheme 367



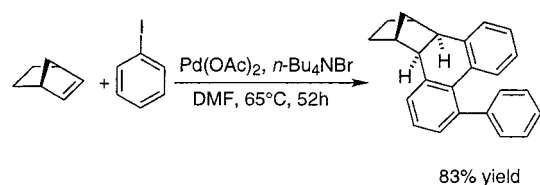
To accelerate the coupling reaction in the case of electron-donating groups, the addition of LiI was shown to give the best results (Scheme 368).

Scheme 368



Meijere et al.<sup>662,663</sup> reported the palladium-catalyzed domino-coupling reactions of aryl halides with itself and norbornene derivatives. In the presence of Pd(OAc)<sub>2</sub> as a catalyst, norbornene, dicyclopentadiene, norborneol, and norbornone reacted with unsubstituted as well as substituted bromo- and iodobenzene, 2-bromothiophene, 3-iodo-6-methylpyridine, and 4-iodopyridine to give the coupling products in moderate to good yields. The products were then transformed into a variety of cyclopentadiene-annulated polycyclic aromatic compounds by photocyclization/dehydrogenation and/or flash vacuum pyrolysis (Scheme 369).

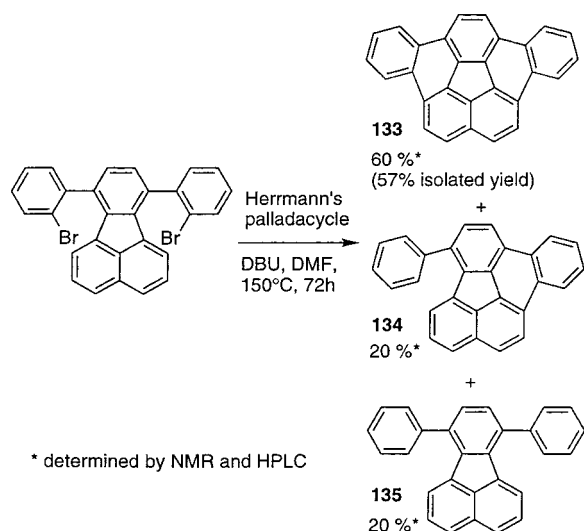
Scheme 369



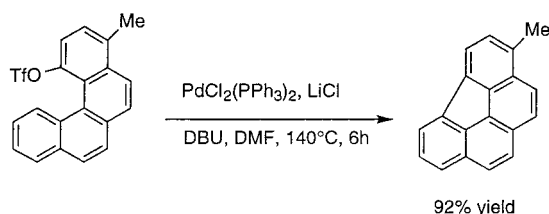
Recently, Scott et al.<sup>664</sup> prepared dibenzo(*a,g*)-corannulene by intramolecular palladium-catalyzed arylation reactions. 7,10-Di(2-bromophenyl)fluoranthene was transformed into the C<sub>28</sub>H<sub>14</sub> bowl-shaped fullerene fragment dibenzo(*a,g*)corannulene **133**. The best results were obtained using Herrmann's palladacycle. The reductive debromination of the 2-bromophenyl groups gave either **134** or **135** (Scheme 370).

Shevlin et al.<sup>665</sup> reported an efficient synthesis of benzo(*g,h,i*)fluoranthenes by palladium-mediated intramolecular coupling using bromides, triflates, and chlorides as leaving groups. Excellent yields were obtained by using bis(triphenylphosphine)palladium(II) chloride (Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>) in DMF or DMA (Scheme 371).

Scheme 370

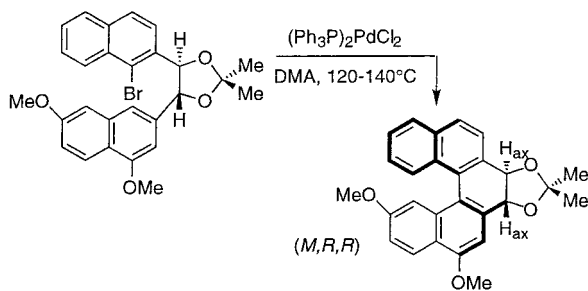


Scheme 371



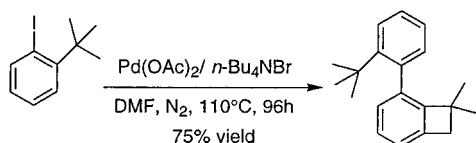
Bringmann et al.<sup>666</sup> reported a new approach for the atropenantioselective synthesis of biaryls (Scheme 372).

Scheme 372



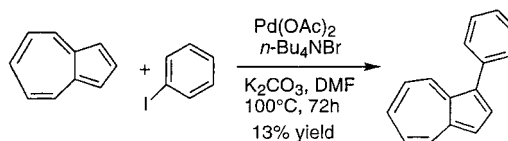
Dyker et al. also reported a palladium-catalyzed C–H activation of *tert*-butyl groups which allowed the synthesis of substituted 1,2-dihydrocyclobutabenzene and indene derivatives<sup>667</sup> (Scheme 373).

Scheme 373



Very recently, the same authors<sup>668</sup> reported the first intermolecular palladium-catalyzed arylation of unfunctionalized aromatic hydrocarbons (Scheme 374). The arylation of azulene by iodobenzene and by 4-nitro-chlorobenzene gave the coupling products in moderate yields.

Scheme 374



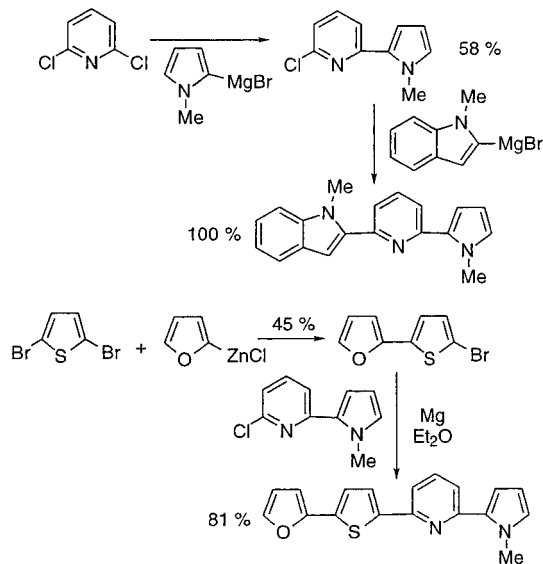
## 16. Application of Palladium-Catalyzed Aryl Coupling to the Synthesis of Conjugated Polymers

A review concerning the preparation of oligomers with electrical and/or photoelectrical properties was published in 1992.<sup>669</sup> Since this date, numerous applications have been published regarding aryl–aryl bond formation catalyzed by palladium. In addition, several new types of materials (and properties) have been described.

### A. Polymerizations of Aromatic Substrates Involving Magnesium Derivatives

Kumada et al.<sup>670</sup> reported in 1984 the preparation of various mixed heteroarene oligomers from heteroarene dihalides via stepwise coupling with heteroaryl Grignard reagents catalyzed by a palladium–phosphine complex (PdCl<sub>2</sub>–dppb). Interestingly, they demonstrated the possibility of preparing a trimer consisting of three different nitrogen heteroarenes (Scheme 375) by introducing, in successive steps,

Scheme 375

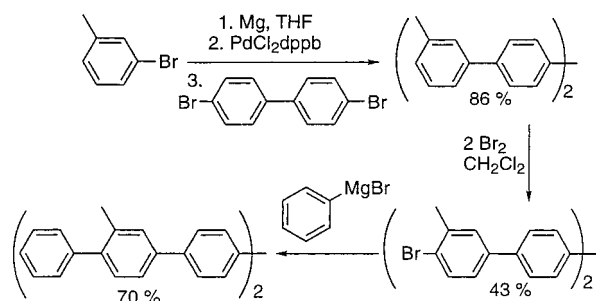


different types of heteroaryl groups into a symmetrical heteroarene dihalide.

By this method, they were able to produce mixed heteroarene oligomers with control of the number, kind, and position of linked heteroarenes.

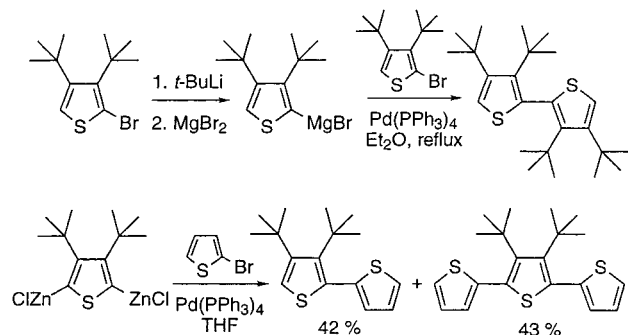
This methodology was used by Kauffman<sup>671</sup> to prepare 2',3'''-dimethyl-*p*-sexiphenyl, a useful scintillation fluor with high stability and fast response time. This three-step synthesis (Scheme 376) allows the preparation of the desired compound in a 26% overall yield. The catalyst used is PdCl<sub>2</sub>–dppb (1 mol %).



**Scheme 376**

Following a similar methodology, Mikami et al.<sup>672</sup> prepared a series of oligo-*p*-phenylene to be anchored on porphyrins. They synthesized a terphenyl oligomer by a double Grignard cross coupling between an arylmagnesium bromide and 4,4'-dibromobiphenyl. The corresponding tetramer was, however, obtained through a Suzuki-coupling reaction with an aryl boronic acid ester in an overall yield of 16%.

Nakayama et al.<sup>673</sup> were interested in the synthesis of highly congested oligothiophenes for the detailed study of the rotational isomerization between individual thiophene rings in thiophene oligomers. They thus prepared bi- and terthiophenes carrying two *tert*-butyl groups in adjacent positions. The Grignard cross coupling of tetra-*tert*-butyl-2,2'-bithiophene using a nickel catalyst remained unsuccessful. This is probably due to steric congestions. This product could however be obtained by the Kumada coupling depicted in Scheme 377, catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub>, in 33% yield.

**Scheme 377**

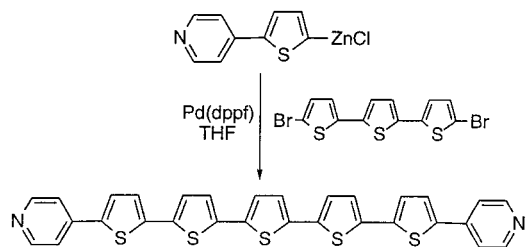
yield.

Attempts to yield a terthiophene by this procedure failed. Nevertheless, the authors were able to obtain a mixture of bi- and terthiophene by preparing the corresponding zinc derivative and reacting it through a palladium-catalyzed coupling with 2-bromothiophene.

**B. Polymerizations of Aromatic Substrates Involving Zinc Derivatives**

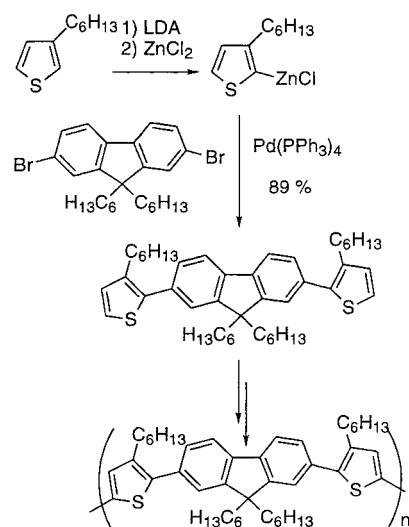
The analogous reaction, involving the use of zinc as an activating metal instead of magnesium, has been reported by Albers et al.<sup>674</sup> for the preparation of di(4-pyridyl)thiophene oligomers as models for transmembrane molecular conductors.

No indication of yields is given. It is however noted that large amounts of the product of monocoupling are isolated. The authors report furthermore that the

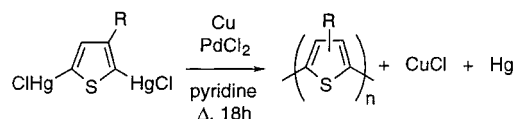
**Scheme 378**

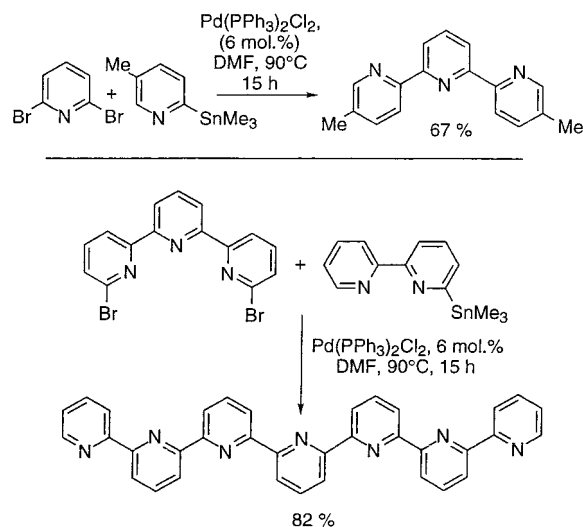
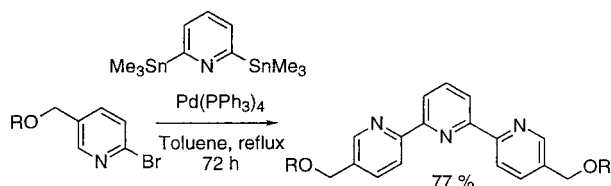
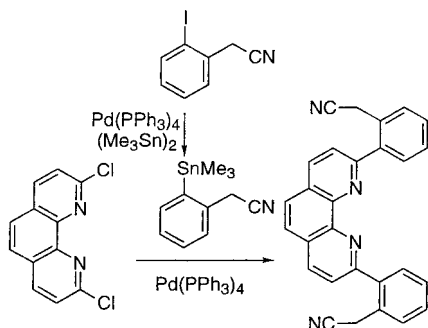
route via the Grignard intermediate and the Ni(dppp) catalyst yields very minor amounts of the desired product in comparison with the product of homocoupling. The authors assume the difference in efficiency between both cross-coupling methods to be probably due to the formation of a zinc complex as the reaction product which propagates the reaction. Attempts to prepare longer oligomers failed, however, probably due to the low solubility of these compounds.

In general, palladium-catalyzed cross coupling of zinc derivatives is not efficient for polymerization but it can allow the preparation of various important oligomers. Recently, such syntheses of initial shorter oligomers have been described for cyclic oligophenylene<sup>675</sup> alkyl end-capped oligoheterocycles<sup>676</sup> and a green electroluminescent conjugated polymer: poly-[2,7-bis(4-hexylthienyl)-9,9-dihexylfluorene]<sup>677</sup> (Scheme 379).

**Scheme 379****C. Polymerizations of Aromatic Substrates Involving Mercury Derivatives**

Curtis<sup>678</sup> described the polymerization via the preparation of organomercurials. This synthesis is based on the coupling of 2,5-bis(chloromercurio)-3-alkylthiophenes in the presence of copper and catalytic quantities of PdCl<sub>2</sub> (Scheme 380).

**Scheme 380**

**Scheme 381****Scheme 382****Scheme 383**

Soluble random homopolymers were synthesized in good yield (65–80%) from these difunctional monomers, indicating that this coupling reaction showed very little steric discrimination, contrary to the preceding examples.

#### D. Oligo- and Polymerizations of Aromatic Substrates Using Organostannyl Derivatives

The Stille cross-coupling reaction has been used for the synthesis of several oligopyridines. These molecules were proven to be useful building blocks in metallosupramolecular chemistry. Cardenas and Sauvage<sup>679</sup> developed a direct synthesis of 2,6-oligopyridines by cross coupling of pyridyl stannanes with bromopyridines in the presence of  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ . Although the prepared compounds possessed coordinating ability, the authors did not observe any problems due to lack of compatibility of the substrates and products with the catalyst.

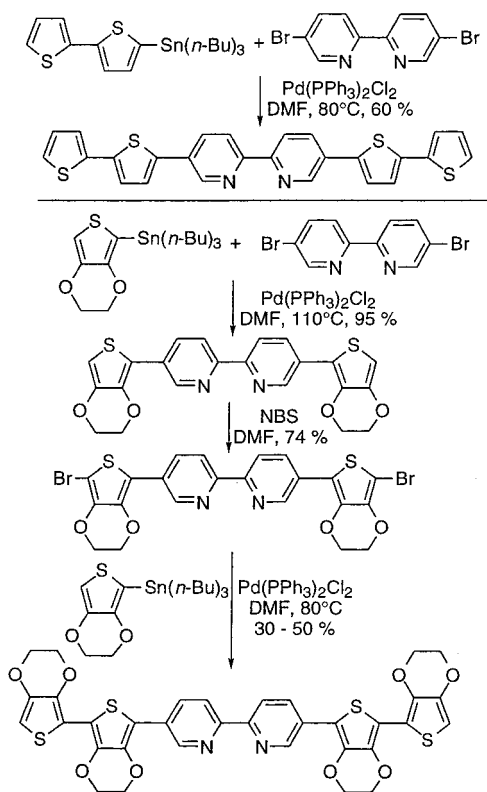
This extension of the Stille cross-coupling reaction allowed the preparation, for the first time, of unsubstituted septipyridine.

Following the same objectives, Schlüter et al.<sup>680</sup> prepared substituted terpyridines through palladium-catalyzed cross-coupling reactions. The couplings were performed under Stille conditions with yields between 30% and 70%. Similarly, Schubert et al.<sup>681</sup> prepared 2,6-bis(trimethyltin)pyridine as the main intermediate for the direct access to 5,5''-bifunctionalized terpyridines.

This strategy was also used for the synthesis of ligands imposing tetrahedral coordination: 1,10-phenanthroline-2,9-bis(phenyl-2-acetic acid) was prepared via palladium-catalyzed cross coupling of an aromatic halide and an *ortho*-substituted aryl stannane.<sup>682</sup>

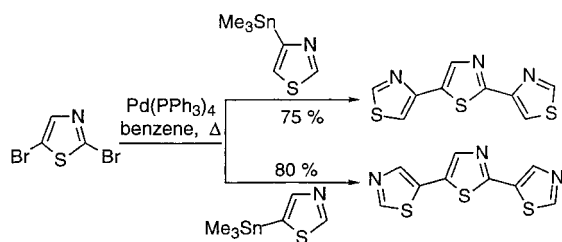
Zhu and Swager<sup>683</sup> also used the Stille coupling to prepare a polymerizable monomer, useful for both the synthesis of a polymerizable monomer and the synthesis of polymetallorotaxanes, by complexation with a macrocyclic phenanthroline.

The monomer containing the 3,4:3',4'-bis(ethylenedioxy)[2,2'-bithiophen]-5-yl (BEDOT) unit showed an especially high electron-rich character and was easily electropolymerized. The authors studied the electrochemical, conducting, and optical properties of these materials. The same team<sup>684</sup> investigated the similarly obtained bithienyl-bipyridine oligomers as ligands for Ru(II) derivatives that were further polymerized. They found these materials to display important electronic interactions between the metal complexes through the conjugated polymer backbone (Scheme 384).

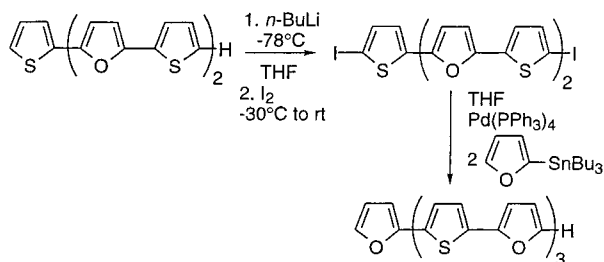
**Scheme 384**

Zotti and Berlin<sup>685</sup> similarly reported the synthesis of 5,5'-bis(3,4-(ethylenedioxy)thien-2-yl)-2,2'-bipyridine and its 4,4'-dimethyl and 4,4'-diheptyl homo-

## Scheme 385



## Scheme 386



logues. They studied their oxidative polymerization and characterized the resulting polymer films.

The synthesis of heteroarene oligomers has often been based on the palladium-mediated cross-coupling reaction. These oligomers constitute a class of heterocyclic compounds of increasing interest owing to their use as building blocks in synthesis and their biological properties. Dondoni<sup>686</sup> prepared thiazole oligomers this way by reacting bromothiazoles and stannylthiazoles.

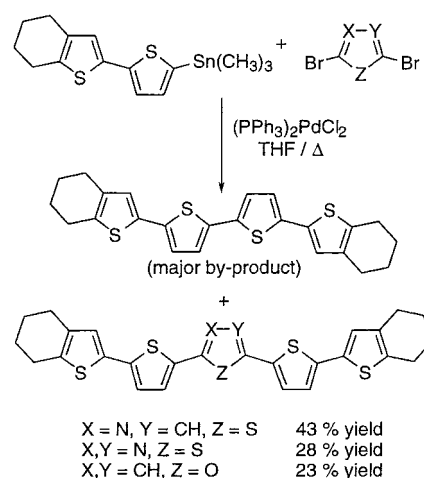
Hucke and Cava<sup>687</sup> were interested in the preparation of mixed thiophene/furan oligomers for their promising electrical, optical, and electrochemical properties, especially for field-effect transistors. Oligomers consisting of up to 11 rings were obtained via organometallic Stille coupling. In some cases, symmetrical coupling products were isolated in addition to cross-coupling products.

The yield of formation of this fairly soluble thiophene/furan oligomer with seven rings was not indicated in the publication. Bäuerle<sup>688</sup> described the synthesis and characterization of mixed oligoheterocycles based on end-capped oligothiophenes. The authors were interested in evaluating the influence of electronegative heteroatoms, such as oxygen and nitrogen, or the  $\pi$ -system and the optical and electrochemical properties. The synthesis of thiophene/thiazole, thiophene/1,3,4-thiadiazole, or thiophene/furan was achieved by a Stille-type palladium-catalyzed cross-coupling reaction of the corresponding 2,5-dibrominated heterocycle and a central stannylated bithiophene as depicted in Scheme 387.

In each case the homocoupling product was isolated as the main byproduct. The main difficulties in these syntheses lie in the low solubility of the products and hence in the fastidious purifications.

Various oligomers were further synthesized following this methodology: Tamao<sup>689</sup> prepared silole (silacyclopentadiene)–pyrrole co-oligomers (containing up to nine rings) as a promising combination for the development of novel low-band-gap  $\pi$ -conjugated polymers. The monomer unit, pyrrole-silole-pyrrole three-ring compounds, was obtained by palladium-

## Scheme 387



catalyzed cross coupling of dihalogenosiloles with 2-stannylpyrrole.

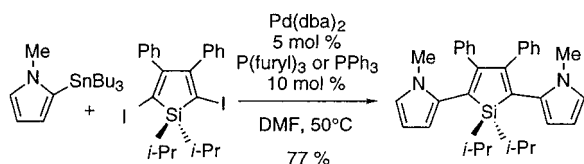
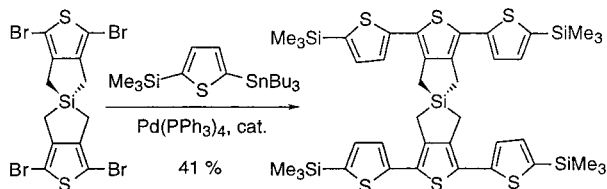
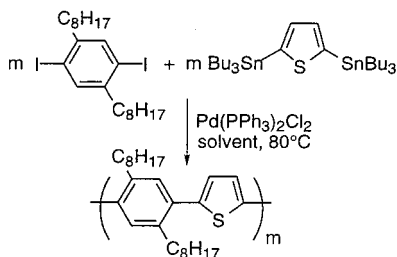
A convergent synthetic route to orthogonally fused conjugated organic oligomers has been described by Tour et al.<sup>690</sup> extensively using organopalladium-catalyzed procedures. The central monomer is based on a spirobithiophene moiety with a central silicon atom leading to a system with a potentially conducting chain fused perpendicularly to a second potentially conducting chain via a  $\sigma$ -bonded network.

Using methylated thiophene monomers to ensure good solubility of the final compound, they successfully performed preparations of longer oligomers (approximately 34 Å).

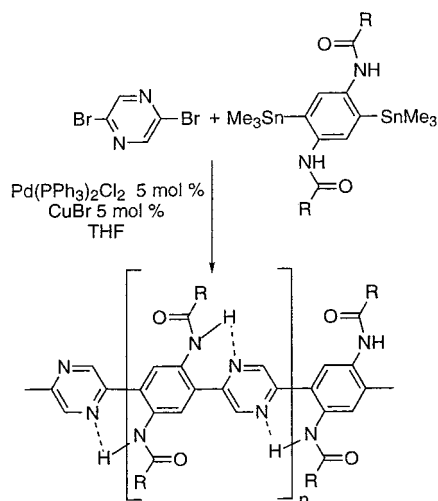
Yu et al.<sup>691</sup> investigated the possibility of performing Stille-coupling reactions in the preparation of functional polymers. This reaction can indeed be performed under mild conditions and generally produces high yields. The authors explored the influence of several factors on the reaction course (and especially the molecular weight of the polymers): the catalyst composition and concentration, different solvents and ligands, and structures of monomers. Generally, THF and DMF were appropriate solvents to be used for their ability to keep the macromolecules in solution and to stabilize the Pd(0) catalyst. Furthermore, a combination of an electron-rich distannyl monomer and an electron-deficient dihalide (or ditriflate) monomer forms polymer with high molecular weights. Following these principles, the authors prepared various types of conjugated polymers with different properties and applications (liquid crystalline conjugated polymers and conjugated photorefractive polymers) to demonstrate the versatility of the Stille reaction.

The authors were furthermore able, using these optimized Stille reaction conditions, to synthesize metalloporphyrin-containing polymers. Thus, this coupling reaction is compatible with the synthesis of metal-containing polymers.

Meijer et al.<sup>692</sup> applied this methodology to the preparation of  $\pi$ -conjugated oligomers with a ladder-like structure. This self-assembly into ladders was due to strong intramolecular hydrogen bonding between neighboring rings. The authors thus aimed to synthesize substituted soluble polymers in which the

**Scheme 388****Scheme 389****Scheme 390**

side chains do not force consecutive aromatic units away from coplanarity. They were further interested in the use of secondary interactions in supramolecular chemistry. Using the Stille procedure, they thus prepared the polymer depicted in Scheme 391 in 62% yield.

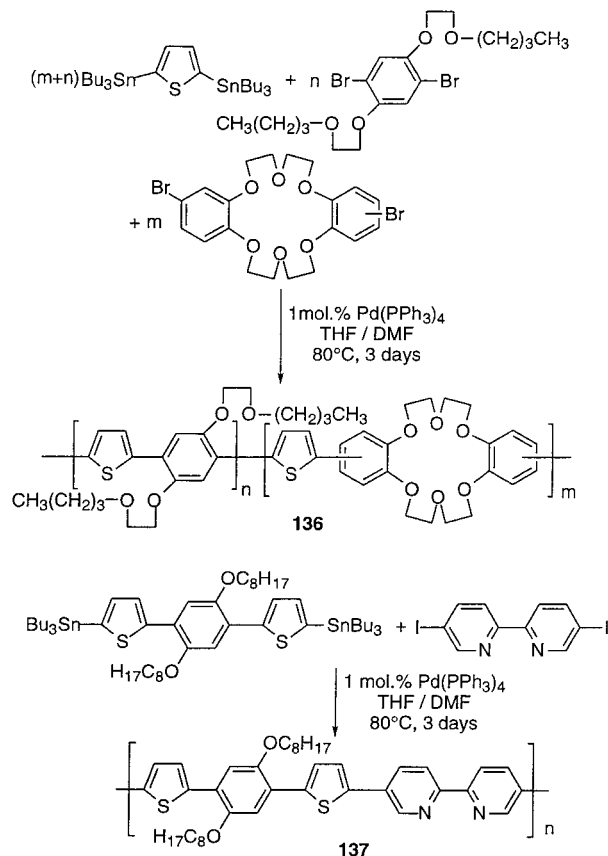
**Scheme 391**

Addition of 5 mol % of  $\text{CuBr}$  was necessary for its accelerating effect and to guarantee high yields and high selectivities. By cyclic voltammetry measurements, the authors could demonstrate the extended  $\pi$ -conjugation of the self-assembled ladder system.

Moreau et al.<sup>693</sup> prepared other copolymers by this method that were functionalized by chelating subunits.

NMR studies indicated that the two dibromo compounds exhibit a similar reactivity toward the tin

reagent; their incorporation to the polymer chain **136** follows the initial concentration ratio of the two monomers. The average degree of polymerization was estimated at between 12 and 26. However, no ionic properties were observed in the presence of alkaline metals. Reversible ionochromic responses in the presence of transition-metal ions were found when complexation was performed via bipyridine units (structure **137**, in Scheme 392). Thus, polymer **137**,

**Scheme 392**

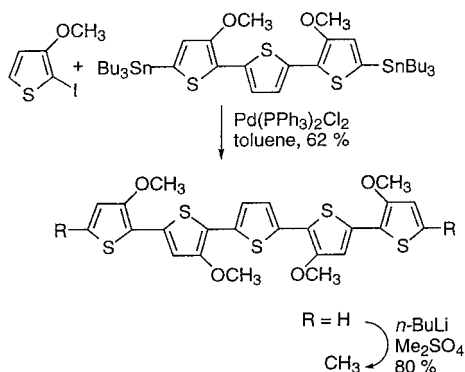
a good candidate for the elaboration of ion sensory materials, was synthesized from the palladium-catalyzed condensation between 5,5'-diiodo-2,2'-bipyridine and the bis(tributylstannyl)thiophene-containing trimer. Its average degree of polymerization was 5 under those conditions.

The Stille reaction was of course widely used for the preparation of thiophene oligomers and homopolymers. In particular, Miller and Yu<sup>694</sup> reported this method to be efficient for the preparation of structurally defined end-capped methoxyoligothiophenes for modeling the structure of polythiophene by observing stable oligomer cation radicals. An example of oligothiophene obtained by Stille coupling is given in Scheme 393.

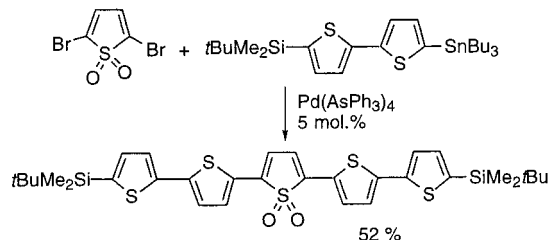
In these cases, the Kumada cross coupling with  $\text{Ni}(0)$  of thienyl Grignard reagents and bromothiophenes or Suzuki coupling using organoboranes remained unsuccessful.

Barbarella et al.<sup>695</sup> tested this procedure to prepare oligothiophenes *S,S*-dioxides as useful synthetic intermediates for the preparation of various types of organic compounds since they may undergo Diels–

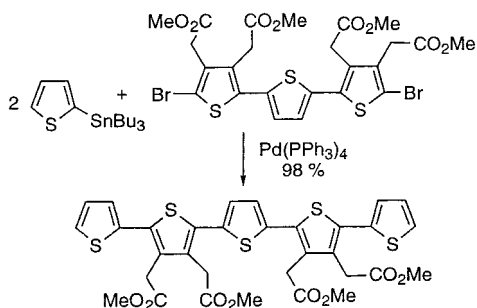


**Scheme 393**

Alder or other diene reactions. The authors reported the facile coupling of brominated thiophene *S,S*-dioxides with thienyl stannanes in the presence of a Pd(0) catalyst. They chose  $\text{Pd(AsPh}_3)_4$ , generated in situ as the catalyst, reported to lead to the best reaction yields in the synthesis of oligothiophenes (52% in the synthesis depicted in Scheme 394).

**Scheme 394**

This Stille coupling has been extended for the preparation of numerous oligothiophenes bearing various functionalities. For example, Gabriele and Salerno<sup>696</sup> described the synthesis of pentathiophene derivatives in very high yield (Scheme 395) in which

**Scheme 395**

the thiophene rings are alternating 3,4-substituted with (methoxycarbonyl)methyl chains.

Fréchet used this procedure successfully to prepare a new class of optoelectronic materials based on hybrid structures containing oligothiophenes and dendrimers.<sup>697</sup> The group prepared unsymmetrically substituted oligothiophenes with a terminal carboxylate functionality to allow the simple attachment of dendritic blocks and an unsubstituted thiophene end piece.<sup>698</sup>

The heptadecamer obtained here is one of the longest oligothiophenes yet reported, with a very attractive overall yield of 47% from the dimer. This

oligomer is however not soluble in common organic solvents, but dilute solutions can be prepared in hot carbon disulfide. The monodisperse dendrimer-terminated undecamer is highly conjugated and soluble in common organic solvents and presents interesting properties for the design of light-emitting devices or field-effect transistors.<sup>699</sup>

The Stille-coupling reaction has been further used as a powerful synthetic tool for the regioregular homopolymerization of functionalized thiophene units. McCullough<sup>700</sup> was interested in preparing regioregular, water-soluble polythiophenes that were able to generate a self-assembled conducting polymer aggregate via H-bond stabilization. The thus obtained materials evidenced high electrical conductivities and very small band gaps. The regioregular oxazoline–polythiophene shown in Scheme 397 was prepared in high yields by using a CuO-modified Stille homo-coupling of a bifunctionalized oxazoline–thiophene monomer. NMR analyses of the polymer salt indicated a complete regioregularity with nearly 100% head-to-tail couplings.

Iraqi<sup>701</sup> studied in detail the Stille cross-coupling reaction as an alternative synthetic route to regioregular head-to-tail poly(3-alkylthiophenes) by using 2-iodo-3-alkyl-5-tri-*n*-butylstannyl-thiophene derivatives as kinetic, air- and moisture-stable monomers (Scheme 398).

According to the solvent used for the polymerization step (THF, 1,2-dichloroethane, or toluene), the authors were able to obtain materials with a high degree of polymerization (up to 97). Careful treatment of polymers obtained by the reaction in toluene allowed the separation of materials with preservation of both iodo- and tri-*n*-butyltin end groups. The authors were able to treat polymers with a low degree of polymerization (around 14) with catalytic amounts of  $\text{Pd(PPh}_3)_4$  in refluxing toluene to yield polymers with a higher degree of polymerization (around 28). This preliminary experiment opens the possibility of preparing block copolymers with different substituents on alternating blocks by using such short telechelic polymer chains.

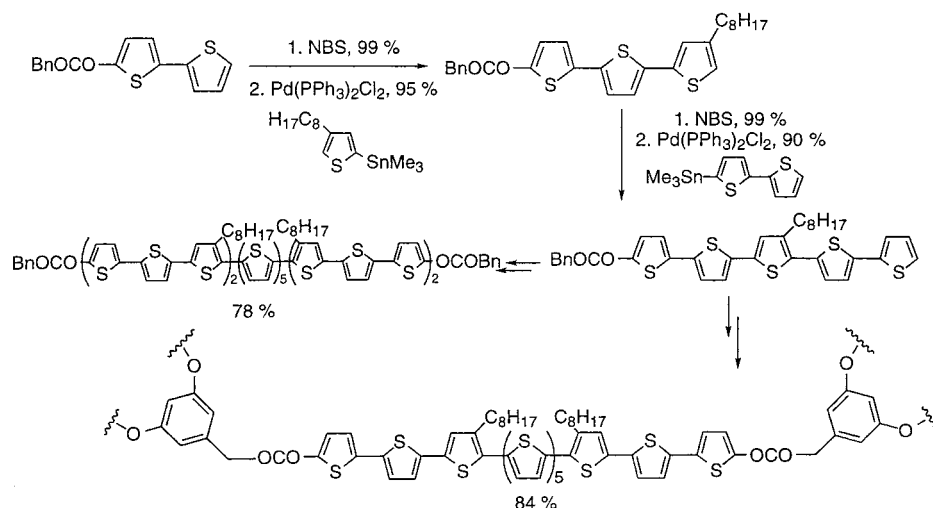
Lère-Porte et al.<sup>702,703</sup> used the same cross-coupling reaction for the preparation of regioregular poly(alkylbithiophenes).

They obtained polymers with a low dispersity (around 1.2) and an average degree of polymerization corresponding to 120 repeated units per chain. Interestingly, the authors noticed, by UV–vis experiments, that the decrease in steric hindrance by reducing the number of alkyl substituents along the chain (compared to classical poly(alkylthiophenes)) resulted in a better planar arrangement of the conjugated segments.

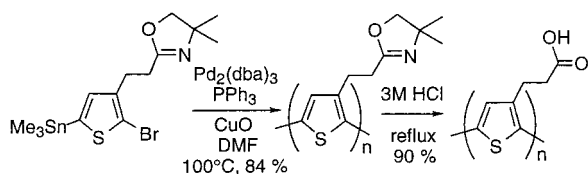
*E. Suzuki Aryl–Aryl Cross Coupling Applied for Oligo- or Polymerization*

The Suzuki polycondensation has been intensively developed for the synthesis of aryl oligomers, polyarylenes, and related polymers. Indeed, this procedure allows the preparation of regiospecific polymers with high molecular weights and further shows a high compatibility with various functional groups.

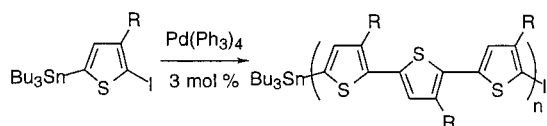
## Scheme 396



## Scheme 397



## Scheme 398

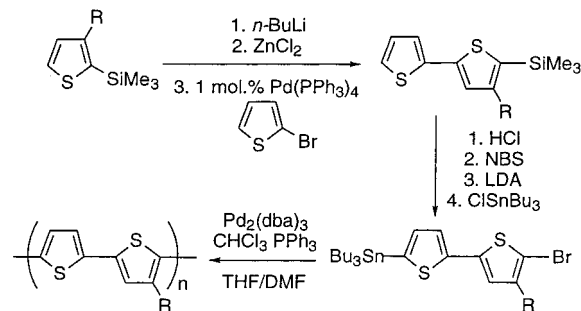


The Pd-catalyzed coupling of polyhalo-substituted aromatic compounds with aromatic boronic acids has been widely used for the preparation of functionalized oligomers. Gronowitz<sup>704</sup> was interested in the preparation of terheterocyclic compounds for application in many biologically active substances. Such compounds were usually synthesized via Kumada–Corriu cross coupling by Ni(0) catalysis. This method was however limited to substrates whose functional groups do not react with the organometallic reagent and often suffered from the unavoidable formation of symmetrical byproducts. Gronowitz thus described the preparation of various heterocyclic compounds containing thiophene, furan, selenophene, pyridine, and thiazole rings by the Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed coupling of dihalo-substituted heterocyclic compounds with heterocyclic boronic acids, using sodium bicarbonate as the base and a 1,2-dimethoxyethane/water mixture as the solvent.<sup>705</sup> Some representative examples are shown in Scheme 400.

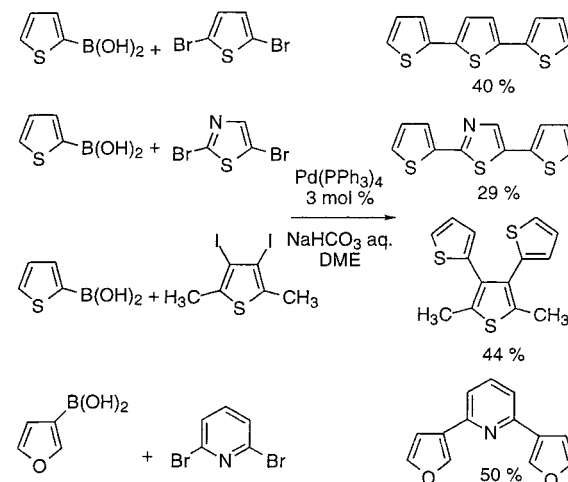
The repetitive use of the Suzuki coupling was described by Bidan et al.<sup>706</sup> for the stepwise synthesis of a series of head-to-tail alkyl-substituted oligothiophenes (Scheme 401).

In their iterative synthesis, the authors chose to introduce a chloride atom as the blocking group to protect one of the two reactive  $\alpha$ -positions to the sulfur throughout the entire synthesis. Since heteroaryl chlorides were unreactive toward boronic acids, when using Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst, a regi-

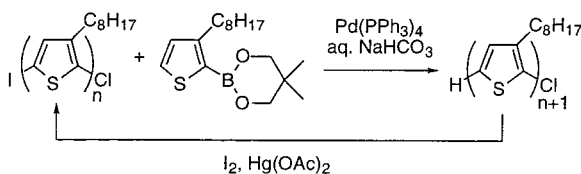
## Scheme 399



## Scheme 400

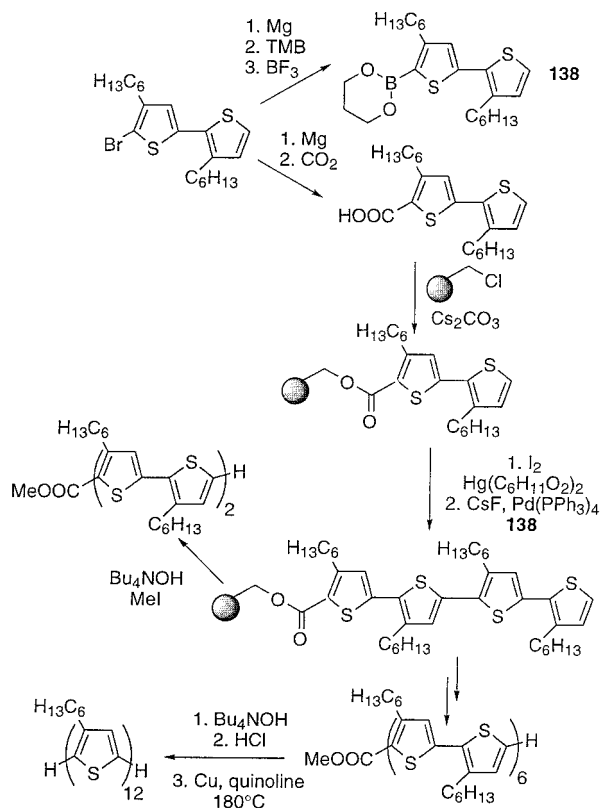


## Scheme 401



oselective synthesis became possible. Oligomers, up to the hexamer, were obtained by this method with yields varying around 80%. Free-end oligomers were obtained by reductive dehalogenation using either H<sub>2</sub> over Pd/C or tributyltin hydride in the presence of azobisisobutyronitrile. However, this method suffered

## Scheme 402



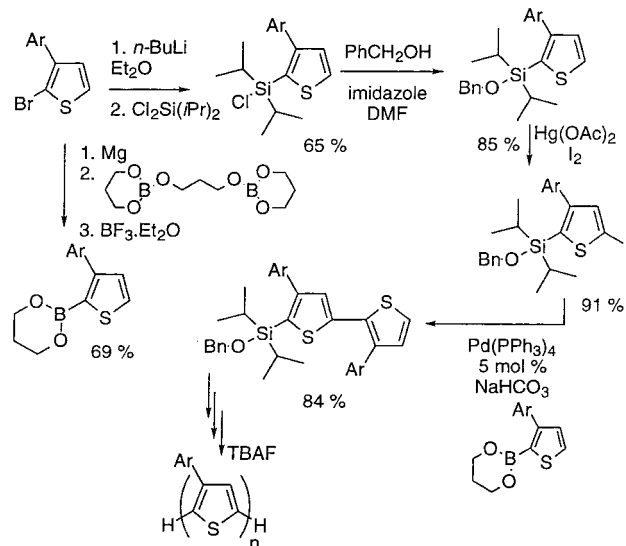
from the formation, albeit in low yield, of homocoupling products, in particular for longer oligomers. This complicated the purification processes. To overcome these problems, Bäuerle et al.<sup>707</sup> developed the solid-phase synthesis of isomerically pure head-to-tail oligo(3-hexylthiophene)s using sequences of iodination and Suzuki cross-coupling reactions.

5-Bromo-3',4'-dihexyl-2,2'-bithiophene was the key monomer for this synthesis since it could be converted into both the boronic ester building block and the corresponding bithiophene carboxylic acid which is the anchoring group to the solid support (a chloromethylated polystyrene resin). In an iterative process consisting of halogenation and subsequent Suzuki cross coupling, oligomers were built up and cleaved off the resin. The tetramer was obtained in a 93% yield over 4 steps, the octamer in 54% over 8 steps, and the dodecamer in 15% over 12 steps. Simple resin washings facilitated the purification processes, and byproducts resulting from homocoupling were nearly suppressed thanks to this method.

Bäuerle also proposed another strategy to prepare regioregular head-to-tail-coupled oligo(3-arylthiophene)s by utilizing a traceless silyl linker in solution-phase synthesis and on solid support.<sup>708</sup>

Terminal diisopropylsilyl groups were fixed to 3-arylthiophenes as traceless, stable, broadly compatible resin linkers. Benzyl alcohol was chosen to mimic the anchoring group of the polystyrene matrix. The stepwise activation–elongation sequence shown in Scheme 403 involving a palladium-catalyzed cross-coupling reaction led to regioregular oligomers with high yields. This synthesis was successfully transferred onto solid support using commercially available hydroxymethyl-substituted polystyrene, instead

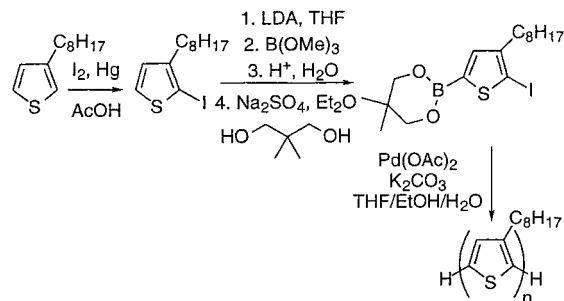
## Scheme 403



of benzyl alcohol. Iodination was however performed via an *ortho*-lithiation step. Here indeed, the mercuration/halodemercuration procedure led to significant halodesilylation. Removal of the conjugated oligomers from solid support was successfully achieved by TBAF treatment.

The Suzuki-coupling reaction has since been widely used for the preparation of polymers. For example, and following the procedure they described for the preparation of oligomers, Guillerez and Bidan prepared a polymerizable precursor to obtain regioregular poly(3-octylthiophene).<sup>709</sup> The monomer, bearing both an iodo- and a boronic-ester derivative in the 2- and 5-positions, respectively, was obtained in two steps from 3-octylthiophene. The polymerization reaction was then carried out by homocoupling this bifunctionalized monomer in a palladium-catalyzed Suzuki reaction using 1 mol % palladium acetate and 1.5 equiv of potassium carbonate as the base. Poly(3-octylthiophene), containing around 96% head-to-tail couplings (determined from NMR experiments) and with an average molecular weight of 27 000 g/mol, was obtained in a 55% yield after the removal of short-length oligomers (Scheme 404).

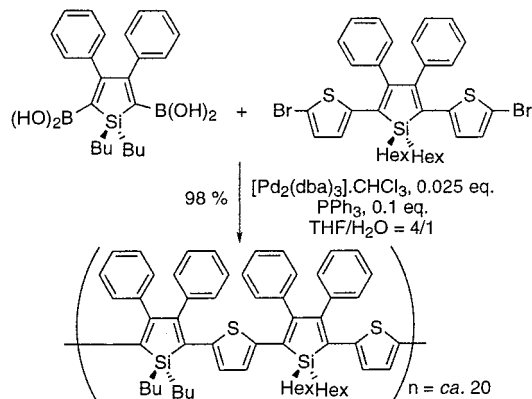
## Scheme 404



Tamao et al.<sup>710</sup> reported the preparation of silole–thiophene copolymers as interesting  $\pi$ -conjugated polymer targets for creating a narrow-band-gap material. The Suzuki coupling of the silole-2,5-diboronic acid with the 2,5-bis(5-bromo-2-thienyl)silole was carried out under basic conditions with the

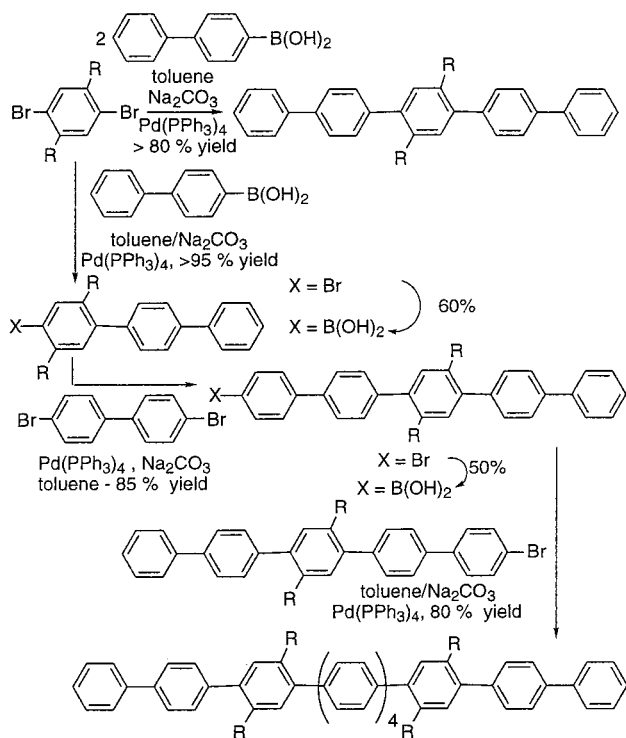
catalyst system:  $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3/4 \text{ PPh}_3$ . This produced the alternating copolymer in a 98% yield (Scheme 405).

Scheme 405



The Suzuki procedure has been applied to the preparation of oligo-*p*-phenyls. These derivatives are of great interest for chemists as model compounds for studying the spectroscopic and redox properties of polyaromatic systems. Functionalized oligo-*p*-phenyls have gained in importance with regard to many applications because of their solubility. Galda and Rehahn<sup>711</sup> published a high-yield palladium-catalyzed procedure for the preparation of constitutionally homogeneous *n*-alkyl-substituted oligo-*p*-phenyls. 2,5-Dialkyl-1,4-dibromobenzene derivatives were the central starting materials. They reacted in excellent yields with either 1 or 2 equiv of biphenylboronic acid in the heterogeneous system of toluene/ $\text{Na}_2\text{CO}_3$  (aq) with catalytic amounts of  $\text{Pd}(\text{PPh}_3)_4$  (Scheme 406). The authors prepared oligomers containing up to 15 phenyl rings with this regioselective method

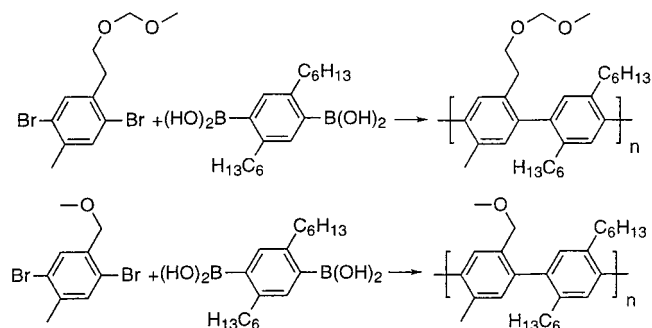
Scheme 406



without detecting, in appreciable amounts, any side reactions such as reductive dehalogenation or hydrolysis of boronic acid species. They assumed the synthesis to be affected in some cases only by the restricted solubility of certain intermediates or final products. Indeed, oligomers were found to be soluble in common organic solvents if two alkyl side chains were introduced for every five phenyl rings.

Schlüter et al.<sup>712</sup> studied in detail the mechanism of the Suzuki polycondensation and, in particular, described the quantification of the extent to which phosphorus is incorporated into polymer backbones. Indeed, most of the  $\text{Pd}(0)$  complexes used in this coupling reaction typically carry stabilizing aryl phosphine ligands. It has been suggested that a potential side reaction could arise from an aryl-aryl exchange between the palladium center and phosphine ligands in  $\text{Pd}(\text{II})$  complexes. Such scrambling of aryl groups could be disadvantageous if high-molecular-weight polymers are desired. The authors prepared polymers depicted in Scheme 407 by various

Scheme 407

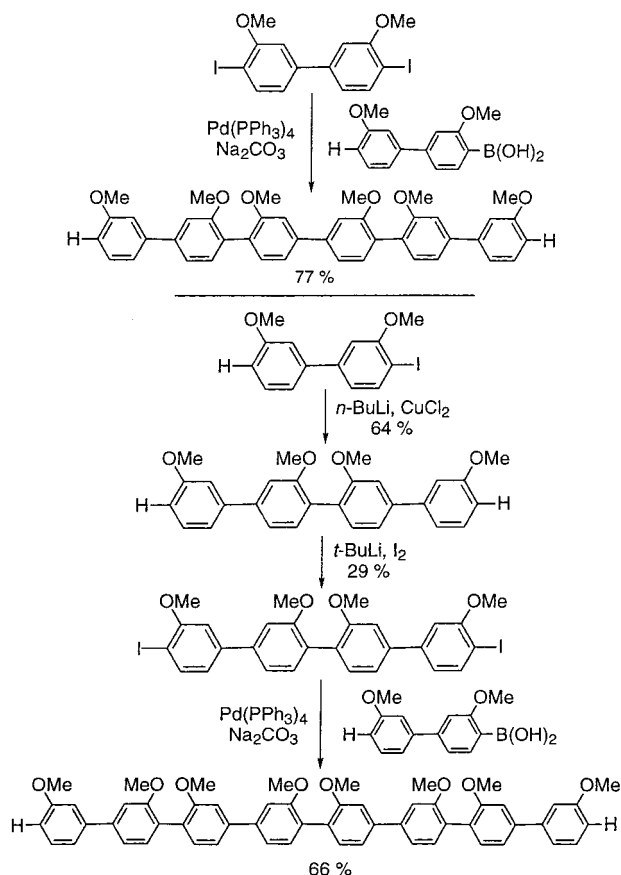


aryl-phosphine-containing catalysts and quantitatively evaluated the degree of P-incorporation by  $^{31}\text{P}$  NMR analyses. All the polymers thereby obtained contained phosphorus atoms, but the degree of incorporation was very low since one phosphorus was found to be present per 3–7 polymer chains (for the higher molecular-weight polymers). Most chains were in fact free of any phosphorus atoms.

Substituted oligo(*p*-phenylene)s have applications not only in the field of conducting polymers but also as artificial ion channels. Matile et al.<sup>713</sup> were interested in studying specific hydrophobic interactions which exist in nonpeptide natural products forming ion channels in biomembranes. They thus synthesized substituted oligo(*p*-phenylene)s carrying hydrophilic substituents, selected as model rigid-rod molecules. Their synthesis used an oxidative coupling with *n*-BuLi/ $\text{CuCl}_2$  to reach a tetramer (Scheme 408). The key step for the hexamer synthesis involves a Suzuki coupling (77%) between the boronic acid and the diiodo derivative. The regioselectively iodinated tetramer was elongated in an identical way to give the corresponding octamer with a 66% yield. These oligomers were evaluated as artificial ion channels that specifically recognize biomembranes by their thickness. The authors demonstrated that these molecules, especially the octamer, facilitated ion transport across lipid bilayers, although the mechanism of transport remains to be elucidated. This



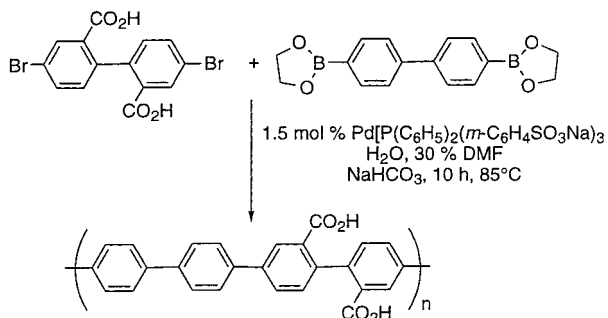
## Scheme 408



group recently studied the synthesis of octa(*p*-phenylenes)-bearing azacrowns as side chains.<sup>714</sup> They proved that high-yield side-chain construction before low-yield oligomerization resulted in a better global yield for the formation of the expected product, in comparison with the inverse sequence of reactions.

Novak et al.<sup>715</sup> reported the homogeneous synthesis, in water, of a structurally well-defined rigid-rod poly(*p*-phenylene) derivative using a water-soluble palladium(0) catalyst. The successful preparation of high-molecular-weight rigid-rod polymers via step-growth processes requires that the growing polymer chains remain soluble during all stages of the polymerization. The authors chose to synthesize two water-soluble monomers for the preparation of poly(*p*-quaterphenylene-2,2'-dicarboxylic acid) by adapting a Pd(0) cross coupling of boronic acids and aryl halides (Scheme 409). They prepared a water-soluble zerovalent palladium catalyst from PdCl<sub>2</sub> and mono-

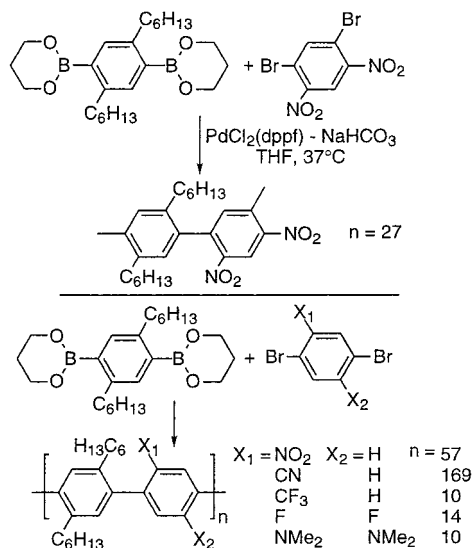
## Scheme 409



sulfonated triphenylphosphine. The resulting complex allowed the synthesis of the desired polymer, which was then analyzed by NMR, thermogravimetry, and IR. The molecular weight ( $M_w$ ) of this polymer was evaluated at around 50 000 g/mol by poly(acrylamide) gel electrophoresis.

Kowitz and Wegner<sup>716</sup> reported the synthesis of various functionalized poly- and oligophenylenes by the Suzuki cross coupling of functionalized aryl dibromides with the 1,3-propanediol diester of 2,5-dialkyl-1,4-phenylenediboronic acid. Some representative examples are shown in Scheme 410. In par-

## Scheme 410



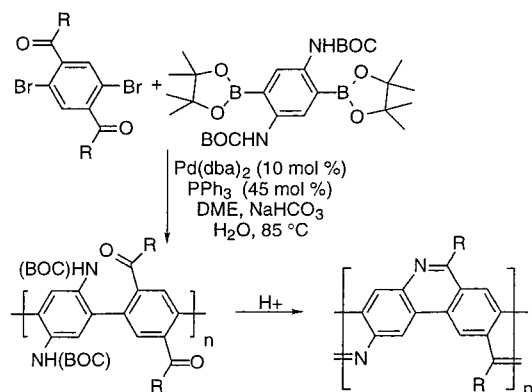
ticular, optimized reaction conditions were developed for the polymerization of nitro-group-containing monomers with the catalyst dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II). Polymers were obtained with an acceptable degree of polymerization (ca. 30). Polyphenylenes carrying nitro, fluoro, nitrile, trifluoromethyl, and dimethylamino substituents have been prepared. Polymers of very high molecular weight were obtained from the nitrile-substituted monomer.

Tour et al.<sup>717</sup> used this methodology to synthesize a planar poly(*p*-phenylene) derivative in order to maximize the extended  $\pi$ -conjugation. They prepared a ladder polymer derivative containing a double-bonded unit to keep the consecutive aryl units planar, allowing the lowering of the band gap (Scheme 411).

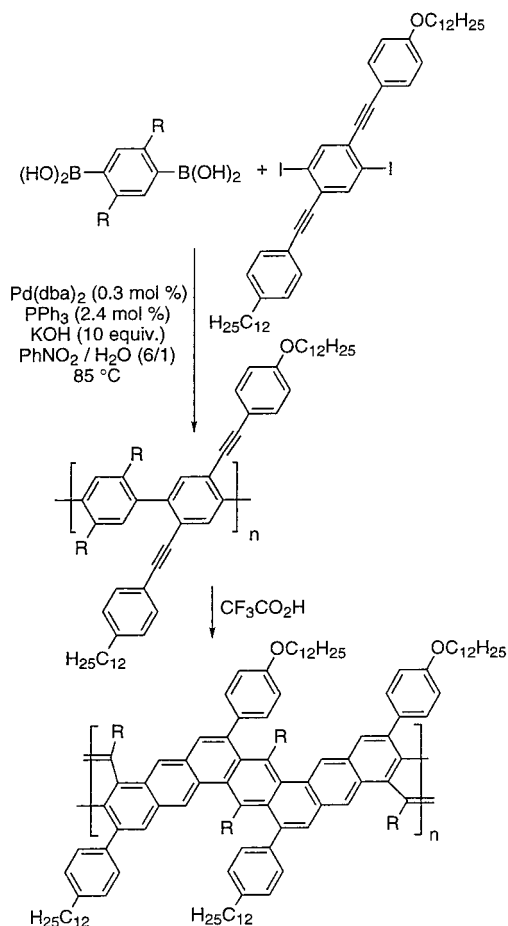
Goldfinger and Swager<sup>718</sup> prepared an all-carbon conjugated system by palladium-catalyzed Suzuki cross coupling and subsequent electrophile-induced cyclization reactions leading to fused polycyclic aromatics (Scheme 412). The polymerization was conducted with a catalyst loading as low as 0.3 mol %. The polymers are obtained with an average molecular weight of around  $5 \times 10^4$  g/mol. After treatment with trifluoroacetic acid, a graphite ribbon is obtained in the form of a yellow/orange solid with an increased degree of two-dimensional structure, such as a ladder polymer, showing interesting electronic and optical properties with an important stability.

Hodge<sup>719</sup> similarly prepared a copolymer containing alternating anthracene 2,6-diyl and *p*-phenylene

## Scheme 411



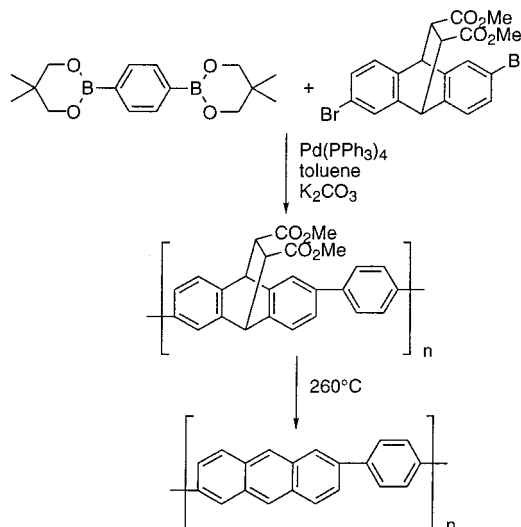
## Scheme 412



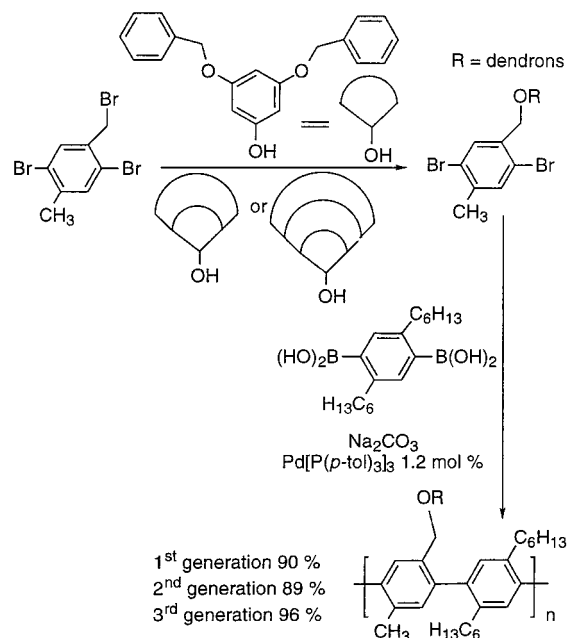
units. Interestingly, they synthesized this insoluble polymer via the preparation of a soluble precursor polymer which led to the insoluble target by heating via a retro-Diels–Alder reaction.

Poly(*p*-phenylene)s have been used as backbones for the preparation of dendrimers with a cylindrical shape in solution.<sup>720</sup> Two different approaches were tested. The first one started from functionalized poly(*p*-phenylene)s whose functional groups were used to anchor dendrons. The second method used benzene-derived monomers that already carried dendrons and were transferred into the corresponding polymers by the Suzuki polycondensation (Scheme 414). The last approach presented the advantage of producing the polymers completely covered by dendrons. Despite

## Scheme 413



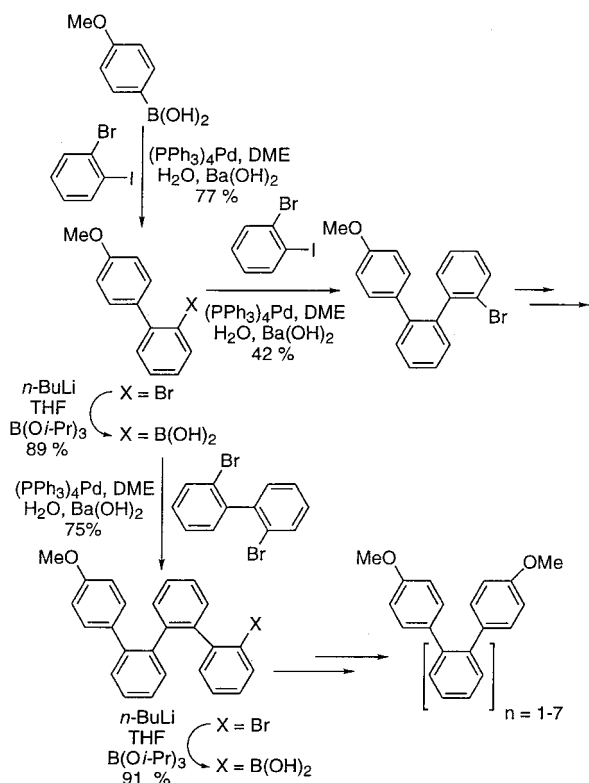
## Scheme 414



the steric crowding of the coupling sites in the second strategy, the molecular weights were at least as high as the ones in the first approach.

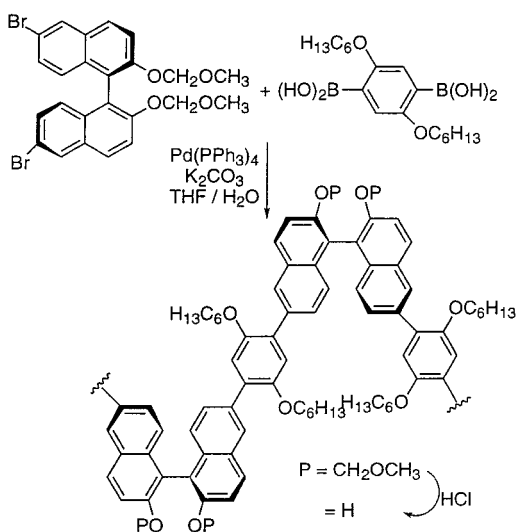
In addition to the formation of poly(*p*-phenylene)s, Suzuki coupling has been used for the preparation of *ortho*-polyphenylene oligomers with 3–9 rings.<sup>721</sup> The strategy of the synthesis, depicted in Scheme 415, implied the coupling of a commercially available boronic acid with 1-bromo-2-iodobenzene. Homologation to higher polyphenylene boronic acids occurred by metal–halogen exchange followed by quenching with triisopropylborate. Repetition of this sequence allowed the preparation of the required polyphenylenes having up to nine rings. Hexamer X-ray analyses indicated that this product adopted the conformation of a tight helix. With a pitch of around 3.7–3.9 Å, the first ring approximately overlaid the fourth one. The authors are now exploring applications of these compounds in the areas of novel materials, chiral polymers, immobilized reagents, and catalysts.

## Scheme 415



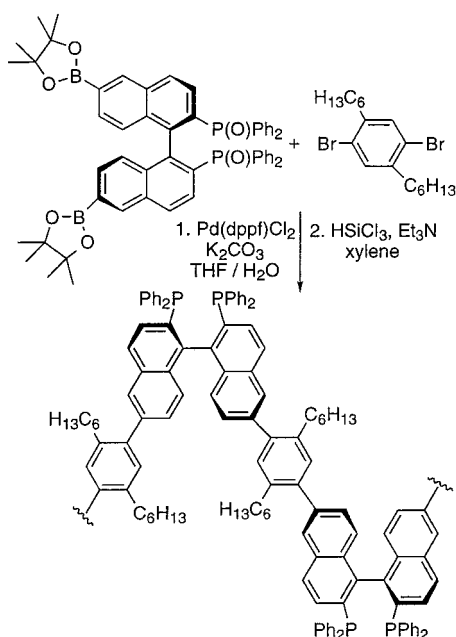
This strategy has been applied for the preparation of various chiral polybinaphthyls by Pu et al.<sup>722</sup> The synthesis of a functionalized chiral polybinaphthyl, soluble in organic solvents, is depicted in Scheme 416.

## Scheme 416



The polymerization was carried out by refluxing an equimolar mixture of the two monomers in THF in the presence of 5 mol %  $\text{Pd(PPh}_3)_4$  and aqueous  $\text{K}_2\text{CO}_3$  leading to the required polymer in an overall yield of 85%. The molecular weight of this polymer was evaluated as  $M_w = 18\,500$  g/mol by gel permeation chromatography. Other polymers were similarly prepared by carrying out the polymerization at the 3,3'-positions of a binaphthyl monomer. The authors further studied the application of these chiral polymers in the asymmetric reaction of aldehydes

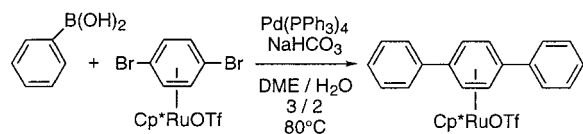
## Scheme 417



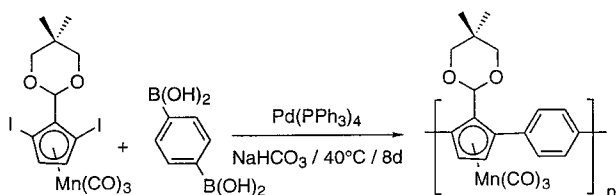
with diethylzinc, some of which led to excellent enantioselectivities. These catalysts, due to their high molecular weights, were easily recovered and reused without loss of either catalytic activity or enantioselectivity.

Very recently, the same authors reported the application of the same methodology to the preparation of a rigid and optically active poly(BINAP).<sup>723</sup> The Suzuki coupling was carried out between a chiral binaphthyl monomer, where the phosphine groups were protected as phosphinoxy groups, and an aryl dibromide, bearing two long alkyl chains to ensure the solubility of the polymer. The molecular weight was estimated by gel permeation chromatography to be around 5800 g/mol ( $M_w$ ), relative to polystyrene standards. This polymer was used to prepare rhodium and ruthenium complexes for the asymmetric hydrogenation of dehydroamino acid derivatives and methyl aryl ketones, respectively. In both cases, very good enantioselectivities were obtained analogous to those observed for the monomeric BINAP catalysts. These results demonstrated that the catalytic properties of an enantioselective monomer catalyst can be preserved in a rigid and sterically regular polymer backbone. These polymeric complexes were furthermore insoluble, allowing their easy recovery and reuse.

The Suzuki coupling is run under very mild conditions. This allows the coupling of an organometallic halide with an aromatic boronic acid for the preparation of organometallic oligomers. For example, Schulze and Bunz<sup>724</sup> performed the Suzuki coupling of  $[\text{Cp}^*\text{Ru}(\textit{p}\text{-C}_6\text{H}_4\text{Br}_2)\text{OTf}]$  with phenylboronic acid as depicted in Scheme 418. The quantitative yield of the oligomeric structure was obtained when the reaction was run in a DME/ $\text{H}_2\text{O}$  mixture, in which the organometallic moiety is completely soluble. The organometallic oligomer is air-stable and soluble in common organic solvents. The corresponding organometallic poly(*p*-phenylene)s should be interesting due to its stereochemical and electronic properties.

**Scheme 418**

Bunz also described the synthesis of a rigid-rod phenylene–cymantrenylene copolymer using the Suzuki coupling as the polymer-forming reaction.<sup>725</sup> The synthesis of 2,5-diiodocymantrene (Scheme 419) was

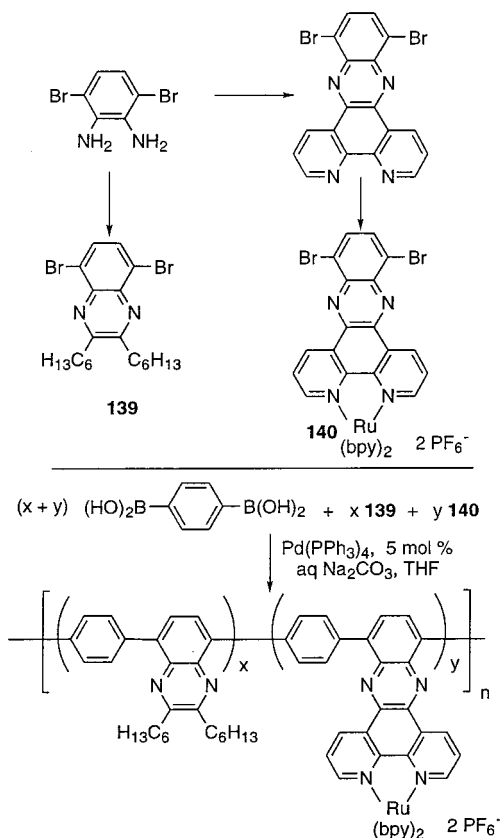
**Scheme 419**

performed via preparation of an acetal (from formylcymantrene and 2,2-dimethylpropanediol). This acetal, by virtue of its *ortho*-directing power, allowed the preparation of the dilithio and then the diiodo derivative in a 77% yield. 1,4-Phenylenediboric acid was coupled with this diiodocymantrene by a Suzuki cross coupling catalyzed by 0.25 mol % of Pd(dppf)Cl<sub>2</sub> to form the corresponding polymer in an 80% yield. Gel permeation chromatography analyses indicated a degree of polymerization of around 30 with regard to the phenylene cymantrenylene unit, suggesting that 60 bonds were formed during the polymerization.

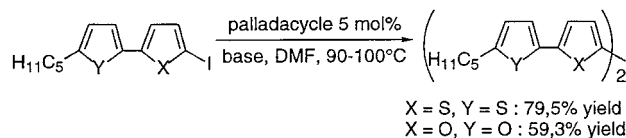
Metal-containing polymers have potentially interesting applications as photoconductors. With this objective, Chan et al.<sup>726</sup> described the preparation and evaluation of quinoxaline-based conjugated polymers containing ruthenium(II) bipyridine metal complexes. The authors chose the palladium-catalyzed Suzuki reaction, allowing the metal content and physical properties of the polymers to be easily adjusted by changing the ratio of different monomers. Polymers were synthesized by polymerizing 1,4-benzenediboric acid with different ratios of monomers which may or may not contain a complexed ruthenium atom, using Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst. The authors found that the yield and molecular weight of the resulting polymer decreased in inverse proportion to increases in the metal-containing monomer. They assumed this to be due to bulkiness leading to a less reactive monomer.

#### F. Oligothiophene Synthesis in a Palladium-Catalyzed Reaction without Additional Organometallics

In view of their numerous applications, there are many methods for the polymerization of alkylthiophenes. Organometallic methods lead to high molecular weights and to regioregular head-to-tail poly(alkylthiophenes). The main drawbacks of these methods are the difficulty of accessing the pure monomer and the requirement of stoichiometric amounts of organometallic intermediate. Recently, the palladium-catalyzed polymerization has received much attention. Luo et al.<sup>727</sup> reported the synthesis

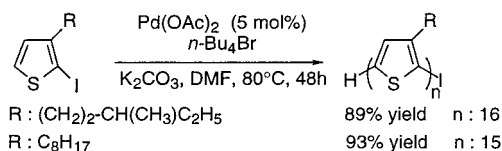
**Scheme 420**

of oligoheterocycles (thiophene/furan) via a reductive coupling reaction using palladacycle catalyst<sup>728</sup> (Scheme 421).

**Scheme 421**

X = S, Y = S : 79,5% yield  
X = O, Y = O : 59,3% yield

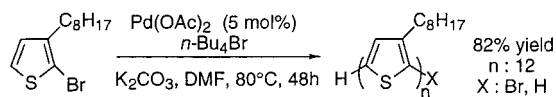
Lemaire et al.<sup>729–731</sup> showed the direct arylation of activated thiophenes by iodoaryls using a Heck-type reaction with a mixture of Pd(OAc)<sub>2</sub> and phase-transfer agent as the catalyst system. In light of these results, the authors recently developed a new method for the polymerization of 2-iodo-3-alkylthiophenes in the presence of Pd(OAc)<sub>2</sub> as the catalyst<sup>732,733</sup> (Scheme 422)

**Scheme 422**

R : (CH<sub>2</sub>)<sub>2</sub>-CH(CH<sub>3</sub>)C<sub>2</sub>H<sub>5</sub>      89% yield    n : 16  
R : C<sub>8</sub>H<sub>17</sub>                                93% yield    n : 15

Several analytical techniques such as MALDI-TOF and <sup>1</sup>H NMR showed that these polymers are regioregular and functionalized by an iodine atom at the chain end. The 2-bromo-3-octylthiophene has also been tested in this new catalytic polymerization<sup>734</sup> (Scheme 423). A mixture of regioregular brominated



**Scheme 423**

and debrominated polymers with a DP of 12 is obtained according to  $^1\text{H}$  NMR, UV, and MALDI-TOF analyses.

This method presents several advantages compared with reported methods, for example, functionalized monomers are easily available.

## V. Aromatic Ring Coupling Using Nucleophilic Substitution as well as Radical and Oxidative Processes

### 1. Aryl–Aryl Bond Formation by Nucleophilic Aromatic Substitution

Some examples of nucleophilic aromatic substitution have been described for the formation of biaryls, using organometallic aryls as nucleophilic reagents (mostly organolithium reagents or Grignard derivatives) and activated arenes with electron-withdrawing substituents, such as oxazoline, ester, sulfinyl, sulfonyl, or diphenylphosphinyl groups. Gant and Meyers<sup>735</sup> reviewed these reactions in 1994; thus, we will here report only some recent additional examples. Kamikawa and Uemura<sup>736</sup> used this methodology for preparing axially chiral biaryls, by the nucleophilic substitution of planar chiral arene tricarbonylchromium complexes.

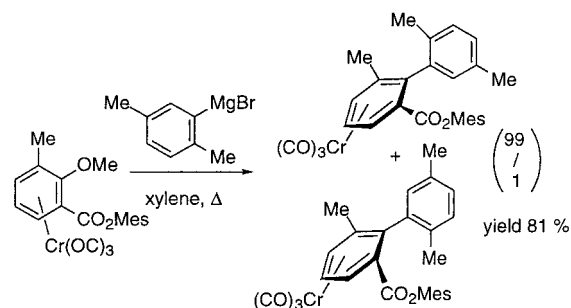
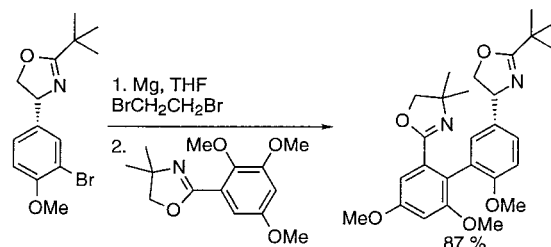
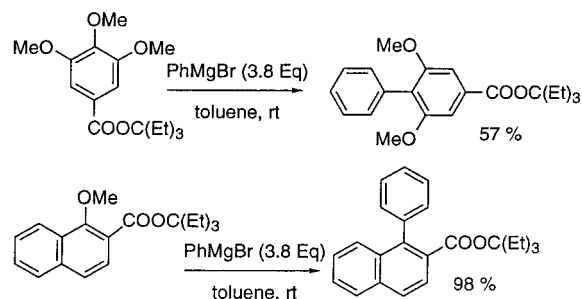
High *anti*-diastereoselectivities were achieved by nucleophilic additions of aryl Grignard reagents, based on the Grignard approach from the *exo*-side via coordination of magnesium to two oxygen atoms. The axial chirality was controlled by steric interactions during the rearomatization of the intermediate and the loss of the methoxy substituent. This procedure was applied to the asymmetric synthesis of actinoidic acid derivatives, intermediates for vancomycin total synthesis.<sup>737</sup> The key step in this preparation involves an intermolecular nucleophilic substitution reaction between two aryl oxazolines, one bearing the chiral moiety.

Kotsuki et al.<sup>738</sup> applied this methodology to the regioselective nucleophilic aromatic arylation (and alkylation) of *o*- or *p*-methoxy-substituted aromatic carboxylic acids via their triethylcarbinyl ester derivatives.

The use of more-hindered triethylcarbinyl ester was found to be convenient for facilitating the methoxy substitution in view of its effectiveness and ready accessibility. This method has been particularly useful for achieving regioselective alkylation of 1-methoxy-2-naphthoic acid derivative to produce sterically congested molecules in high yields.

Tomioka<sup>739</sup> developed a method for asymmetric nucleophilic aromatic substitution, giving binaphthyls, in which aryllithium derivatives were controlled by a catalytic amount of asymmetric mediator.

This reaction was the sum of two stereoselective processes: enantioselective conjugate addition of the naphthyllithium–diether complex followed by the

**Scheme 424****Scheme 425****Scheme 426**

elimination of the LiF–diether complex from the intermediate compound, in which transfer of central chirality to axial chirality occurred. The use of fluorinated intermediates was essential to provide a rapid and efficient regeneration of the naphthyllithium–diether complex through ligand exchange from LiF–diether complex, thus allowing the propagation of the asymmetric process.

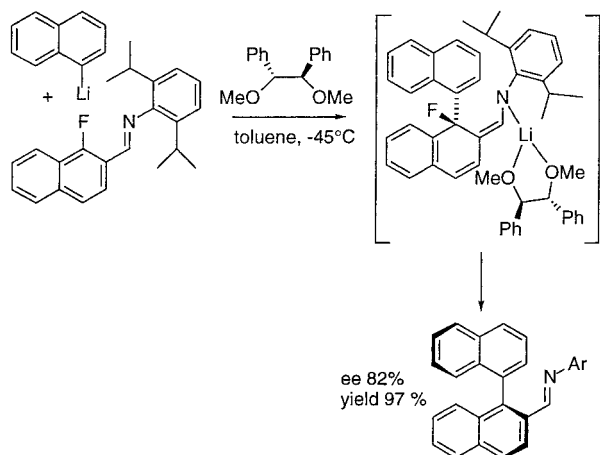
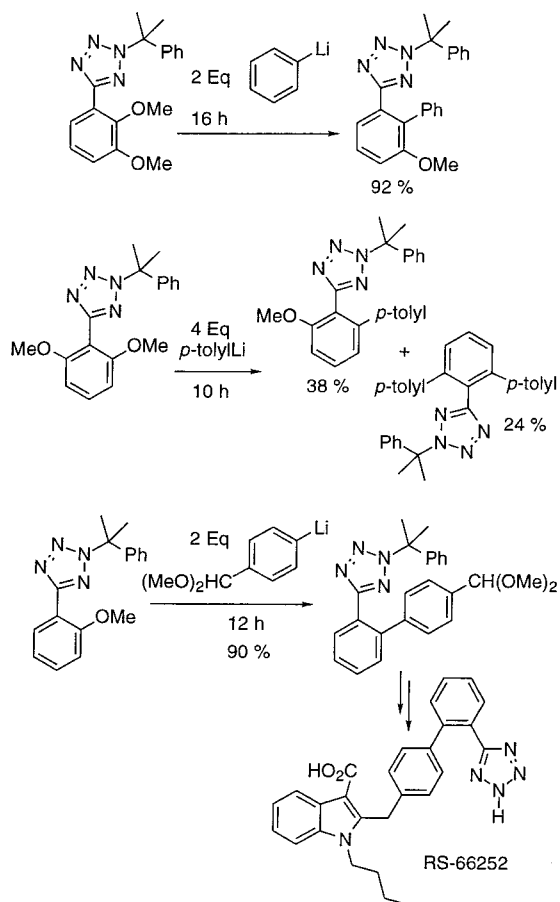
As a synthetic route to 5-(2-biaryl)-tetrazoles, Flip-pin et al.<sup>740</sup> studied the use of a protected tetrazole ring as an efficient activating group for nucleophilic aromatic substitution reactions. Protection with an *N*-cumyl group allowed the reaction, with a variety of common organolithium reagents, to give  $\text{S}_{\text{N}}\text{Ar}$  from either one or two nucleofugic methoxy groups situated *ortho* to the activating tetrazole ring (Scheme 428).

The authors applied this procedure to the preparation of a biaryl tetrazole intermediate, a convenient precursor to the angiotensin II antagonist RS-66252.

### 2. Aryl–Aryl Bond Formation Using Photochemistry and/or Radical Initiation

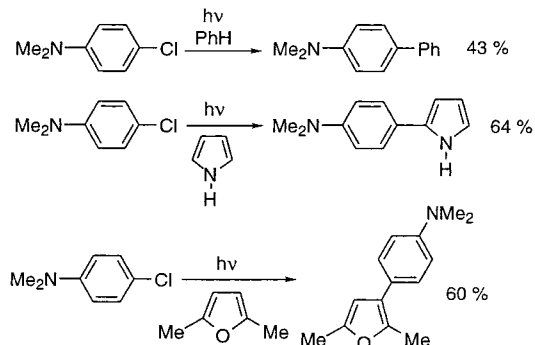
#### A. Photochemistry

Some methods have been described for preparing biaryls, involving photochemistry. Hence, in 1969, Wynberg and Kellogg<sup>741</sup> studied the interaction of the

**Scheme 427****Scheme 428**

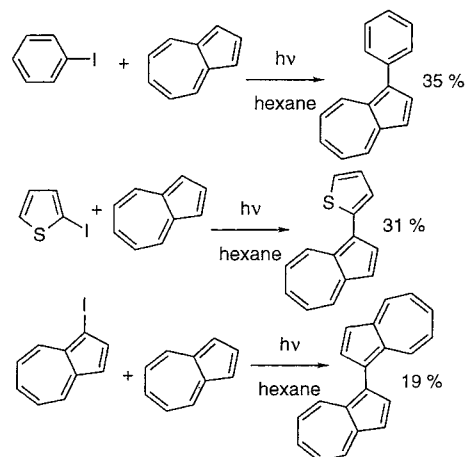
3-pyridylradical with thiophene. 2-(3'-Pyridyl)thiophene was isolated with a 40% yield by chromatographic separation of the reaction mixture. In 1981, Terashima<sup>742</sup> studied the photoreaction of halopyridines with benzene. The reaction mechanism of the arylation by photolysis of halobenzenes was initially recognized as a radical mechanism. Recently, Albini et al.<sup>743</sup> proposed a carbocation intermediate, proving that the photolysis of chlorobenzene and fluorobenzene was facilitated by the presence of an electron-donating group at the *para*-position. This methodology was applied to the preparation of 2-dimethylaminophenylfurans, -pyrroles, and -thiophenes from the photolysis of 4-chloro-*N,N*-dimethylaniline, prob-

ably involving heterolytic cleavage of the C–Cl bond in the triplet state of the aniline.<sup>744</sup> The desired aryl heterocycles were formed in reasonable yield (Scheme 429) in addition to 10–15% of *N,N*-dimethylaniline

**Scheme 429**

and traces of 2-(4'-*N,N*-dimethylaminophenyl)-4-chloroaniline.

Performing photoirradiation of aryl iodides, Ho et al.<sup>745</sup> observed the regioselective arylation of azulenes, which were attacked preferentially at the C<sub>1</sub> electron-rich site (Scheme 430). The isolated yields

**Scheme 430**

were quite modest, because in many cases the conversion reached only around 30–40%, and dehalogenated aryl compounds were also obtained.

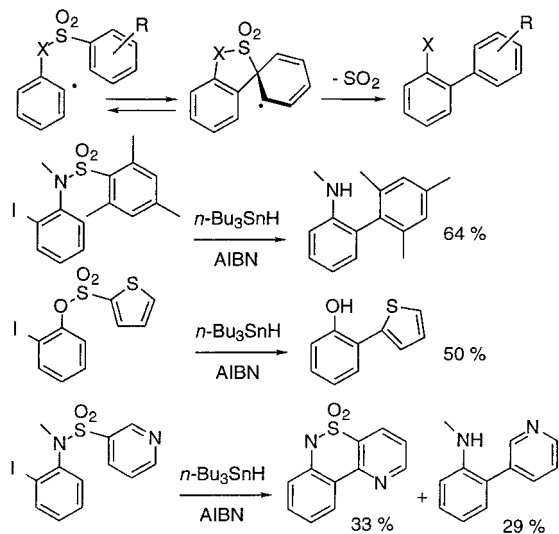
**B. Aryl–Aryl Bond Formation with Radical Initiation**

Recently, special attention has been devoted to the intramolecular transfer of aryl groups by a radical mechanism for evaluating the synthetic possibilities of the process. This methodology often involved the presence of a tethering functionality between two aromatic groups that were subsequently linked. For example, Motherwell et al.<sup>746</sup> described the synthesis of biaryls and heterobiaryls by intramolecular free-radical [1,5] *ipso* substitution using sulfonamide- and sulfonate-tethering chains. They were thus able to perform intramolecular radical–aryl migration from sulfur to aryl radicals.

To avoid direct addition, both the nature of the linker and the electronic character and position of the R-substituents were found to be of crucial importance. This methodology could thus compete with

many metal-catalyzed aryl–aryl bond formations, in the sense that it was advantageous when sterically congested products were required. The authors also proved (Scheme 431) that the location of a heteroa-

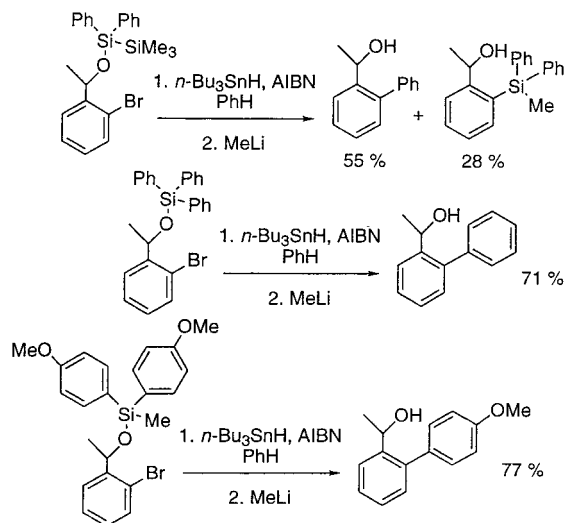
Scheme 431



tom made this strategy suitable for the synthesis of heterobiaryls. The study of benzylic sulfonates and their corresponding *N*-methylsulfonamide derivatives as substrates in potentially free-radical [1,6]-*ipso* substitution reactions revealed that [1,7] addition was the favored pathway.<sup>747</sup>

Tethering chains possessing other functions have been recently described. Studer et al.<sup>748</sup> published a method for the preparation of biaryls via intramolecular-[1,5]-aryl-migration reaction from silicone in silyl ethers to aryl radicals. Phenyl migrations were obtained by the slow addition of AIBN and Bu<sub>3</sub>SnH to a solution of the silyl ether in benzene. The desired biphenyl derivatives were obtained in moderate to good yields (Scheme 432) after desilylation.

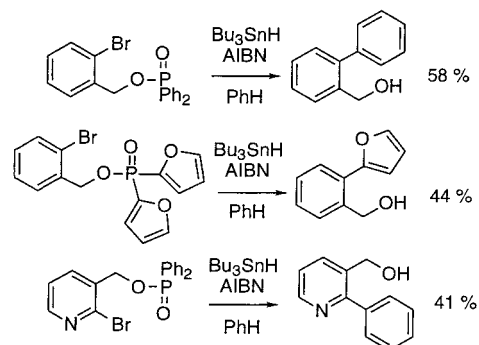
Scheme 432



Clive and Kang<sup>749</sup> successfully described the transfer of aromatic units to synthesize biaryls within the phosphinate compound class. The starting compounds were available in good yields from the parent

alcohol by esterification with the desired diarylphosphinic chlorides. The radical rearrangements were performed in refluxing xylene to give biaryls in satisfying yields (Scheme 433). The authors assumed

Scheme 433

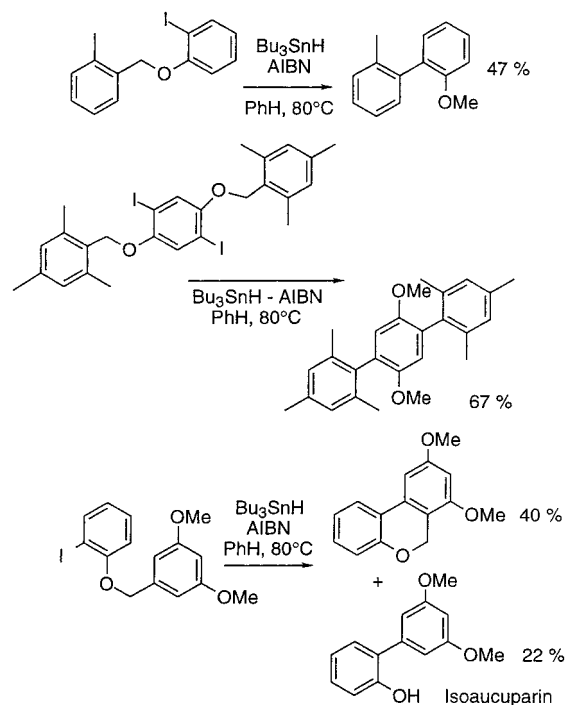


that the mechanism involved an initial radical transfer occurring via a six-membered transition state.

Harrowven et al.<sup>750</sup> performed analogous intramolecular *ipso* substitutions initiated by the addition of aryl radicals to benzyl ethers.

The first substrate tested (Scheme 434), an *o*-tolyl

Scheme 434

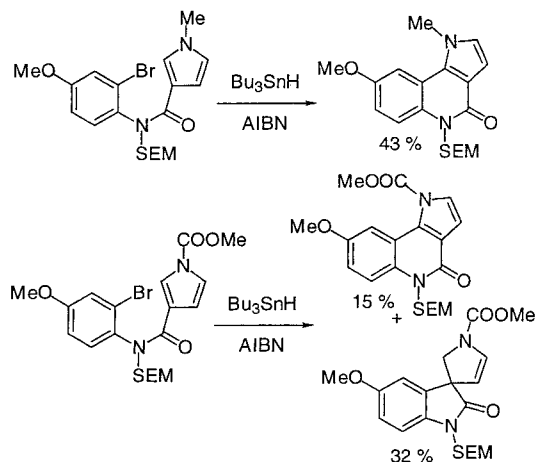


ether, predominantly gave a biaryl methyl ether as the major product in 47% yield. This reaction was interestingly further applied in a cascade sequence to a diiodide to give a substituted terphenyl compound in 67% yield. This methodology was also applied to a short synthesis of isoaucuparin, a natural product found in the sapwood tissue of *Sorbus aucuparia*.

Aryl radical cyclization reactions have often been used in the synthesis of natural products or their precursors, since they allow the formation of fused heterocycles. As an example, Escolano and Jones<sup>751</sup>

showed that the regiochemistry of cyclization of an aryl radical onto a pyrrole was dependent on the *N*-substituent of the pyrrole. They were thus able to selectively prepare a pyrrolo[3,2-*c*]quinoline product with an electron-donating group on the nitrogen atom. Pyrroles substituted on the nitrogen with an electron-withdrawing group, on the contrary, enabled the synthesis of spiropyrrolodinyloxindole (Scheme 435).

Scheme 435



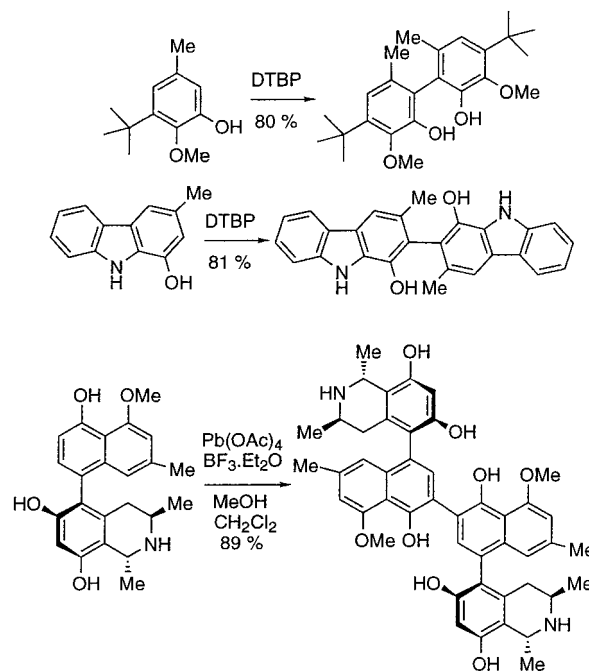
Orito et al.<sup>752</sup> studied the aryl radical cyclizations of 1-(2'-bromobenzyl)isoquinolines toward the formation of aporphines and indolo[2,1-*a*]isoquinolines.

### 3. Formation of Aryl–Aryl Bonds by Oxidative Couplings

Biaryl structures are frequently found in natural products, and for the most part, a biosynthetic origin of the biaryl axis by oxidative phenolic coupling has been envisaged and even demonstrated. Biomimetic syntheses of such compounds have thus been performed with a large variety of oxidizing agents, the choice of which depends, in each case, on the structure of the aromatic portions to be coupled. These aromatic rings must be electron rich, but depending on the steric and electronic requirement, different regioisomers can be formed besides polymers or overoxidized products. These different investigations have been widely reviewed,<sup>753</sup> and here we will briefly discuss only recent new examples. In addition to the oxidative processes using copper or palladium as catalysts which were clearly described in the previous sections, copper-mediated oxidative coupling of aromatic rings specifically has received much attention and leads to the best results so far. Bringmann and Tasler<sup>753</sup> recently reported various couplings of phenolic and nonphenolic aromatics by oxidation with good yields, after carefully optimizing the reaction conditions in each case to avoid complex product mixtures. As indicated in Scheme 436, di-*tert*-butyl peroxide (DTBP) or Pb(OAc)<sub>4</sub>, for example, was a suitable oxidizing agent for the synthesis of biphenyls, biscarbazoles, and bisnaphthylisoquinolines.

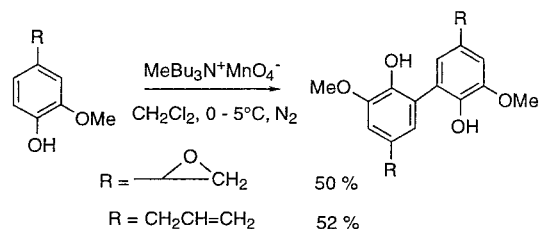
These biomimetic syntheses have thus often been performed with the help of heavy-metal oxidants such as thallium(III). These compounds are highly toxic

Scheme 436



and must be handled with care. Thallium(III) trifluoroacetate–trifluoroacetic acid has been shown to be a good reagent system to generate radical cations of aromatic substrates, and Juliá et al.,<sup>754</sup> in particular, studied the treatment of thiophene and 3-alkylthiophenes using this system to produce polymers. Milder oxidizing species could be used in particular cases. Hence, and owing to the facile oxidation of phenols, Marques et al.<sup>755</sup> studied the oxidative coupling of 4-substituted 2-methoxy phenols using methyltributylammonium permanganate as the oxidizing agent. They performed their reactions in dichloromethane in which the permanganate anion exhibited a lower oxidizing power than in aqueous solutions. Thus, phenols, bearing easily oxidizable functions with permanganate anions in water, were selectively oxidized to biphenols (Scheme 437).

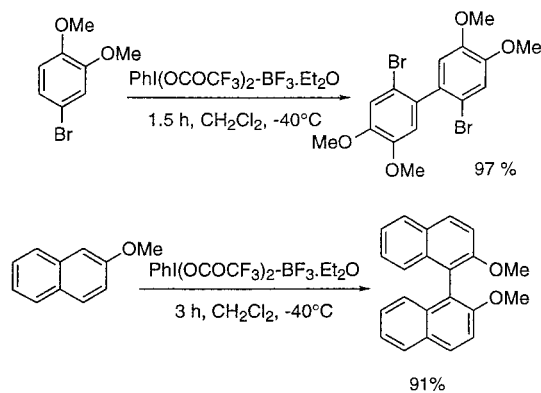
Scheme 437



Kita et al.<sup>756</sup> studied the oxidative biaryl coupling reaction of phenol ether derivatives using hypervalent iodine(III) reagents. In particular, phenyliodine(III) bis(trifluoroacetate) (PIFA) received attention due to its low toxicity, easy handling, and reactivity, which is similar to that of heavy-metal-containing reagents. The intermolecular couplings of trimethoxybenzene derivatives or the corresponding naphthyl rings (Scheme 438) were performed by treatment with PIFA–BF<sub>3</sub>·Et<sub>2</sub>O in dichloromethane at low temperatures, giving rise to the corresponding dimers in high yield. Interestingly, the authors replaced



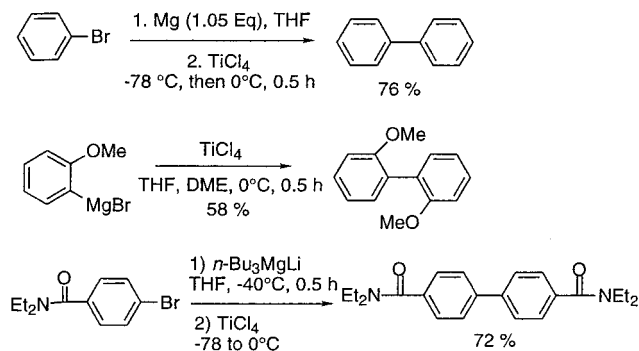
## Scheme 438



PIFA with a polymer-supported hypervalent iodine reagent (polymer-supported bis(trifluoroacetoxyiodo)benzene, PSBTI), which was prepared by oxidation of polyiodostyrene with 30%  $\text{H}_2\text{O}_2$ – $(\text{CF}_3\text{CO})_2\text{O}$ . This polymer showed high efficiency for the oxidative coupling of aryl derivatives. It was easily recovered and recycled without loss of activity.

Oshima et al.<sup>757</sup> recently reported the oxidative self-coupling of various arylmagnesium bromides with  $\text{TiCl}_4$  in moderate to good yields at  $0^\circ\text{C}$ . They also described an alternative method, involving halogen–magnesium exchange followed by a titanium tetrachloride-induced coupling reaction, to provide a one-pot synthesis of biaryls containing functional groups such as esters, amides, or nitriles (Scheme 439).

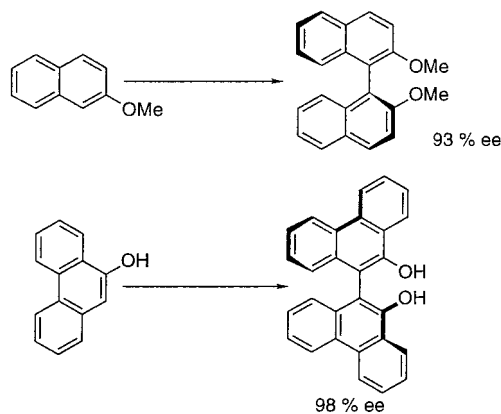
## Scheme 439



Since optically active binaphthyls have been used in a great variety of asymmetric catalytic transformations, much attention has been devoted to their synthesis, via asymmetric oxidative coupling of 2-naphthols. This has mainly been performed with copper(II) amine complexes as oxidants. Electrocatalytic enantioselective oxidative coupling has been reported by Osa et al.<sup>758</sup> They performed the electrolysis, at constant potential, of various substrates (Scheme 440) on a TEMPO-modified (4-amino-2,2,6,6-tetramethylpiperidin-1-yloxy) graphite-felt electrode in the presence of (–)-sparteine. This method allowed the preparation of (S)-binaphthyl-type dimers in high isolated yields with over 88% current efficiency and high enantioselectivity.

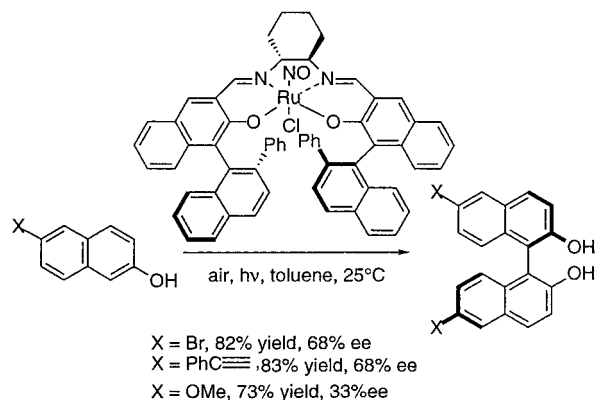
Katsuki studied the asymmetric aerobic oxidative coupling of 2-naphthol derivatives with chiral (NO)-Ru(II)–salen complexes as catalysts.<sup>759</sup> The reaction was performed in air under irradiation with a halo-

## Scheme 440



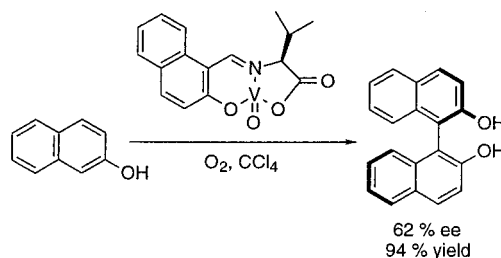
gen lamp. Although the mechanism is still not fully understood, the procedure itself is a new methodology for catalytic asymmetric C–C bond formation triggered by an electron-transfer process. By varying the structure of the chiral ligand and optimizing the reaction conditions (e.g., solvent, loading of catalyst), the authors were able to achieve the photopromoted asymmetric aerobic oxidative coupling of 2-naphthol derivatives (Scheme 441) with up to 71% ee.

## Scheme 441



Very recently, this reaction has also been successfully performed using chiral tridentate oxovanadium(IV) complexes.<sup>760</sup> These complexes were prepared from 2-hydroxy-1-naphthaldehyde and valine (or phenylalanine) and allowed the catalytic asymmetric coupling of 2-naphthols to binols in good yields, with enantioselectivities of up to 68% (Scheme 442). The

## Scheme 442

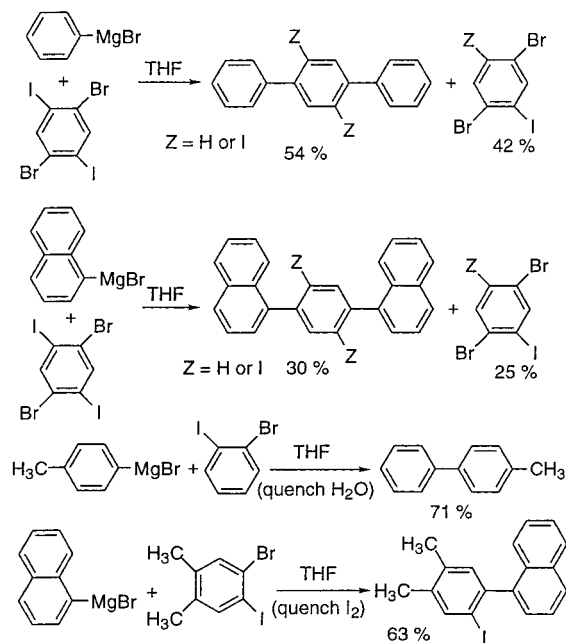


coupling of 2-aminonaphthalene was performed in the same way with poorer chemical yield (48%) and low enantioselectivity (ca. 10%).

#### 4. Formation of Aryl–Aryl Bonds via Aryne Intermediates

Another method for aryl–aryl bond formation that has remained limited for synthetic applications is the nucleophilic addition of aryl organometallics to arynes. This reaction was discovered by Wittig<sup>761</sup> and Huisgen<sup>762</sup> but was often considered to be a side reaction in the preparation of aryne intermediates from aryl halides and phenyllithium, for example. Hart et al.,<sup>763</sup> however, were able to apply this methodology to the one-step synthesis of *p*-terphenyls and unsymmetric biaryls. 1,4-Dibromo-2,5-diiodobenzene was used as a diaryne equivalent by reaction with excess Grignard reagent through metal–halogen exchange. Subsequent nucleophilic addition generated a terphenyl compound (diiodo-substituted if quenching occurred with iodine) and the starting dibromodiiodobenzene. A variety of aryl Grignard reagents were tested and gave the terphenyl compounds depicted in Scheme 443. The authors also applied this method to the

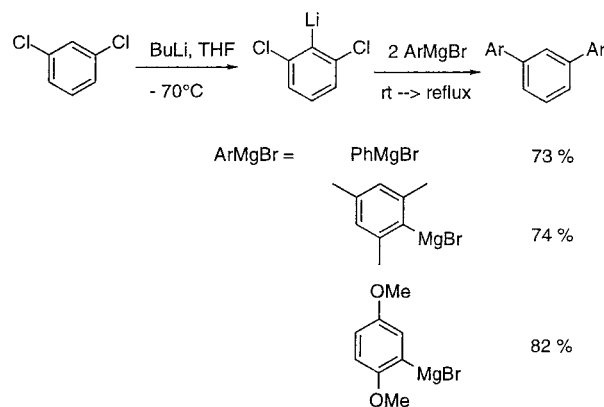
**Scheme 443**



preparation of unsymmetric biaryls. They naturally chose the structure of bromoiodoarenes so that the derived arynes would be symmetrical to give a single product on nucleophilic addition of the Grignard reagent.

Numerous coupling reactions were described indicating that at least one iodine was needed on the arene for the formation of the aryne under these mild reaction conditions. Although the mechanism is unclear, the *p*-terphenyl synthesis involved an intermediate organometallic aryne while the biaryl synthesis proceeded via ordinary aryne formation. Hart<sup>764</sup> completed this work later with the synthesis of *m*-terphenyls via 2,6-dichlorophenyllithium (prepared from regioselective lithiation of 1,3-dichlorobenzene). Further addition of at least two equivalents of the desired arylmagnesium compound allowed the synthesis of various terphenyl derivatives (Scheme 444) in good yields (60–93%).

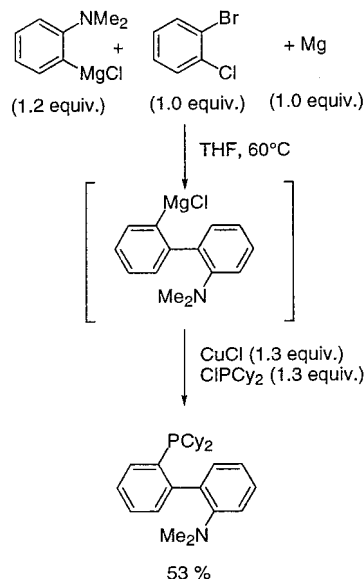
**Scheme 444**



A variation of this methodology was also described using 1,3-dichlorobenzene and an excess (3–5 equiv) of an aryllithium at room temperature. Both methods yield similar amounts of isolated products, and their choice depends on the availability of the aryl Grignard or the aryllithium reagent.

Buchwald et al.<sup>765</sup> recently developed this methodology for the preparation of functionalized biphenyl-based phosphine ligands. They thus prepared functionalized dicyclohexyl- and di-*tert*-butylphosphinobiphenyl ligands through the reaction of arylmagnesium halides with benzyne, followed by the addition of a chlorodialkylphosphine. In particular, the synthesis of the aminophosphine shown in Scheme 445 resulted from the reaction between the Grignard

**Scheme 445**



derivative of 2-chloro-*N,N*-dimethylaniline and chlorodicyclohexylphosphine.

A wide range of functionalized phosphines have thus been prepared by this less expensive and time-consuming method, with overall yields varying from 20% to 60%.

The examples described here are of course not exhaustive. The method developed by Buchwald, in particular, shows how a very old method can be efficiently used today to prepare phosphine ligands as key compounds for modern asymmetric catalysis.

Other examples of this methodology can certainly be expected in the literature in future.

## VI. Conclusion

Although a tremendous amount of work devoted to the extension of the Suzuki reaction has been published over the past few years, the formation of C–C aryl–aryl bonds has been characterized during the same period by the extreme diversity of approaches. Obviously most of the efficient diastereo- or enantioselective formations of aryl–aryl bonds resulted from using copper in both oxidative and reductive processes. On the other hand, the recent improvements in the preparation of zinc derivatives may induce renewed interest in nickel-catalyzed aryl–aryl bond formation. Palladium-catalyzed aryl–aryl bond formation appears to be the ubiquitous method in synthetic applications. In this field, Santelli et al.<sup>564</sup> recently reported the aryl–aryl bond formation using the Suzuki-coupling reaction with a turnover number as high as  $28 \times 10^6$ . These increasing successes have unfortunately occurred simultaneously with a rapid increase of the price of palladium metal, and it is therefore not surprising that many efforts have been made to improve the turnover of the catalyst systems and/or to allow easy recovery and recycling of the catalyst. Besides tin and boronate derivatives, most of the other nucleophilic organometallic reagents have been used, often with success. This has allowed a wide scope of applications including the use of substrates bearing almost all kinds of chemical function.

The only drawback to these methods is the general requirement of a highly reactive organometallic reagent in order to prepare the nucleophilic compound (i.e., boronic or tin derivatives). In the case of the Suzuki reaction, the increasing commercial availability of boronic derivatives should allow many practical applications.

Addition–eliminations of aromatic halide onto aromatic substrate, bearing specific chemical functions, are among the more intriguing results in the area of aryl–aryl bond formation. Indeed, the results described by Miura (section IV.15.C) show that bond formation could be obtained without using organometallic or other nucleophilic reagents. Understanding the mechanism of these particular reactions may have great potential for the future. The evolution of aryl–aryl bond formation has followed the general evolution of organic synthesis and specifically of organometallic chemistry from stoichiometric to catalytic methods. From the point of view of ecology and atom economy, the oxidative methods using catalytic amounts of metals appear to be timely, and today, methods using copper have proved to be the most successful in this field.

## VII. Notations and Abbreviations

acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
alaphos	2-(dimethylamino)propyldiphenylphosphine
Ar	aryl

bdmim	1-butyl-2,3-dimethyl-imidazolium
BEDOP	3,4:3',4'-bis(ethylenedioxy)thiophene
bmim	1-butyl-3-methyl-imidazolium
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	2,2'-bis(hydroxy)-1,1'-binaphthyl
BOC	<i>tert</i> -butyloxycarbonyl
bpy	bipyridine
COD	1,5-cyclooctadiene
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DIPHOS	1,2-bis(diphenylphosphino)ethane
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMC	dichloromethane
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethyl sulfoxide
DP	degree of polymerization
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTDP	<i>di-tert</i> -butyl peroxide
ee	enantiomeric excess
EtOH	ethanol
FG	functional group
MeOH	methanol
MMF	monomethylformamide
Mn	number-average molecular weight
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NiCRA	nickel-containing complex reducing agent
NIS	<i>N</i> -iodosuccinimide
NMP	<i>N</i> -methylpyrrolidone
Ox	oxazoline
PD	polydispersity
PEG	poly(ethylene glycol)
PG	protecting group
Ph	phenyl
phen	phenanthroline
PTC	phase-transfer catalysis
PVP	polyvinylpyridine
Py	pyridine
rt	room temperature
SCAT	alumina-supported copper(II) sulfate
TBAF	tetrabutylammonium fluoride
TBHP	<i>tert</i> -butyl hydroperoxide
TEA	triethylamine
TFA	trifluoroacetic acid
tfp	tri(2-furyl)phosphine
THP	tetrahydropyran
TMEDA	<i>N,N,N,N</i> -tetramethyl-1,2-ethylenediamine
TOF	turnover frequency
TON	turnover number
TPPTS	triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt
Tr	triphenylmethyl

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