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Review

# Recent advances in the cross-coupling reactions of organoboron derivatives with organic electrophiles, 1995–1998☆

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**Abstract**

The palladium-catalyzed cross-coupling reaction between organoboron compounds and organic halides or triflates provides a powerful and general methodology for the formation of carbon–carbon bonds. Recently, this reaction has been called the Suzuki coupling, Suzuki reaction, or Suzuki–Miyaura coupling, although we never referred to it as such previously. In this review, this name will be used with hesitation, simply in order to express the coupling reaction. The availability of the reagents and the mild reaction conditions all contribute to the versatility of this reaction. The coupling reaction offers several additional advantages, such as being largely unaffected by the presence of water, tolerating a broad range of functional groups, and proceeding generally regio- and stereoselectively. Moreover, the inorganic by-product of the reaction is non-toxic and easily removed from the reaction mixture thereby making the Suzuki coupling suitable not only for laboratories but also for industrial processes. We published previously a comprehensive review of the reaction (see N. Miyaura, A. Suzuki, Chem. Rev. 95 (1995) 2457 and A. Suzuki, in: F. Diederich, P.J. Stang, (Eds.), Metal-Catalyzed Cross-coupling Reactions, VCH, Weinheim, 1998, pp. 49–97), which covered mainly the references until the end of 1994. Thereafter, a large number of papers related to the coupling reaction have been reported. Consequently, such new results presented from 1995 to May 1998 are summarized in this review. 

*Keywords:* Organoboron compounds; Cross-coupling reactions; Palladium catalysts; Suzuki coupling

## 1. Cross-coupling of arylborane derivatives

### 1.1. With haloarenes

Porphyrin synthesis arouses continuing interest in biological, material, and inorganic chemistry. Substituents at the β-position of porphyrins exert much larger steric and electronic effects on the porphyrin ring than substituents at the *meso*-aryl positions. The β-substituents also induce the porphyrin ring into a non-planar conformation which may control the biological properties in tetrapyrrole systems like the photosynthetic centers, vitamin $B_{12}$, coenzyme $F_{430,}$ and P-450. The synthesis of these β-substituted porphyrins often requires the relatively inaccessible 3-substituted or 3,4-disubstituted pyrroles for either protic or Lewis acid-catalyzed cotetramerization with aldehydes. Furthermore, regioisomeric mixtures which require difficult and tedious chromatographic purification often result in the preparation of unsymmetrical porphyrins. Since β-brominated porphyrins are obtained easily from the controlled bromination of porphyrins or metalloporphyrins, the transformation of the bromine substituents into other functional groups would provide a facile entry into β-substituted porphyrins. Chan and his

☆ Dedicated with deep respect to both Professor J. Tsuji and Professor R.F. Heck.

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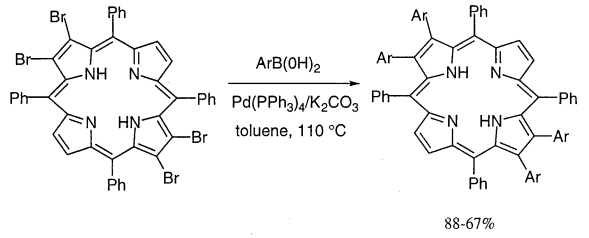
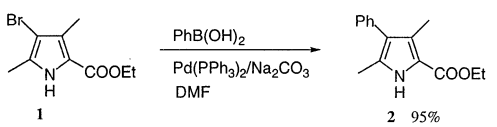



Scheme 1.

coworkers reported on the synthesis of β-aryl substituted tetraphenylporphyrins by the Suzuki cross-coupling with the corresponding β-bromoporphyrins [3].

β-Monobromo-, β-tetrabromo- and β-octabromotetraphenyl porphyrins all under smooth coupling reactions with *p*-substituted arylboronic acids give high yields of β-aryltetraphenyl porphyrins, one such example is shown in Scheme 1. In comparison with the synthesis of porphyrins via the co-tetramerization of pyrroles with aryl aldehydes, this method is complementary. The same reaction was recently published by Zhou et al. [4] for the synthesis of β-mono-, tetra-, and octasubstituted tetramesitylporphyrins in good yields by the coupling of β-bromotetramesitylporphyrins with aryl- and alkylboronic acids. A facile synthesis of porphyrin dimers linked between the *meso*-position and the β-position by phenel groups has been presented through the key Suzuki cross-coupling [5].

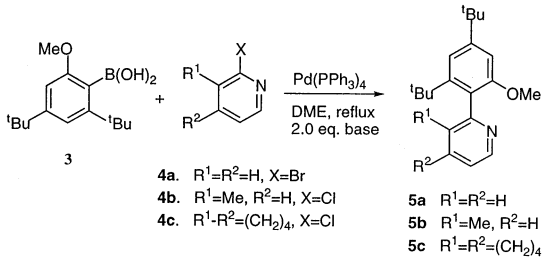
In connection with such syntheses, Chang and Bag [6] also reported a synthetic method of tetramethyltetraphenylporphyrin from a pyrrole derivative. For the synthesis of such pyrroles, they attempted to use a bromopyrrole (**1**) and phenylboric acid using Pd(0)-catalyzed cross coupling. The reaction proceeds well in DMF to give essentially a quantitative yield of the product (**2**) Eq. (1).




(1)

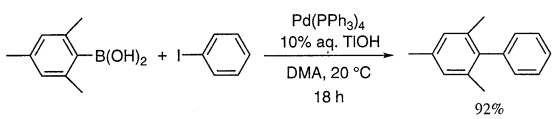
Zhang and Chan observed that base has a remarkable effect on acceleration of the rate of Suzuki coupling of sterically bulky boronic acid with halopyridines in non-aqueous solvent [7]. For instance, in the reaction of the extremely sterically bulky arylboronic acid (**3**) with halo-pyridines (**4a, b**, and **c**), the strong base potassium *t*-butoxide (KO*t*-Bu) gives the best result among the bases examined (Scheme 2, Table 1).

Sakata et al. published the synthesis of a series of oligo-*para*-phenylene substituted new porphyrins by the combinations of aryl–aryl coupling reactions and Lindsey's pyrrole condensation reactions [8]. A concise synthesis of two new indoloquinoline alkaloids, cryptosanguinolentine and cryptotackieine have been reported by the Suzuki coupling [9].




Scheme 2.

The restricted rotation around the biaryl axis caused by bulky substituents leads to the existence of atropisomers. Depending upon the degree of steric hindrance from the *ortho* substituents, three or four substituents are needed to produce a sufficient barrier to rotation at room temperature. This particular form of axial chirality is not generally resistant to heat. To produce acceptable yields of hindered biaryls under Suzuki conditions, high temperatures (60–110°C) [10,11] are needed with multihour reaction times. In atropisomer selective reactions, these conditions would be deleterious to the discrimination between diastereomeric transition states and could racemize the biaryls formed. As a consequence, ways of carrying out such Suzuki reactions at ambient temperature have been looked at. There are few examples of ambient temperature Suzuki-type biaryl couplings. More recently, conditions involving $Pd(OAc)_2$ and 95% ethanol have been used to form mono-*ortho* substituted biaryls at 20°C [12]. The cross-coupling of mesitylboronic acid with iodobenzene was achieved in excellent yield in the presence of $Pd(PPh_3)_4$ with aqueous base and temperatures of 80–100°C [10]. Anderson and Namli have coupled mesitylboronic acid and iodobenzene in the presence of $Pd(PPh_3)_4$ with 10% aq. TlOH in various solvents at 20°C [13]. From the solvents screened only DMA gave a good yield of the coupled product, as shown in Eq. (2). Under similar conditions, the coupling reactions of mesitylboronic acids with *o*- and *p*-substituted halobenzenes give the corresponding biaryls in good to excellent yields.



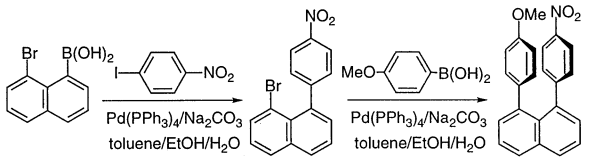

(2)

Table 1
Base effect on the cross-coupling of arylboronic acid with halopyridines, yield (%)/reaction time (h)

| Base | 5a | 5b | 5c |
|---|---|---|---|
| $Na_2CO_3$ | 26/90 | 0/90 | 0/90 |
| NaOH | 40/140 | 22/24 | 44/26 |
| NaOEt | 74/4 | 0/12 | 45/26 |
| KO*t*-Bu | 86/4 | 83/16 | 77/10 |

Nonlinear optics (NLO) has become a focus of attention for material scientists in the expectation that revolutionary progress will be associated with the transition from electronics to photonics. In this connection, it would be desirable to synthesize 1,8-di(hetero)aryl naphthalene derivatives, in which one aryl substituent is rendered electron-rich by an electron donor and/or hetereoarene, while the other reduces electron density as a result of an electron-withdrawing group such as **6**. Few 1,8-di(hetero)arylnaphthalenes are known because of the lack of a general synthetic method. The preparation of known derivatives [14] cannot be generalized, because the methods do not allow an unsymmetrical functionalization and/or greatly restrict the range of substituents.

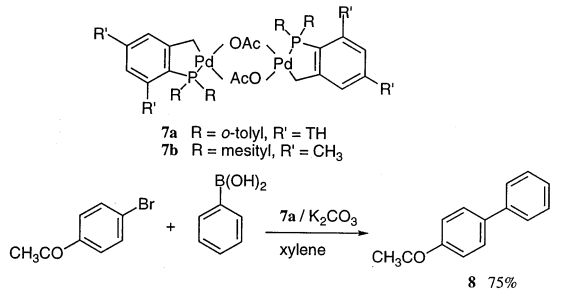
Grahn et al. [15] attempted to produce such 1,8-di(-hetero)arylnaphthalene derivatives using the Suzuki coupling, and obtained nice results. One of such examples is depicted in Eq. (3).



(3)

In recent years, a large number of palladium-mediated syntheses for complex synthetic building blocks and also for structurally simple, industrially important intermediate products have been found and further developed. However, the quality of the used catalysts is generally not sufficient for industrial demands. As a result of the increasing importance of unsymmetrically substituted biaryl derivatives, for example, as drug intermediates, the transferability of the catalytic properties of the palladacycle complexes (**7a,b**) to the cross coupling between aryl halides and arylboronic acids [16] has been examined and it has been reported that palladacycles (**7**) catalyze this type of reaction with an unusual efficiency. When 4-bromoacetophenone is treated with phenylboronic acid under conditions (bromophenone (10 mmol), phenylboronic acid (15 mmol), $K_2CO_3$ (20 mmol), catalyst **7a** (0.001 mol%), *o*-xylene (30 ml), and reaction temperature 130°C), the expected coupling product (**8**) is obtained in 75% yield, and the turnover number (TON) 75 000 is achieved with only 0.001 mol% **7a** as catalyst (Scheme 3).

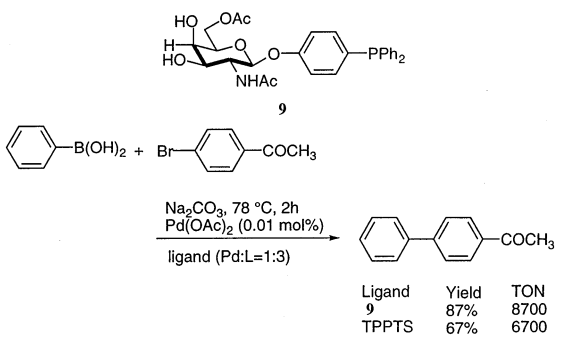
The two basic problems of homogeneous catalysis, separation and recycling of the catalyst, can be solved by using two-phase catalysis. Here, the catalyst is in a hydrophilic phase in which the organic products are insoluble. In order to implement this principle, it is necessary to develop new ligands that are soluble in hydrophilic phases. Diphenylphosphinoacetic acid and the TPPTS ligand (TPPTS, trisodium salt of



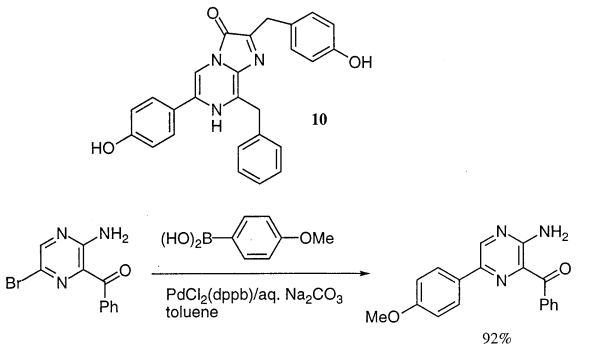

Scheme 3.

triphenylphosphane trisulfonate) are used on the tonne-scale for the most important industrial two-phase processes. To attain sufficient solubility of the ligands in polar media (particularly water), inorganic groups (sulfonic acid and carboxylic acids, quaternary aminoalkyl/aryl groups, and phosphonium salts) are usually used as substituents in the phosphanes. Beller et al. have recently reported a new class of polar, hydrophilic triarylphosphanes for two-phase catalysis, which are aryl-β-*O*-glycosides of glucose, galactose, and glucosamine [17]. Thus, the ligand (**9**) shows a high catalytic activity in the Suzuki reaction. An example is shown in Scheme 4.

The imidazopyrazine ring system is found in the luminescent chromophores of a number of marine organisms. Coelenterazine (**10**) was isolated from the bioluminescent jellyfish *Aequorea victoria*, and its role in the bioluminescent process has been the subject of extensive studies as it is triggered by $Ca^{2+}$ ions and provides a very sensitive method for the detection and quantification of $Ca^{2+}$. As part of a project to explore a wide range of analogs of coelenterazine, it is desired to find a more flexible approach to the imidazopyrazine ring system synthesis than that afforded by the only literature synthesis, which involves the synthesis of a substituted pyrazine early on by a condensation reaction. For such a purpose, Jones et al. [18] investigated the Suzuki coupling of a suitable 5-halopyrazine with arylboronic acids and proved that the reaction is of



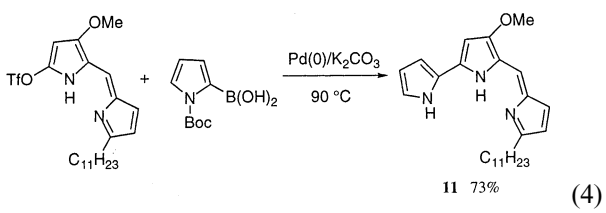

Scheme 4.




Scheme 5.

exceptional utility for the synthesis of aryl pyrazines. According to their results, 1,4-bis(diphenylphosphino)butane palladium(II) chloride catalyst gives excellent yields, as shown in Scheme 5.

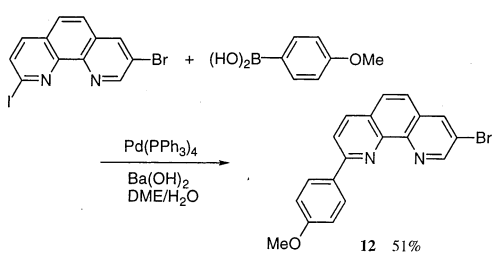
Recently, undecylprodigiosine (**11**) was reported to inhibit T-cell proliferation at doses which are not cytotoxic, this is particularly attractive with regard to its potential clinical indications. The total syntheses of prodigiosins published so far involve several steps and are not suitable to be scaled up in case of a possible lead development. D'Alessio and Rossi [19] found a new synthetic pathway in order to produce a consistent amount of undecylprodigiosine, which is illustrated in Eq. (4).



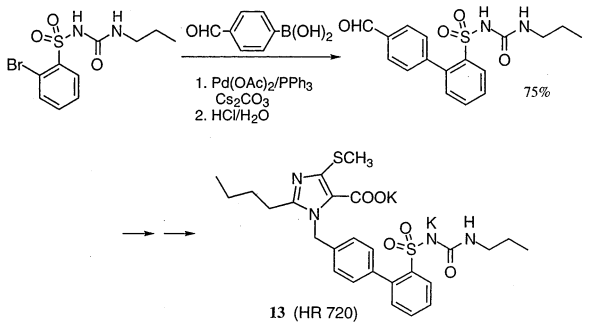

(4)

Because of the different reactivity of iodine and bromine groups toward the Suzuki reaction, the selective coupling is realized. For example, 8-bromo-2-(4-methoxyphenyl)-1,10-phenanthroline (**12**) is prepared by reacting 4-boronic acid of anisole with bromo-iodophenanthlorine under Suzuki conditions (Scheme 6) [20].

Nortopsentins A, B, C, and D, antifungal 1,4-bisindolylimidazole marin alkaloids isolated from a sponge, have been synthesized through palladium-catalyzed




Scheme 6.

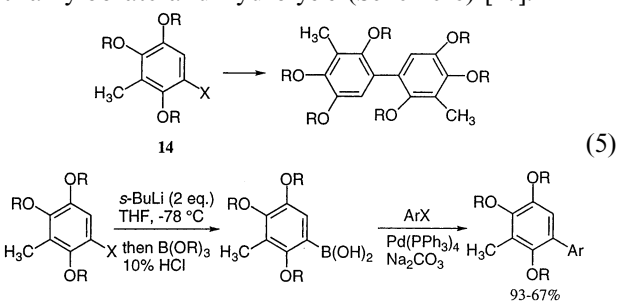



Scheme 7.

cross-coupling of 3-indolylboronic and 6-bromo-3-indolylboronic acids with haloimidazoles in good yields as the key reaction [21]. Benzofuranylindole derivatives were prepared by the coupling of benzofuranyl boronic acids with bromoindoles [22].

Antagonists of the angiotensin II (ANG II) receptors are the newest entity in the therapeutic armory for the treatment of hypertensive diseases. Recently, (imidazolylbiphenylyl)sulfonyl-ureas and -sulfonylcarbamates have been described as new non-tetrazole ANG II receptor antagonists. The most promising compound derived from this series is the orally active $AT_1$-selective antagonist HR 720 (**13**). Originally, **13** was synthesized like many other ANG II antagonists by a convergent approach via *N*-alkylation of the appropriate imidazole with the requisite 4′-bromomethyl-1,1′-biphenyl [23]. Most recently, Heitsch et al. have demonstrated an alternative preparative access for **13** by the Suzuki reaction as shown in Scheme 7 [24].

In the course of studies on the formation of polycyclic quinoidal systems, it would be desirable to effect the dimerization of aryl halides of type **14** (Eq. (5)). Copper and nickel catalyzed methods [25] failed, and the palladium-mediated coupling of magnesium or lithium compounds [26] afforded biaryls in poor yields (10–18%). Benbow and Martinez have discovered that the coupling reaction of arylboronic acids with aryl halides provides biaryl in synthetically useful quantities, and the intermediate boronic acids were formed from the corresponding aryl halides via a standard metal–halogen exchange reaction followed by the addition of a trialkylborate and hydrolysis (Scheme 8) [27].

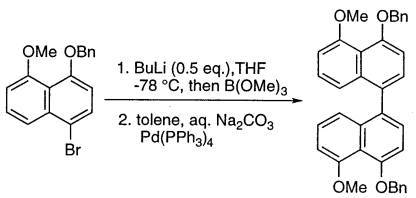



(5)

Scheme 8.

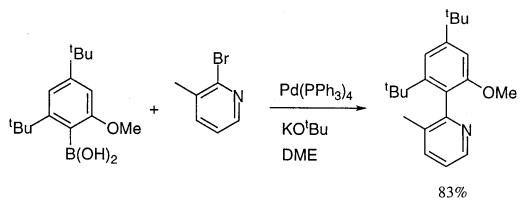
Moreno-Manas et al. [28] reported a palladium-catalyzed Suzuki type self-coupling of arylboronic acids for the preparation of symmetrical biaryls, and proposed the mechanistic cycle of the reaction.

Recently, a one-step modified in situ Suzuki coupling method for the production of $C_2$-symmetric biaryls which eliminates the need for boronic acid isolation [29] has been developed, as shown in Eq. (6). Moderate to excellent yields are obtained and a wide variety of functional groups are tolerated. Moreover, this in situ method is synthetically useful for the synthesis of natural products and the preparation of $C_2$-symmetric biaryl ligands.



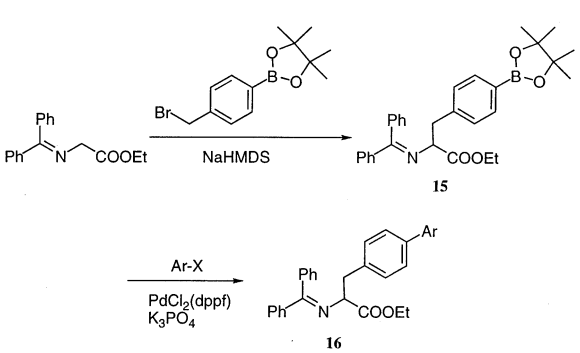

(6)

A highly sterically hindered pyridylphenol derivative was synthesized through the Suzuki cross-coupling [30] (Eq. (7)).

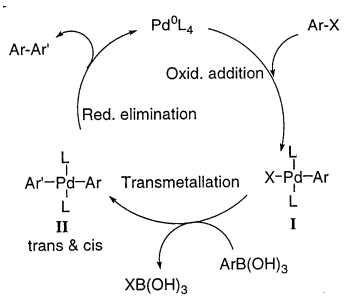



(7)

The increasing importance of unnatural amino acids as building blocks in designing peptide-based biologically active molecules has led to rapid progress in the development of synthetic methodologies for the construction of such compounds. As a novel synthetic method, the following procedure has been reported recently. The protected racemic phenylalanine derivative (**15**) was readily prepared by alkylation of ethyl glycinate benzophenone imine with the pinacol ester of 4-bromomethylphenylboronic acid. Palladium-catalyzed coupling reactions with aromatic halides provide biarylalanines (**16**) in moderate to good yields. Groups such as aldehydes and esters are well tolerated [31] (Scheme 9).

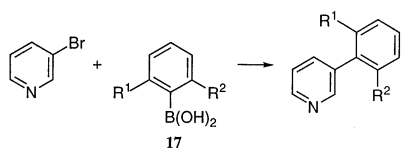



Scheme 9.



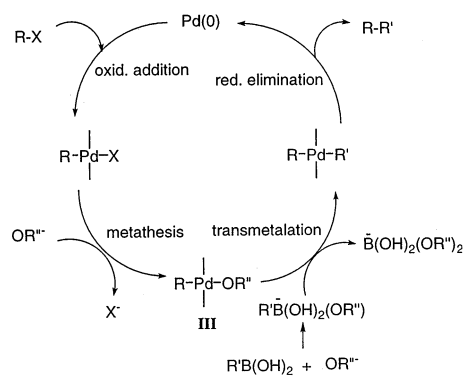

Scheme 10.

Electrospray ionization mass spectrometry (ESI-MS) was used to analyze the reaction mixture of the Suzuki coupling reaction [32]. Namely, Aliprantis and Canary carried out such an experiment in the reaction between 3-bromopyridine and a phenylboronic acid (**17**) (Eq. (8)), and observed the species of **I** $[(pyrH)Pd(PPh_3)_2Br]^+$ and **II** $[(pyrH)(R^1R^2C_6H_3)Pd(PPh_3)_2]$. Consequently, they concluded that the reaction mixture contains the two key intermediates (**I** and **II**), as shown in the catalytic cycle (Scheme 10).

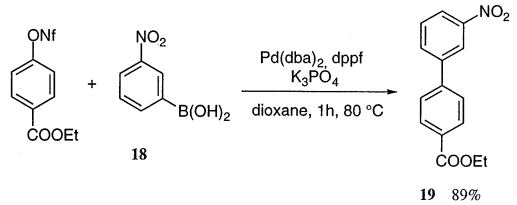



(8)

On the other hand, we previously reported the reaction mechanism of a 1-alkenylboron compound and a 1-alkenyl halide via the catalytic cycle indicated in Scheme 11 [33], although we have never investigated the mechanism of the coupling between haloarenes and aryl halides. Consequently, we think that there is a possibility of the formation of an intermediate (**III**) even in the catalytic cycle in the aryl–aryl coupling reaction.




Scheme 11.

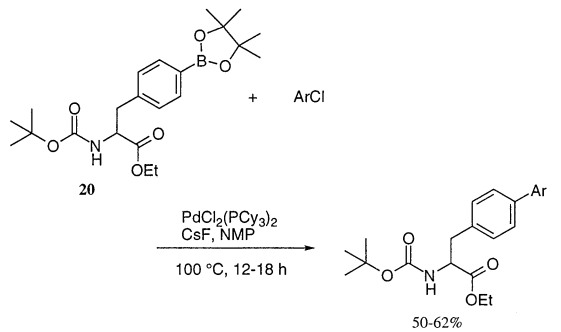



Scheme 12.

Aryl halides often used in the Suzuki reaction are bromides and iodides. Aryl chlorides do not participate in the coupling, except when used in conjunction with electron-deficient groups. Aryl triflates are also often employed [1,2]. As triflates are base sensitive and thermally labile, mild reaction conditions were developed for the cross-coupling reaction of arylboronic acids with triflates. These include the selection of more efficient catalysts such as $PdCl_2$(dppf), the utilization of weak nonaqueous basic conditions such as powdered $K_3PO_4$ suspended in polar solvents (THF, dioxane), and the addition of an alkali metal halide to promote the cross-coupling and/or to prevent the premature catalyst decomposition [1]. One of the challenges in the Suzuki-type cross-coupling is to extend this reaction from electron-rich aryl triflates to less reactive aryl sulfonates and aryl chlorides, which show poor reactivity toward oxidative addition in the catalytic cycle. A recent approach to this problem involves the activation of aryl triflates by complexation of electron-withdrawing $Cr(CO)_3$ to the arene moiety [34]. Alternative sulfonate leaving groups besides triflates were reported to be active in Suzuki-type reactions [35]. Aryl mesylates, benzenesulfonates, and tosylates are much less expensive than triflates and are unreactive toward palladium catalysts.

Recently Percec et al. reported the Ni(0)-catalyzed Suzuki-type cross-coupling reaction of various aryl sulfonates including mesylate with arylboronic acids in the presence of $K_3PO_4$ [36]. The Ni(0) catalyst is generated in situ from $NiCl_2$(dppf) and Zn. This reaction, which yields unsymmetrical biaryls in reasonable yields under mild conditions, is highly regiospecific and tolerates various functional groups. The reactivity of various Ni(0) catalysts was compared to that of the less reactive Pd(0) catalysts.

Due to the moderate reactivity of aryl triflates and the high cost of the triflate functionality, aryl fluoroalkanesulfonates [$ArOSO_2(CF_2)_nCF_3$] have been proposed as an alternative to triflates, because they are easily prepared using commercially available fluoroalkanesulfonic anhydrides or halides. Especially attractive are aryl nonaflates ($ArONf = ArOSO_2$-$(CF_2)_8CF_3$) which are readily prepared and are stable to flash column chromatography. Most recently, Rottländer and Knachel [37] have demonstrated that the treatment of the nonaflate with boronic acid (**18**) provides, under typical conditions

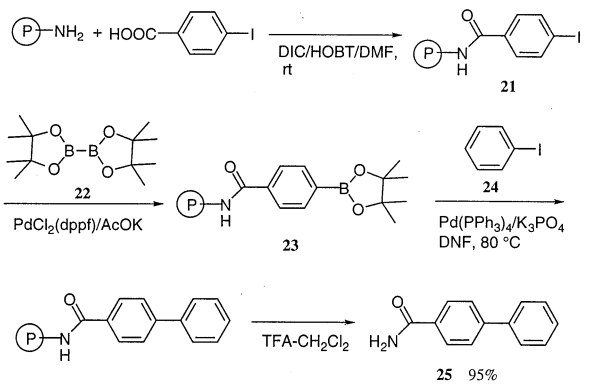



Scheme 13.

for Suzuki coupling, the expected product (**19**) in 89% yield (Scheme 12).

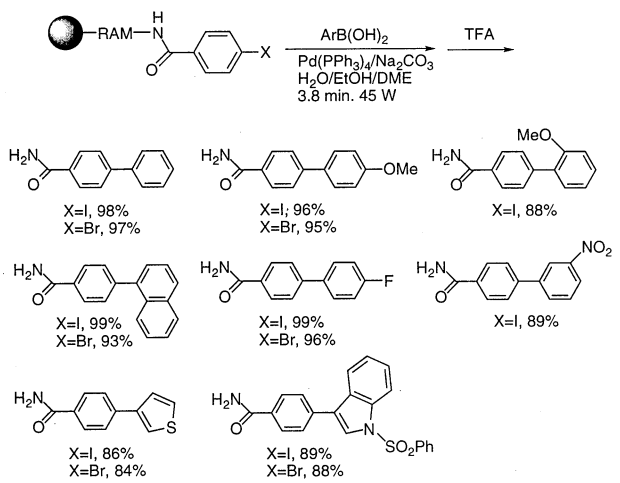
The Boc-derivative of (4-pinacolylborono)phenylalanine ethyl ester (**20**) or the corresponding boropnic acid, undergo Suzuki–Miyaura coupling reactions with aromatic chlorides in the presence of catalytic amounts of $PdCl_2(PCy_3)_2$, or $NiCl_2$(dppf), respectively, to produce 4-substituted phenylalanine derivatives (Scheme 13) [38].

Constructing libraries of nonpolymeric, small organic molecules by solid phase techniques have been the focus recently of combinatorial synthesis. While many pharmacologically interesting molecules have been prepared on solid support in the last few years, most of the linkers (e.g. OH, COOH, NHR) employed in these syntheses were inherited from those used in generating peptide, oligonucleotide and oligosacharride libraries. The adaptation of the Suzuki reaction for C–C bond formation to resin mounted procedures has been presented. Efforts to prepare the boronic acid on solid-phase using classical methodology met with little success. Most recently Pietre and Baltzer have found that application of Miyaura's conditions [39] (pinacol ester of diboron (**22**) (two equivalents), $PdCl_2$(dppf) (0.03 equivalents), KOAc (three equivalents) in DMF at 80°C for 20 h to a model polymer-bound *p*-iodobenzamide (**21**)) leads to a solid-phase boronate (**23**) (Scheme 14). Then the reaction of **23** with aryl halide such as **24** in the presence of $Pd(PPh_3)_4$ (0.02 equivalents)/$K_3PO_4$ (five equivalents)/DMF at 80°C to give **25** in 95% yield (Scheme 14) [40].




Scheme 14.

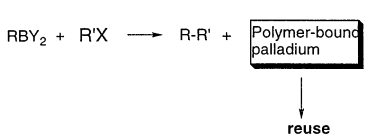
Table 2
Suzuki coupling on solid-phase assisted by microwave irradiation




A method for attaching haloarylsilanes to polymer support was also developed. Namely, the polymer bound aryl halides were reacted with a variety of $ArB(OH)_2$ under the Suzuki cross-coupling conditions and the coupled resins were cleaved by different electrophiles to give *ipso*-substitution products in good yields [41]. A similar type of reaction by the coupling of polymer bound aryl iodides with various boron reagents in the presence of $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ and $K_2CO_3$ was reported [42].

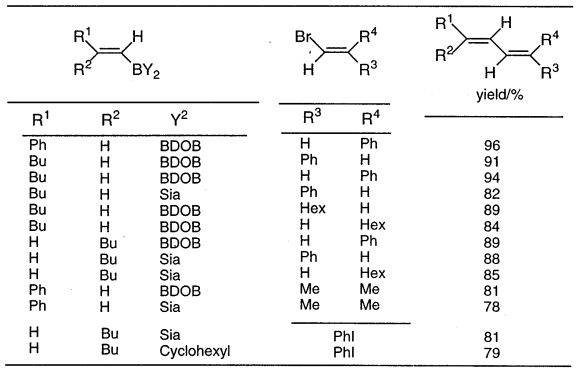
The advantages of solid-phase organic chemistry to combinatorial organic synthesis are well recognized. In combinatorial chemistry the reaction times and reaction temperatures required are frequently crucial factors. Microwave irradiation is used to enhance reaction rates [43]. Larhed et al. have recently published that microwave-assisted palladium-catalyzed coupling of aryl and heteroaryl boronic acids with iodo- and bromo-substituted benzoic acids, anchored to TentaGel S RAM, provides after a reaction time of 3.8 min (45 W) [44]. The preparative results are summarized in Table 2.

The polymer-bound palladium-catalyzed cross-coupling reaction of electrophiles (halides and triflates) with organoboron compounds to form carbon–carbon bonds has been achieved at mild conditions with very high activity. The polymeric catalyst can be easily separated from a reaction mixture and reused more than ten times with no decrease in activity. Representative results are shown in Eq. (9) and Table 3 [45].




(9)

Table 3
Polymer-bound palladium-catalyzed cross-coupling reaction of organoboron compounds with 1-alkenyl bromides or iodobenzenes[a]

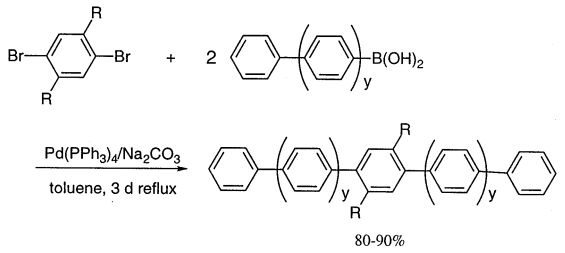


| $R^1$ | $R^2$ | $Y^2$ | $R^3$ | $R^4$ | yield/% |
|---|---|---|---|---|---|
| Ph | H | BDOB | H | Ph | 96 |
| Bu | H | BDOB | Ph | H | 91 |
| Bu | H | BDOB | H | Ph | 94 |
| Bu | H | Sia | Ph | H | 82 |
| Bu | H | BDOB | Hex | H | 89 |
| Bu | H | BDOB | H | Hex | 84 |
| H | Bu | BDOB | H | Ph | 89 |
| H | Bu | Sia | Ph | H | 88 |
| H | Bu | Sia | H | Hex | 85 |
| Ph | H | BDOB | Me | Me | 81 |
| Ph | H | Sia | Me | Me | 78 |
| H | Bu | Sia | PhI | | 81 |
| H | Bu | Cyclohexyl | PhI | | 79 |

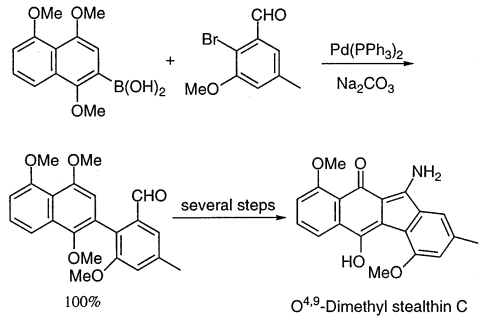
[a] The reaction was carried out at 80°C for 2 h under nitrogen by using polymer-bound palladium (1 mol% pd), NaOEt (two equivalents), and organoborane (1.2 equivalents).

The arylsulfonate ester functionality connecting an alkyl chain to a polystyrene resin is compatible with Suzuki coupling. Cleavage of the resin-bound substrate with amines and other nucleophiles can provide diverse compound libraries [46]. A solid-phase synthesis of isoxazolinoisoquinoline heterocycles via solid-phase Reissert and Suzuki reactions has been developed [47]. The same type of phase synthesis of a 1,3,5-trisubstituted pyridinium salt combinatorial array containing two variable groups was accomplished in good yields. This entailed the incorporation of 5-bromonicotinic acid onto the resin, followed by Pd(0) catalyzed Suzuki coupling, then alkylation of the pyridiner nitrogen and finally cleavage from the resin [48]. Similarly, poly(ethylene glycol) supported liquid phase synthesis of biaryls is reported [49].

Constitutionally homogeneous oligo-*p*-phenyls are materials of considerable current interest for chemists, physicists, and material scientists because such compounds are excellent model compounds for developing a profound understanding of the spectroscopic and redox properties of polyaromatic systems, and of the thermal phase behavior and solution properties of rodlike liquid-crystalline molecules. Furthermore, functionalized oligo-*p*-phenyls have gained some importance as mainchain-stiffening building-blocks in semi-flexible polymers like aromatic polyesters and polyimides. Despite considerable advantages, however, parent oligo-*p*-phenyls have a serious drawback with regard to the above applications: their solubility decreases dramatically with an increasing number of benzene rings. It is known, fortunately, that the attachment of lateral methyl groups to the oligo-*p*-phenyls increases their solubility. Nevertheless, the




Scheme 15.

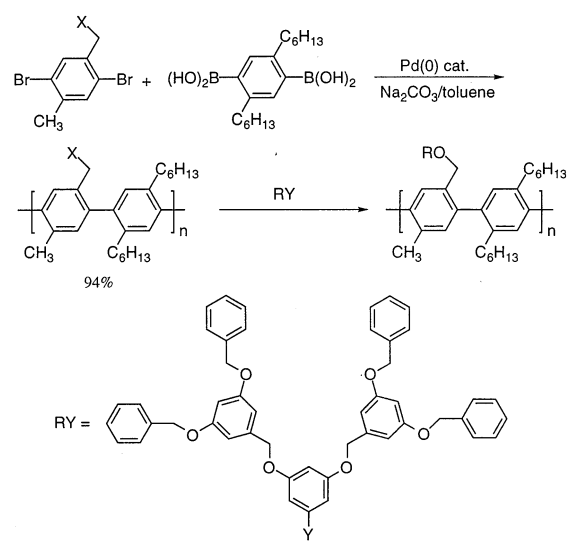



Scheme 17.

solubility effect of methyl groups is insufficient in the case of longer oligo-*p*-phenyls, and the concept of solubilizing flexible side chains is worked out to further increase solubility of rigid-rod molecules such as aromatic polyesters. By taking advantage of this latter concept, Galda and Rehahn [50] have applied the Suzuki coupling as the oligomer formation reaction (Scheme 15) and provided expected oligo-*p*-phenyls in excellent yields. Matile et al. have also realized the synthesis of polymers using polycondensation [51].

Similarly, the synthesis of a novel rigid-rod phenylene-cymantrenylene copolymer using the Suzuki coupling as the polymer forming reaction was reported [52]. The synthesis of a terphenyl derivative complexed by the cationic moiety $Cp^*Ru^+$ by the Suzuki coupling of $[Cp^*Ru^+(BrC_6H_4Br)]OTf$ with phenyl boronic acid under catalysis of $Pd(PPh_3)_4$ in a DME–water mixture at 85°C in quantitative yield was presented [53].

Research on dendrimers first focused on synthetic interests concerning this new class of macromolecules, and a broad range of dendrimers is available, some even commercially. The present study has shifted from merely synthetic problems to questions such as, what are dendrimers good for? and, what are these unique compounds superior to known system? Consequently, much more




Scheme 16.

useful synthetic procedures are requested. Schlüter et al. have reported the synthesis of dendrimers with poly(*p*-phenylene)-PPP derived cores using the Suzuki polycondensation [54]. One of examples is shown in Scheme 16.

A series of functionalized and optically active major-groove polybinaphthyls and minor-groove polybinaphthyls have been most recently synthesized by using the Suzuki coupling and have been spectroscopically characterized [55]. The application of these chiral polymers in the asymmetric addition of diethylzinc to aldehydes was studied. A minor-groove polybinaphthyl was found to be an excellent catalyst for the asymmetric reaction of diethylzinc with a number of aldehydes. The chiral polymer can be easily recovered and reused without loss of catalytic activity as well as enantioselectivity. These rigid and sterically regular chiral polybinaphthyls represent a new generation of enantioselective polymeric catalysts.

A series of novel quinoxaline-based conjugated polymers which contain a ruthenium(II) bipyridine complex were synthesized by the Suzuki coupling reaction [56].

The synthesis of substituted poly(phenylene)s, in particular poly(1,4-phenylene)s by the Suzuki coupling of the 1,3-propanediol diester of 2,5-dialkyl-1,4-phenylenediboronic acid with various aryl dibromides was reported. Optimized reaction conditions for the polymerization of a nitro group containing monomers were developed in this study. For example, poly(4,6-dinitro-2′,5′-dihexyl-3,4′-biphenylylene) was obtained at 37°C with $PdCl_2(dppf)$ in THF and aqueous $NaHCO_3$ in quantitative yield with a number average degree of polymerization of Pa = 27 [57].

In 1992 stealthin A and B were isolated as potent radical scavengers from *Streptomyces viridochromogenes*. Gould and his group synthesized stealthin C and demonstrated its existence in kinamycin biosynthesis [58,59]. Most recently, $O^{4,9}$-dimethylstealthin has been synthesized using the Suzuki coupling as a key step as shown in Scheme 17 [60].

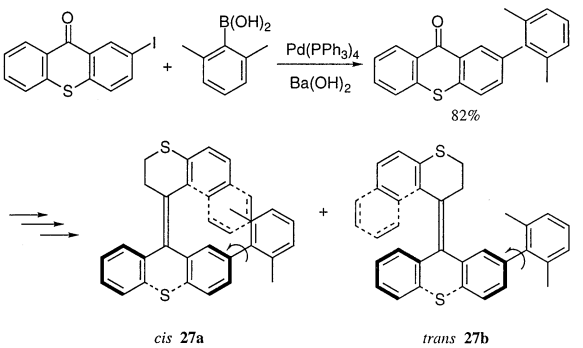
Recently, studies on catalytic cyclophanes have been pursued actively. For instance, Diederich and Mattel [61] reported that the flavo-thiazolio-cyclophane (**26**) was prepared on a gram scale by an 18-step synthesis,

in which the cross-coupling reaction between 7-bromoflavin and flavo-cyclophane is the key step (Scheme 18). The flavo-thiazoliocyclophane (**26**), with both prosthetic groups attached in proximity to the well-defined cyclophane binding site, is a functional model for the enzyme pyruvate oxidase. In basic methanolic solution, **26** catalyzes the oxidation of aromatic aldehydes to their corresponding methyl esters.

In an approach toward a photochemically bistable molecular rotor the synthesis of *cis*-**27a** and t*rans*-**27b** isomers, being sterically overcrowded alkenes functionalized with an *o*-xylyl group as a rotor, has been described. The key step in the synthesis is a Suzuki coupling to attach the xylyl moiety (Scheme 19) [62].

A versatile method for the synthesis of a complex, fused polycyclic aromatic system in high chemical yield has been discovered. Pd-catalyzed Suzuki type cross-coupling allows for the preparation of nonfused skeletal ring systems in high yield. The ring-forming step, which generally proceeds in high yield, utilizes 4-alkoxyphenylethynyl groups and is induced by strong electrophiles such as trifluoroacetic acid and iodonium tetrafluoroborate. The reaction produces phenanthrene moieties which are integrated into extended polycyclic aromatic structures (Scheme 20) [63,64]. Fused polycyclic benzenoids as well as benzenoid/thiophene systems may be prepared utilizing this methodology.

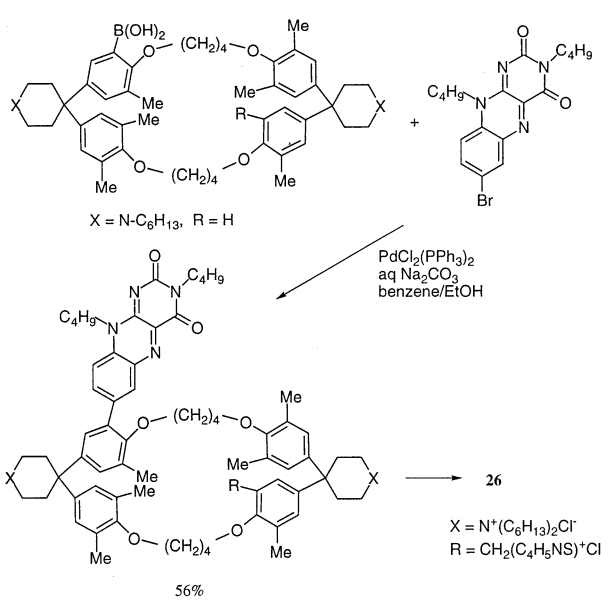
Recently, the *anti*-HIV alkaloids, michellamines A (**30**) and B (**31**) have been noted markedly. The tetraaryl skeleton of the michellamines is constructed by formation first of the inner (nonstereogenic) biaryl axis and subsequently of the two other (stereogenic)



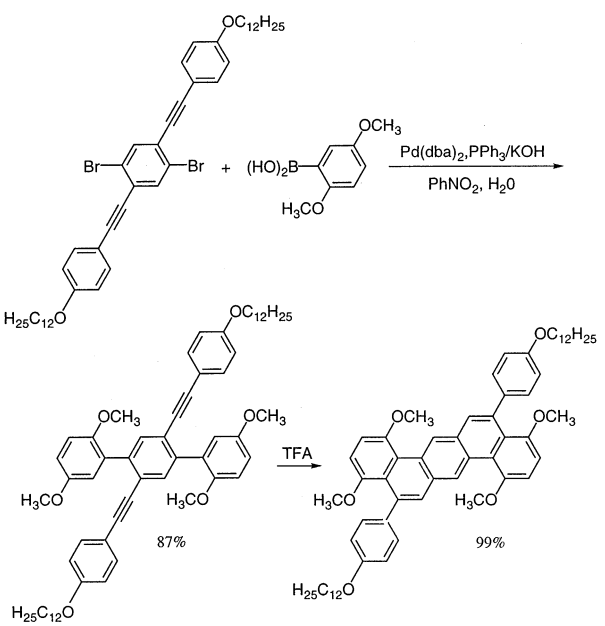

Scheme 19.

axes by using a double Suzuki-type cross-coupling reaction between binaphthalene ditriflate (**28**) and isoquinolineboronic acid (**29**) (Scheme 21) [65]. Dawson et al. also reported stereospecific syntheses of the same alkaloids by the palladium catalyzed cross-coupling of boronic acids with organic halides [66].

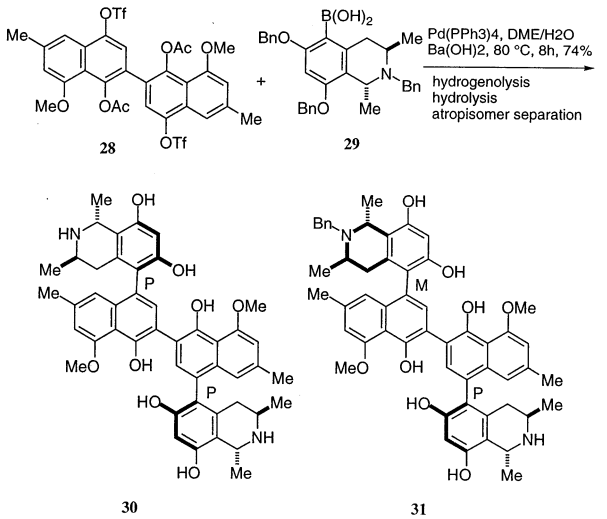
Vancomycin is a polycyclic glycopeptide antibiotic effective against drug-resistant bacterial strains. The daunting synthetic challenge posed by its structure is largely due to the strained nature of the 12-membered biaryl framework (AB ring system) and the two 16-membered biaryl ethers (COD and COE ring systems). Nicolaou and his group have reported a Suzuki coupling approach to the AB–COD bicyclic system of vancomycin [67]. Suzuki coupling of iodide (**32**) with **33** was facilitated by a $Pd(Ph_3)_4$ catalyst and $Na_2CO_3$ to afford a 1:1 mixture of the two atropiso-




Scheme 18.




Scheme 20.

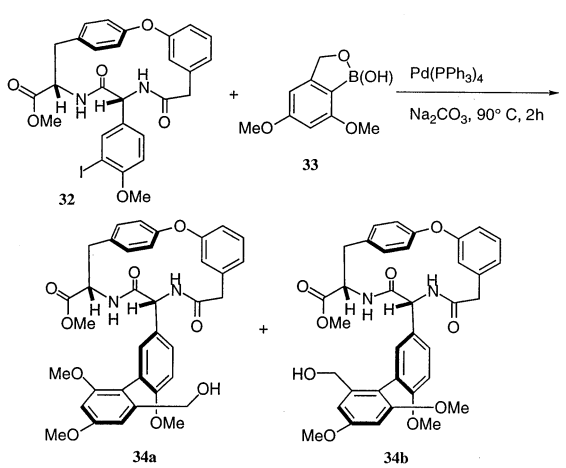



Scheme 21.

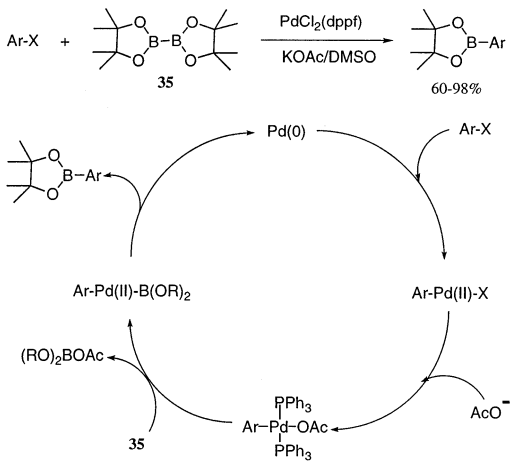
mers **34a** and **34b** in 80% combined yield (Scheme 22). The coupling of the parent boronic acid corresponding to **33** (without methyl groups) with iodide (**32**) led to a single compound.

The palladium-catalyzed cross-coupling reaction of the pinacol ester of diboronic acid [$(Me_4C_2O_2)$-$BB(O_2C_2Me_4)$, **35**] with haloarenes gives a direct procedure for arylboronic esters from aryl halides in a range of 60–98% (Scheme 23) [39]. The reaction is catalyzed by $PdCl_2$(dppf) (3 mol%) at 80°C in the presence of KOAc (three equivalents) in DMSO and available with various functional groups. The *trans*-$ArPd(II)(OAc)(PPh_3)_2$ intermediate was isolated and characterized to propose the catalytic cycle involving the transmetalation between the phenylpalladium(II) acetate and (**35**) (Scheme 23).

The cross-coupling reaction of $(RO)_2BB(OR)_2$ (RO = methoxo or pinacolato) with aryl triflates to give arylboronates has been carried out at 80°C in



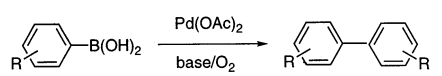

Scheme 22.




Scheme 23.

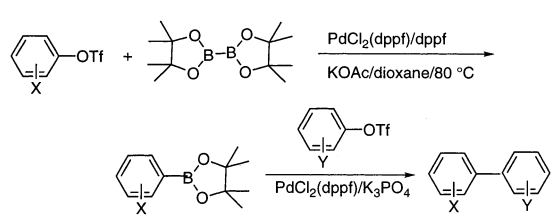
the presence of $PdCl_2$(dppf) (3 mol%), dppf (3 mol%) and KOAc (three equivalents) in dioxane. The reaction is available with various functional groups such as nitro, cyano, ester, keto, aldehyde, and alkoxy groups. The subsequent cross-coupling with the second aryl triflates provides biaryls readily in good yields [68] (Scheme 24).

Although we observed previously that the preparation of biphenyl from phenylboronic acid in anhydrous conditions using $Pd(OAc)_2$ with $PPh_3$ as catalyst and $Cu(OAc)_2$ under nitrogen [69], we have never checked in detail. Recently, Jackson et al. have reported that symmetric biaryls can be obtained under very mild conditions in good yields by palladium catalyzed coupling of arylboronic acids in aqueous ethanol (95%) containing sodium carbonate at ambient temperature and in the presence of oxygen (Eq. (10)) [70]. A paper dealing predominantly with mechanistic aspects of these palladium-catalyzed homocoupling reactions has appeared [28].

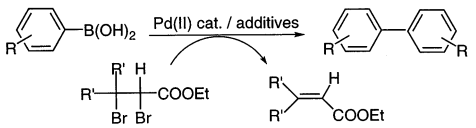



(10)

Tamao and his coworkers also reported the Pd(II)-catalyzed oxidative homo-coupling of areneboronic acids using acrylate dibromide derivatives as effective oxidants (Scheme 25) [71].

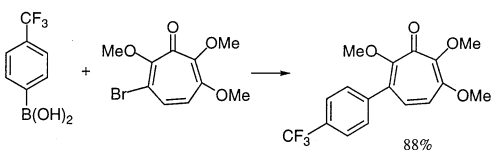



Scheme 24.




Scheme 25.

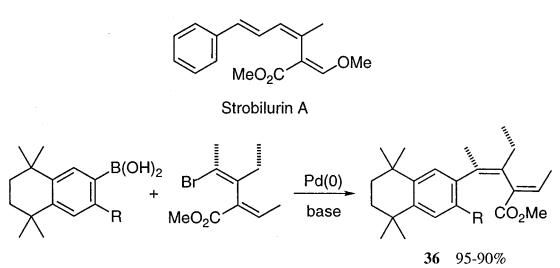
It is observed that 3,7-dihydroxytropolone derivatives are the foremost representatives of a new class of potent, competitive inhibitors of inositol monophosphatase. The first successful preparation of mono- and disubstituted 3,7-dihydroxytropolones has been reported by single or double Suzuki coupling reactions between these permethylated monobromo- and bibromodihydroxytropolone derivatives and a variety of boronic acids [72]. An example is demonstrated in Eq. (11). These compounds were found to be potent inhibitors of inositol monophosphatase with $IC_{50}$ values in the low-micromolar range.



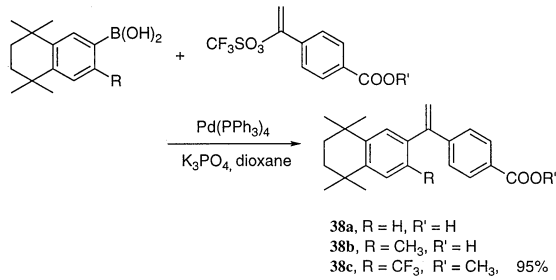

(11)

### 1.2. With other organic halides

The naturally occurring derivatives of β-methoxyacrylic acid such as strobilurin A have become of interest to chemists and biologists because of their unusual structures and a wide range of biological activities. For example, they are able to control the growth of fungi and bacteria, or have insecticidal, antiviral or antitumor activity. However, it was clear that the natural products themselves can not be used directly because of insufficient levels of activity, photochemical instability and volatility. Therefore, research on the synthetic analogs of strobilurin A as fungicides has become of major importance in the agrochemical industry. To obtain highly promising fungicides, the synthesis of double bonds-locked analogs (**36**) of strobilurin was reported (Scheme 26) [73].

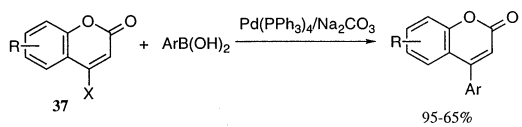



Scheme 26.




Scheme 27.

Palladium-catalyzed coupling of the 4-chloro- or 4-bromo-coumarins (**37**) with arylboronic acids constitutes an efficient access to 4-aryl coumarins in good yields (Eq. (12)) [74].

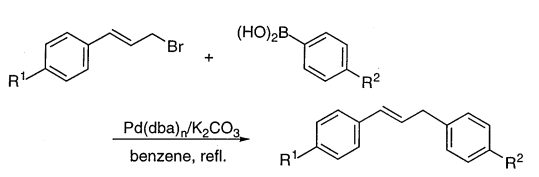



(12)

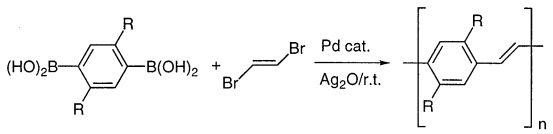
Retinoids, natural and synthetic analogs of vitamin A, play important roles in numerous biological functions including cell proliferation and cell differentiation. Recent evidence has shown that retinoids exert their functions through at least two classes of nuclear receptors: RAR(α,β,γ) and RXR(α,β,γ). Among them, introduction of a 3-methyl substituent to a weakly active RXRs compound (**38a**) resulted in targretin (LGD 1069, **38b**) which selectively binds with high affinity to the RXRs and is currently recognized to have high activity in clinical trials for the treatment of cancer. From this perspective, Qing and Fan attempted the synthesis of 3-trifluoromethyl substituted derivative (**38c**) by using the Suzuki coupling as shown in Scheme 27 [75].

1,3-Diarylpropenes possessing different substituents at the aryl rings are obtained in high yields by a modified Suzuki coupling between cinnamyl bromides and arylboronic acids using the phosphine-free $Pd(dba)_n$ ($n = 1.5–2$) as catalyst in benzene and in the presence of suspended potassium carbonate [76] (Scheme 28).

Rigid-rod polymers with a linear conjugated backbone built up by *para*-linked arylene units are interesting compounds due to their unique properties concerning photoconductivity or use as electrooptically




Scheme 28.




Scheme 29.

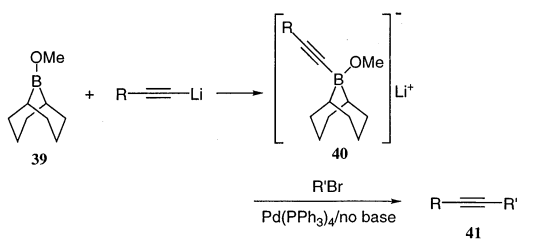
active materials. A typical example is a poly(1,4-phenylenevinylene) derivative (PPV). Different approaches were developed to synthesize PPV such as the Wittig and Horner reaction or the McMurry condensation. By these methods the molecular weight is limited by the insolubility of the higher oligomers. Substituted PPV can be prepared from *p*-dibromobenzenes and ethylene (Heck reaction). However, a drawback of the Heck reaction is that it is not strictly regioselective. Most recently, Koch and Heitz have reported that PPV derivatives are prepared from *trans*-1,2-dibromoethylene and aryldiboronic acids by a Suzuki cross-coupling reaction. The polymers are synthesized in a two-phase system at room temperature using silver oxide and a Pd catalyst (Scheme 29) [77]. Soluble polymers are obtained when the aryldiboronic acid is substituted with long-chain alkoxy groups.

## 2. Cross-coupling of alkynylborane derivatives

Alkynylboranes have long been known to be useful synthetic intermediates [78]. Compared to other organoboranes, they are stronger Lewis acids and are easily hydrolyzed. Because of these features, they have not been employed in the Suzuki–Miyaura coupling, in which the presence of bases is essential [79].

Soderquist et al. found that the addition of B-methoxy-9-borabicyclo[3.3.1]-nonane (**39**) to alkynyllithium reagents gives stable complexes (**40**) which undergo efficient Suzuki coupling to produce a variety of alkynyl derivatives (**41**) (Scheme 30, Table 4) [80].

Almost at the same time, Fürstner and Seidel have reported the same reaction [81]. Namely, the necessary alkynyl borates in the palladium catalyzed C–C bond formation are prepared from 9-methoxy-9-BBN




Scheme 30.

Table 4
Arylacetylenes and enynes from **39**

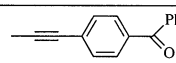
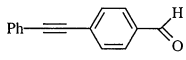
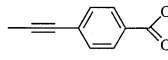
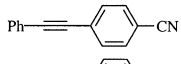
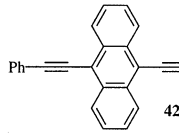
| R | R′ | Product yield (%)[a] |
|---|---|---|
| *n*-B | $C_6H_5$ | 60 (92) |
| $SiMe_3$ | $C_6H_5$ | 64 |
| Ph | $C_6H_5$ | 94 |
| *n*-Bu | *p*-$MeOC_6H_4$ | 62 (68) |
| $SiMe_3$ | $CH_2$=$CC_6H_5$ | 88 |
| *t*-Bu | *cis*-CH=CH-*t*-Bu | 56 |
| $SiMe_3$ | *trans*-CH=CH-*n*-Bu | 55 |

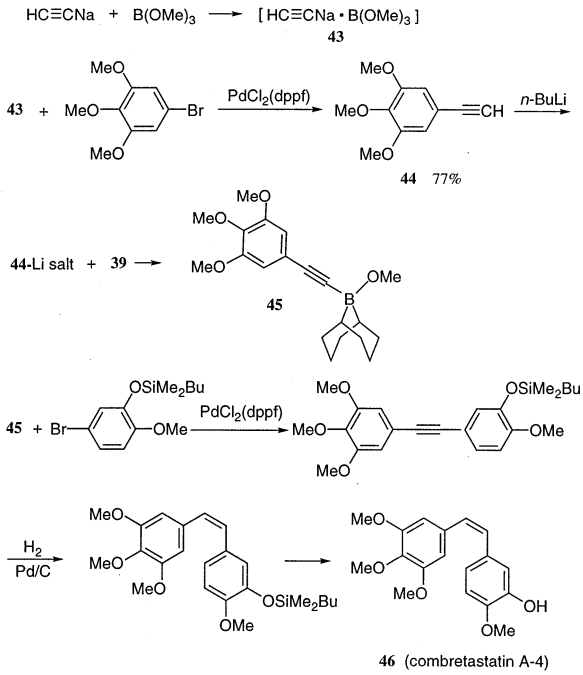
[a] Isolated yields of analytically pure compounds (GC yields).

and a polar organometallic reagent RM, and not as usually from boranes and bases. This approach allows cross-couplings of aryl halides with e.g. alkynyl-, methyl-, or $TMSCH_2$-groups, which are beyond the scope of the conventional Suzuki reaction. The method is highly chemoselective and turned out to be compatible with aldehyde, amide, ketone, ester and cyano functions as well as with basic nitrogen atoms in the substrates. Some of the results are shown in Table 5. This reaction is used to prepare compound **42** which is highly valuable for its chemoluminescence property.

Tubulin as the major protein component of microtubules is a formidable target in search of anticancer chemotherapeutics. Another very promising class of antineoplastic agents which affects this subcellular target is the combretastatin family, consisting of several closely related stilbene, phenanthrene and biphenyl derivatives. The most active among them is combretastatin A-4 (**46**), which is an exceptionally strong inhibitor of tubulin polymerization and belong to the most cytotoxic agents tested so far against murine lymphocytic leukemia, human ovarian and hu-

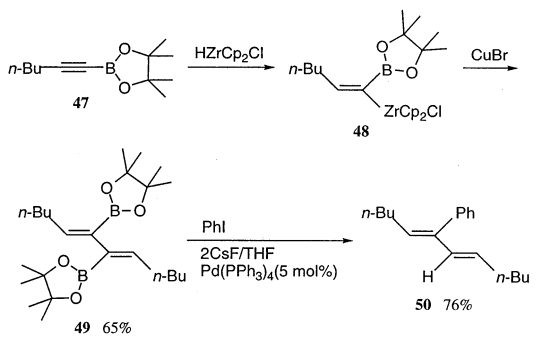
Table 5
Pd-catalyzed arylation of alkynyl metal reagents mediated by 9-MeO-9-BBN
89

| Substrate | RM | Product | Yield/% |
|---|---|---|---|
| 4-bromobenzophenone | MeC≡CNa |  | 89 |
| 4-bromobenzaldehyde | PhC≡CK |  | 77 |
| ethyl 4-bromobezoate | MeC≡CNa |  | 86 |
| 4-bromobenzonitrile | PhC≡CK |  | 93 |
| 9,10-dibromoanthracene | PhC≡CLI |  42 | 84 |

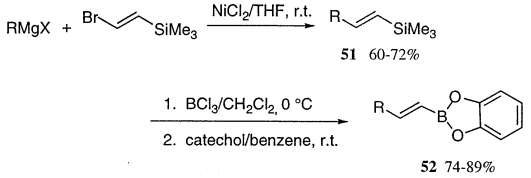



Scheme 31.

man colon cancer cell lines. The simplicity of combretastatin A-4 offers promise for the rational design of new chemotherapeutic agents. Therefore, many efforts have been devoted to the detailed study of the structure-activity relationship of substituted stilbene derivatives of this type. From these investigations it must be concluded that the (*Z*)-configuration of the ethene bridge is essential. The known synthetic approaches to combretastatin A-4 and analogs, however, do not well enable for this feature. As they are based on Wittig reactions, mixtures of the (*Z*) and (*E*) isomers are inevitably formed which are difficult to separate on a preparative scale [82]. Fürstner and Nikolakis have reported on an alternative entry into this highly valuable class of compounds which avoids the problem and allows systematic variations of the arenes for further pharmacological studies [83]. Their approach is based on the (*Z*)-selective Lindlar-type semihydrogenation of




Scheme 32.




Scheme 33.

an appropriate alkyne precursor, which can be readily assembled by two consecutive Suzuki cross-coupling reactions. An example is shown in Scheme 31.

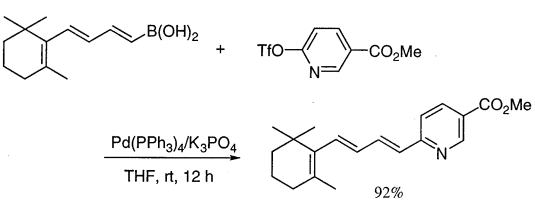
Hydrozirconation of 1-alkynyl pinacolboronates (**47**), with $HZrCp_2Cl$ provides *gem*-bora-zirconocenes (**48**). The latter when treated with CuBr gives the homocoupled (1*E*,3*E*)-2,3-dibora-1,3-butadienes (**49**) in 65% yield. Suzuki–Miyaura coupling of **49** with PhI in the presence of $Pd(PPh_3)_4$ and CsF leads to the replacement of both boron groups by phenyl and hydrogen to give **50** in 76% yield [84] (Scheme 32).

## 3. Cross-coupling of alkenylborane derivatives

A novel and highly efficient conversion of vinylsilanes into vinyl boronates has been presented. For example, the series of (*E*)-vinylsilanes were prepared by the coupling reaction of Grignard reagents with (*E*)-1-bromo-2-trimethylsilylethene in the presence of an Ni(II) catalyst. The vinylsilanes (**51**) were treated with boron trichloride in $CH_2Cl_2$ at 0°C to give an easy *ipso*-borodesilylation. Moreover, when the solution of the resulting haloborane was added to catechol in benzene at room temperature, the 2-[(*E*)-alk-1-enyl]-1,3,2-benzodioxaboroles (**52**) were obtained in good yields (Scheme 33) [85].

de Lera et al. [86] published the application of the Suzuki cross-coupling for the preparation of retinoids, arotinoids and their heteroderivatives. The procedure was shown to be of general application. Remarkably, the reaction is applicable to the synthesis of the thermally unstable common retinoids under very mild conditions. This is exemplified in Scheme 34.

The synthesis of (3*E*,5*E*)- and (3*E*,5*Z*)-3,5-hexadieoic acids was prepared selectively by the palladium-base assisted cross-coupling reaction [87]. Unsaturated amino acids are an important class of natural products

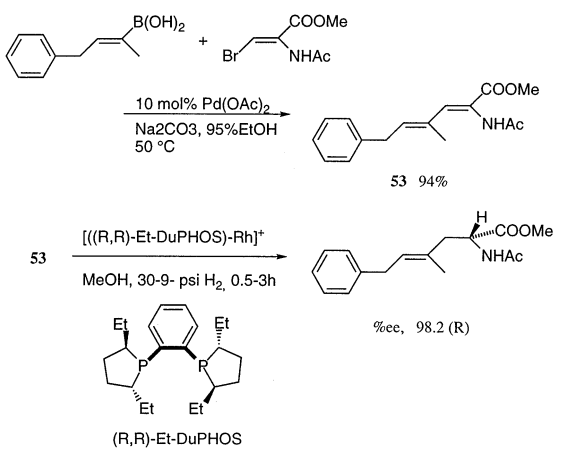



Scheme 34.

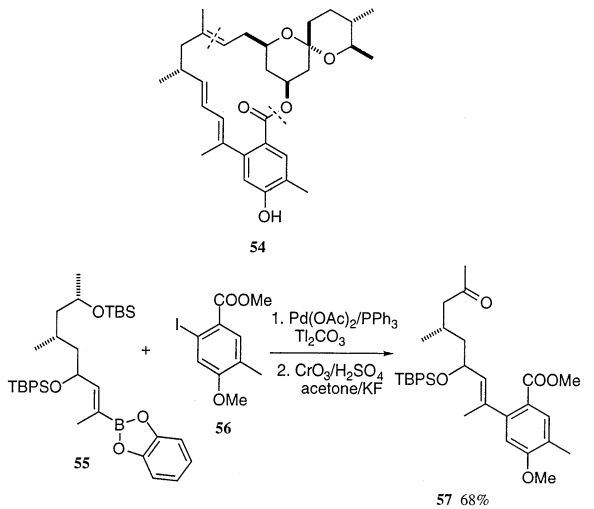
that display an array of interesting biological properties. Specifically, γ,δ-unsaturated amino acids have not only been synthetically challenging targets but also have been isolated from a variety of natural sources and have served as intermediates in the synthesis of complex amino acids and peptides. An extremely efficient method has been found for the catalytic asymmetric hydrogenation of conjugated α,γ-dienamide esters using the Et–DuPHOS–Rh catalyst system. α,γ-Dienamide ester substrates were prepared readily via the Suzuki cross-coupling reaction. Full conversion to the corresponding γ,δ-unsaturated amino acids with very high regio- and enantioselectivity was achieved after short reaction times (Scheme 35) [88].

Milbemycin β3 (**54**) is one of the simplest members of the potent milbemycin/avermectin family of antiparasitic agents. As part of a research programme aimed at the modification of the structure of these anthelmintic agents, Marko and his group [89] reported the efficient synthesis of the left-hand subunit of **54** using a Suzuki coupling. The unique role played by thallium carbonate in this palladium-catalyzed reaction was discovered (Scheme 36). While Kishi showed the usefulness of TlOH as a base in the cross-coupling reactions of vinylboron compounds with vinyl halides [90], Suzuki utilized the corresponding $Tl_2CO_3$ to promote some alkyl–aryl/alkyl–vinyl coupling reactions [91]. The presence of an ester function in the aromatic fragment (**56**) precluded the use of TlOH and they decided to initially study the effect of TlOEt. Disappointingly, a mediocre yield of the product (**57**) (12% yield) was observed. However, in the presence of $Tl_2CO_3$, a smooth reaction took place giving, after simple filtration of the insoluble greenish–yellow TlI, the desired styrene derivative in high yield. Jones oxidation in the presence of KF chemoselectively produced the methyl ketone (**57**) in 68% overall yield from **55** (Scheme 36).

Organic compounds with polyene structure are frequently found in living systems. Not unexpectedly, their



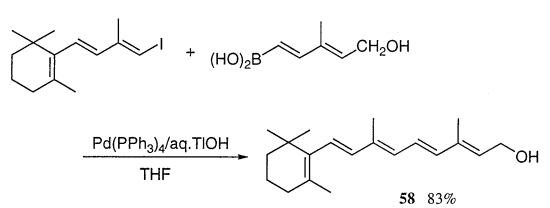

Scheme 35.



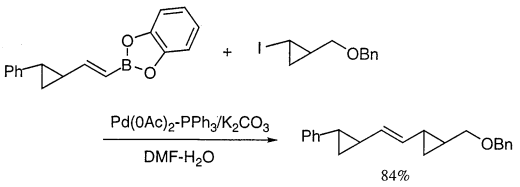

Scheme 36.

ability to elicit a wide range of physiological effects often stems from changes in olefin configuration. In the retinoid field, the first industrial synthesis of vitamin A (**58**) at Hoffmann La Roche was followed by other approaches using olefin-forming reactions. An alternative route to vitamin A is alkenyl–alkenyl coupling catalyzed by a transition metal. Negishi showed that organozinc compounds [92] afford the best yields of vitamin A. de Lera et al. [93] have recently reported a new synthesis of vitamin A (**58**) with essentially complete control of regio- and stereochemistry, which is based on the thallium-accelerated, palladium-catalyzed cross-coupling reaction of an (*E*)-1-alkenylboronic acid and an (*E*)-1-alkenyl iodide under the Suzuki reaction conditions (Scheme 37). They emphasized that the excellent chemo-, regio- and stereoselectivities and homo/cross discrimination of alkenyl iodide-alkenylboronic acid coupling (comparable to those of alkenylzinc coupling [92] allow significant advances in the stereocontrolled construction of polyenes of biological interest.

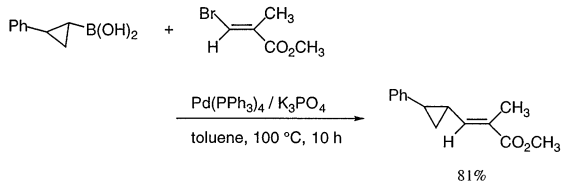
In the previous publication, Genet et al. reported that the palladium-water soluble catalyst prepared in situ from palladium(II) acetate and TPPT is a useful and practical catalytic system for various cross-coupling reactions using π-allyl palladium methodology [94]. Thereafter, they investigated that the palladium(0) catalyzed cross-coupling of boronic acids or esters con-




Scheme 37.




Scheme 38.

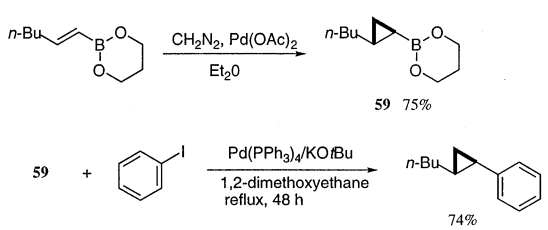



Scheme 40.

ducted with a water soluble catalyst in the presence of organic base allows, under mild conditions, the production of functionalized dienes (60–90% yield) [95].

Although there is no literature precedent for the oxidative insertion of palladium(0) into a cyclopropyl iodide bond, it is considered that this process is feasible since cyclopropanes are known to have some $sp^2$ character [96]. Recently, the palladium-catalyzed Suzuki-type cross-couplings of iodocyclopropanes with boronic acids have been actually reported to give *trans*-1,2-dicyclopropyl alkenes in good yields [97]. An example is shown in Scheme 38. In order to increase the solubility of the base in the organic phase, a phase-transfer catalyst was used as an additive. The addition of tetrabutylammonium chloride with $K_2CO_3$ in DMF–$H_2O$ at 90°C gave quantitative conversion of iodocyclopropasne to the desired coupling product.

The cyclopropane ring is present in many natural products, and is increasingly being incorporated into pharmaceutically interesting mimetics of natural materials. However, the development of a truly general method for the stereoselective asymmetric synthesis of polysubstituted cyclopropanes is still elusive [98]. In the most commonly used strategies, the cyclopropane is inevitably substituted by hydroxy or ethereal directing groups (asymmetric Simmons–Smith protocols [99]) or rhodium catalyzed cyclopropanations by diazoalkanes [100]. The latter method also frequently results in mixtures of geometric isomers. Clearly, a method which allows for the control of both relative and absolute stereochemistry, but requires no activating or directing functionality, would be of great utility. Recently, Hildebrand and Marsden have published a novel stereospecific synthesis of *trans*-1,2-disubstituted cyclopropanes using the palladium(0) mediated cross-coupling of cyclopropylboronic esters with aryl halides (Scheme 39) [101]. This forms the basis of a proposed new asymmetric synthesis of cyclopropanes.

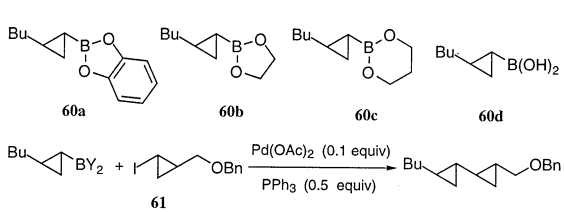



Scheme 39.

Most recently, Deng et al. have reported a stereocontrolled synthesis of cyclopropyl-substituted α,β-unsaturated esters based on the palladium catalyzed cross-coupling reaction of bromoacrylates with *trans*-2-alkyl(or aryl)cyclopropylboronic acids (Scheme 40) [102].

Suzuki cross-coupling reactions between a variety of iodocyclopropanes and cyclopropyl-boronate esters to produce symmetrical or unsymmetrical contiguous cyclopropanes were achieved in good yields (Scheme 41) [103]. As reported by Chan and Zhang for the cross-coupling reaction involving bulky boronic acids [7], the nature of the base has a spectacular effect on the efficiency of the coupling. A dramatic rate enhancement in the Suzuki coupling of cyclopropylboronate esters and iodocyclopropane was observed in the presence of KO*t*-Bu (Table 6).

Previously, we reported a convenient route to *cis*-bis(boryl)alkenes via the platinum(0)-catalyzed diboration of internal and terminal alkynes with bis(pinacolato)diboron (Scheme 42) and the palladium-catalyzed cross-coupling reaction of **62** with two equivalents of iodoarenes gives corresponding bis(aryl)alkenes (**64**) in high yields [104]. Most recently, Miyaura et al. have reported that **62** regioselectively cross-couples with aryl, 1-alkenyl, benzyl, and allyl halides in the presence of a palladium catalyst and a base to give the corresponding pinacol esters (**63**) in good yields [105]. Bis(boryl)alkenes derived from internal alkynes also exhibit the same regioselectivity on the palladium-catalyzed cross-coupling, as was recently demonstrated by Brown and Armstrong [106] for the synthesis of tetrasubstituted alkenes.




Scheme 41.

Table 6
Various attempts to cross-couple boronate esters and acid **39-1-4** and iodocyclopropane **39-5**

| Y | Conditions | Time (h) | Yield (%) |
|---|---|---|---|
| **60a** | DMF, $H_2O$, $K_2CO_3$, $Bu_4NCl$ | 48 | [a] |
| **60b** | DMF, $H_2O$, $K_2CO_3$, $Bu_4NCl$ | 48 | [a] |
| **60c** | DMF, $H_2O$, $K_2CO_3$, $Bu_4NCl$ | 20 | [b] |
| **60b** | DME, $K_2Co_3$, 80°C | 90 | [b] |
| **60b** | DME, NaOH, 80°C | 90 | 10 |
| **60b** | DME, NaOEt, 80°C | 90 | 30 |
| **60b** | DME, KO*t*-Bu, 80°C | 36 | 65 |
| **60c** | Toluene, $P_3PO_4 \cdot 3H_2O$, 80°C | 48 | [b] |
| **60c** | DME, $K_3PO_4 \cdot 3H_2O$, 80°C | 48 | [b] |
| **60a** | DME, KO*t*-Bu, 80°C | 90 | 50 |
| **60c** | DME, KO*t*-Bu, 80°C | 36 | 69 |
| **60d** | DME, KO*t*-Bu, 80°C | 48 | 54 |

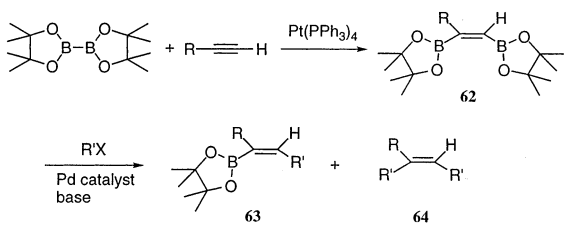
[a] Decomposition of the iodocyclopropane was observed.
[b] Unreacted starting materials were obtained in these cases.

Soderquist and Leon have reported that air-stable *Z*-(α-silylvinyl)boronates easily prepared in a hydroboration–oxidation sequence from 1-trimethylsilyl-1-alkyne provide a particularly effective route to *Z*-vinylsilanes (**65**) through Suzuki–Miyaura coupling (Scheme 43) [107].

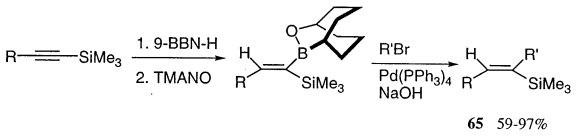
Uenishi et al. have disclosed a new procedure for preparing geometrically pure (*Z*)-1-bromo dienes and (*Z*)-1-bromo enynes based on Pd-catalyzed hydrogenolysis of 1,1-dibromo dienes or 1,1-dibromo enynes with $Bu_3SnH$. The subsequent reaction with vinylboron derivatives gives conjugated trienes stereo- and regioselectively in high yields, one of which examples is shown in Scheme 44 [108]. They also reported the stereocontrolled synthesis of (11*Z*)-retinal and its analogs by the same type of coupling [109].

The cross-coupling of the complex 1,1-dibromo alkene (**66**) with **67** under the Suzuki coupling conditions using TlOH has been carried out by Roush and his group for the synthesis of an intermediate (**68**) of nargenicin $A_1$ [110] (Scheme 45).

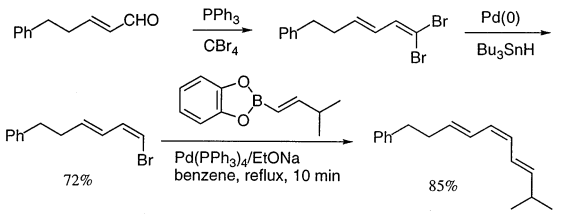
Curacin A (**69**), was first isolated from *L. majuscula* in 1994 and found to have various interesting biological activities. White et al. reported the total synthesis of curacin A (**69**) by using a Suzuki coupling reaction, as indicated in Scheme 46 [111]. Another total synthesis of (+)-curacin A has been realized by Muir and his group



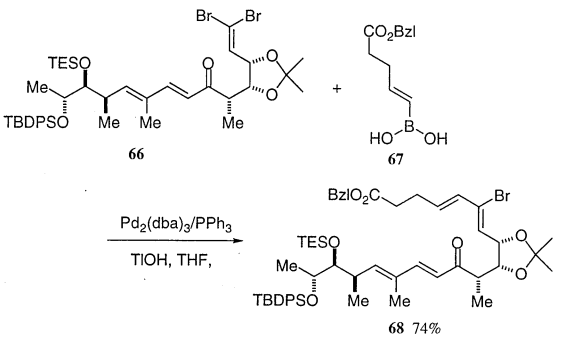

Scheme 42.



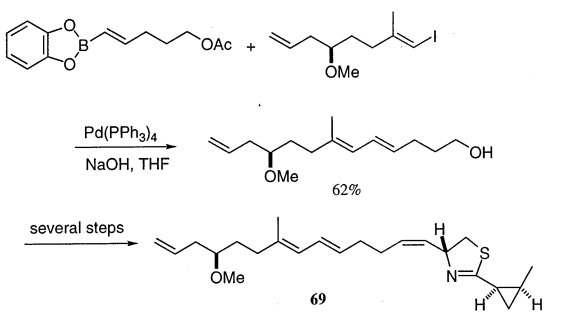

Scheme 43.




Scheme 44.




Scheme 45.



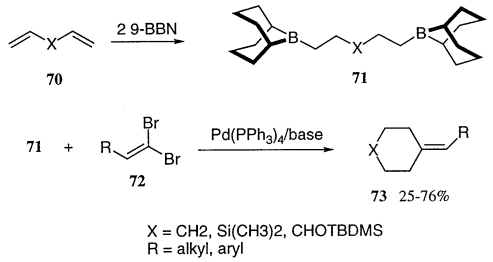

Scheme 46.

[112], in which the Suzuki coupling reaction is also employed as a key step.

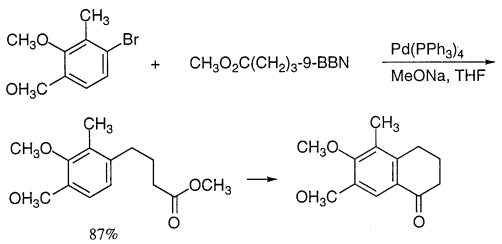
## 4. Cross-coupling of alkylborane derivatives

Although some of alkyl-magnesium, -zinc, -tin, and -aluminum reagents were successfully used for cross-coupling reactions with organic halides, the reaction of alkylborane derivatives is particularly useful when one wishes to start from alkenes via hydroboration.

Both carbo- and heterocyclic six-membered ring systems (**73**) containing an exocyclic carbon–carbon double bond have been prepared (25–76%) from α,ω-dienes




Scheme 47.

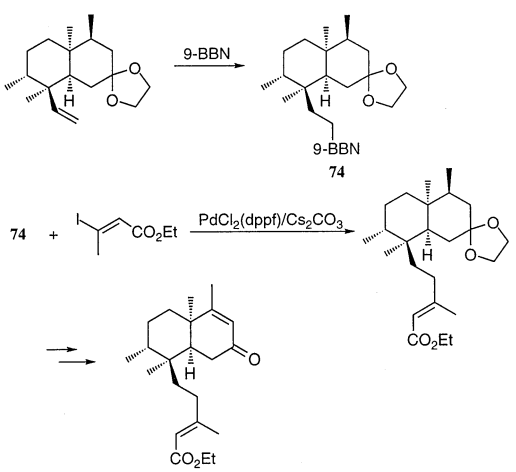



Scheme 48.

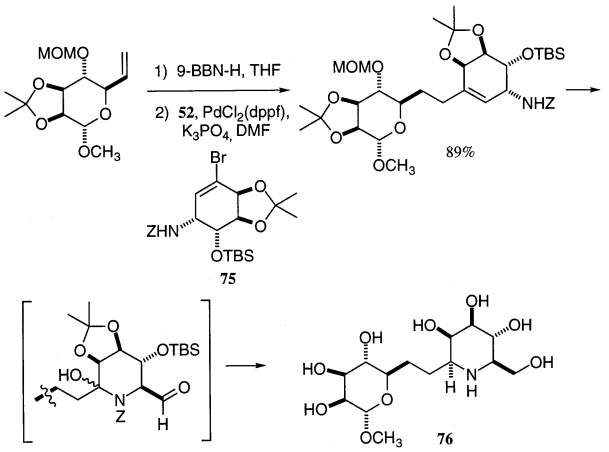
(**70**) through the Suzuki–Miyaura coupling reaction of their dihydroboration products (**71**) with either aromatic or aliphatic vinylidene dibromides (**72**) in a one-pot palladium-catalyzed sequence (Scheme 47) [113]. Attempts to extend this methodology to five-membered ring systems were unsuccessful.

1-Tetralone derivatives have been synthesized from aryl bromides using a Suzuki coupling as a key step followed by intramolecular Friedel–Craft acylation [114]. One of such syntheses is shown in Scheme 48.

The Suzuki–Miyaura cross-coupling of 4-bromo-*i*-butyl-9-BBN produces the 4-hydroxybutyl product evidently arising from a boron-assisted hydroxide substitution. This process was utilized in the synthesis of 2-methoxy-5*Z*-hexadecenoic acid methyl ester, a derivative of the phospholipids isolated from the Caribbean sponge, *Spheciospongia cuspidifera* [115].




Scheme 49.





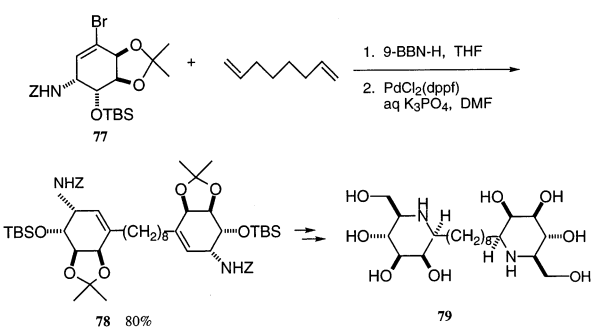


Scheme 50.

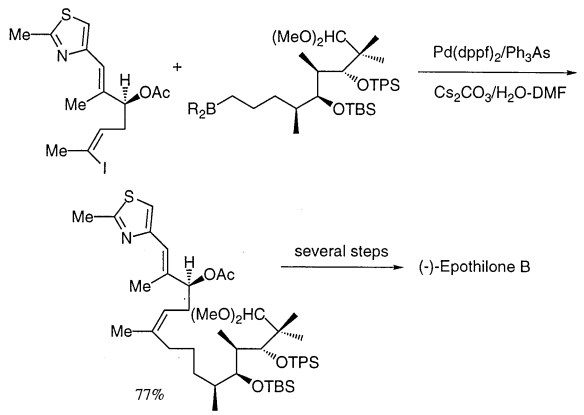
For the stereoselective synthesis of (13*E*)-2-oxo-5α-*cis*-17α,20α-cleroda-3,13-dien-15-oic acid, a *cis*-clerodane diterpenic acid, the palladium-catalyzed cross-coupling reaction of an alkylborane with a 1-alkenyl halide has been employed, as shown in Scheme 49 [116].

Polyhydroxylated piperidines ('azasugars') have received a great deal of attention from the scientific community recently. Aza-C-disaccharides with interesting biological activity were synthesized by a Suzuki coupling. For example, the coupling of **75** with an alkylboron reagent derived from olefinated carbohydrate precursor via hydroboration was used to form the C-glycosidic bond. Ozonolysis and selective reduction of the resultant carbonyl function served to produce the azasugar ring. The synthesis of fully deprotected D-aza-Man-β-(1→b)-D-Man (**76**) is shown in Scheme 50 [117].

Johns and Johnson have recently published that the double Suzuki coupling is achieved with vinyl bromide (**77**) and α,ω-diborane coupling partners derived from the hydroboration of the corresponding diene. Ozonolysis and selective reduction protocols served to provide selectively the polyhydroxylated piperidine ring systems (bis-azasugars). By such a procedure the $C_8$ linked analog (**79**) was obtained, which showed inhibitory activity against glycosidase enzymes (Scheme 51) [118].




Scheme 51.



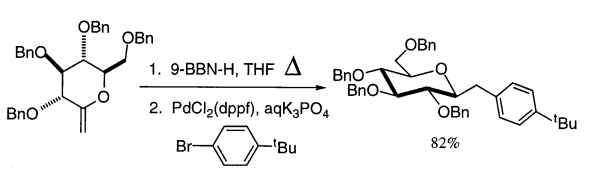

Scheme 52.

Danishefsky et al. have reported a total synthesis of the promising anticancer agent (−)-epothilone B using the Suzuki coupling method as shown in Scheme 52 [119], and a sister compound, epothilone A was also synthesized by a similar procedure [120]. The full paper of the total synthesis of epothilones A and B has appeared recently [121].

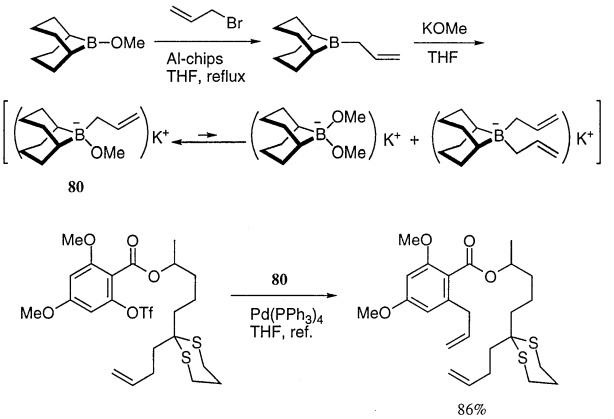
For the total synthesis of the polyene macrolide roflamycoin, a Suzuki homologation using hydroboration of a 1-alkene, followed by the reaction with vinyl bromide has been applied [122]. The similar type of homologation is also employed for the synthesis of agelasimine-A [123]. 2-Iodo-dihydropyran 3-*O*-carbamates obtained via combined metalation undergo Suzuki–Miyaura cross-coupling reaction to afford 2-aryl and heteroaryl dihydropyran *O*-carbamates in excellent yields [124].

It has become extremely apparent that the biological role which carbohydrates play in living systems is greatly underestimated by traditional understanding. Arguably one of the most diverse and structurally complex classes of organic compounds (containing six carbons and five contiguous stereocenters for the hexoses), carbohydrates appear to be the perfect candidate to participate in the regulation of many cellular phenomena. Johnson and Johns reported a novel approach to β-arylmethyl-C-glycosides using a tandem hydroboration/Suzuki cross-coupling strategy involving readily available 1-*exo*-methylene sugar precursors and aryl halides (Scheme 53) [125].

B-Allyl-9-BBN derivatives can be prepared readily from allyl bromide and B-methoxy-9-BBN in the presence of aluminum chips. Addition of one equiva-




Scheme 53.



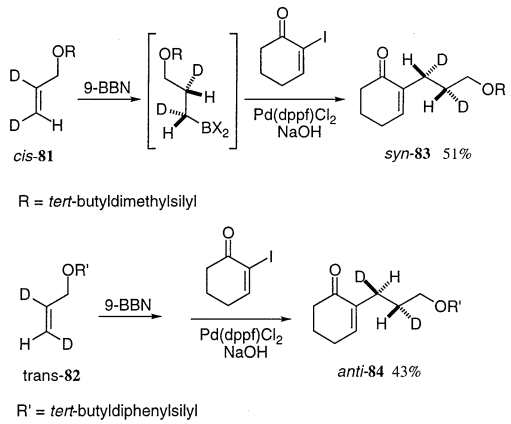

Scheme 54.

lent of KOMe to a solution of this compound in THF leads to a mixture of borate complexes. Among the mixture, K[(MeO)-(allyl)BBN] is the major component which can be deduced from the $^{11}$B-NMR spectrum (Scheme 54). The reaction of aryl halides or triflates with the mixture of borate complexes (**80**) in the presence of 3 mol% of Pd catalyst in reflux THF afforded the desired cross-coupling products in good to excellent yields [126]. One of such reactions is shown in Scheme 54.

A catalytic asymmetric synthesis of halenaquinone and halenaquinol has been achieved using an asymmetric Heck reaction or a cascade Suzuki cross-coupling reaction as a key step by Shibasaki et al. [127]. The use of $Ph_3As$ as a chiral ligand has been found to enhance both the cascade Suzuki coupling and also the Heck reaction.

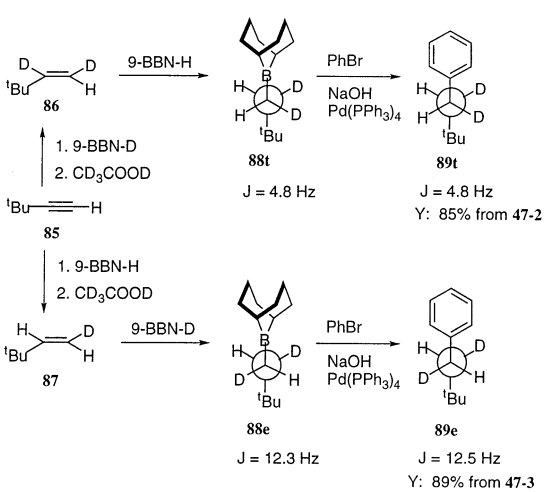
In contrast to stereochemical investigations of the related cross-couplings involving silanes and stannanes, the stereochemistry of the transmetalation of alkylboranes to palladium (either retention or inversion of configuration) has received little attention, although it was suggested to proceed with retention of configuration [1,2]. Recently, it has been confirmed that primary alkylboranes undergo transmetalation to palladium with retention of configuration [128]. Namely, Ridgway and Woerpel have observed that the enones *syn*-**83** and *anti*-**84** are obtained by hydroboration of the respective alkenes *cis*-**81** and *trans*-**82** with 9-BBN followed by addition of 2-iodocyclohexenone, palladium catalyst, and aqueous sodium hydroxide (Scheme 55, the reaction conditions were not optimized). The stereochemistries of the enones *syn*-**83** and *anti*-**84** were assigned by analysis of their $^1$H-NMR spectra.

Most recently, Soderquist and Matos have reported a precise investigation on the mechanism of the cross-coupling reaction between alkylboranes and bromobenzene [129]. Both *erythro* and *threo* isomers of

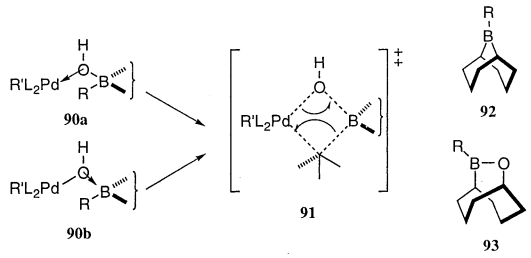



Scheme 55.

B-(3,3-dimethyl-1,2-dideuterio-1-butyl)-9-BBN (**88**) are prepared from 3,3-dimethyl-1-butyne (**85**) through a hydroboration-deuteronolysis-hydroboration sequence employing first 9-BBN-H and then 9-BBN-D, or in reverse order, respectively (Scheme 56). Employing the Whitesides protocol, the stereochemistry of B to Pd alkyl group transfer in the Suzuki–Miyaura coupling of **88** to PhBr has been found to occur with complete retention of configuration with respect to carbon (Scheme 56). The retention process suggested a four-centered hydroxo-$\mu_2$-bridged transition state model (**91**) (Scheme 57). This transition state could arise from the collapse of an intermediate **90**, which could originate from either (a) the reaction of hydroxyborate (i.e. $(HOBR_3)^{-1}$) with Pd(II) (e.g. $R'L_2PdBr$) or (b) from the reaction of $BR_3$ with $R'L_2PdOH$. The collapse of **91** would be expected to facilitate this alkyl group transfer through the $S_e2$(coord) process [1]. This model also suggested that either **90** or **91** should be more accessible for organoboranes that have a higher Lewis acidity. Actually, this hypothesis was tested, and it was confi-




Scheme 56.

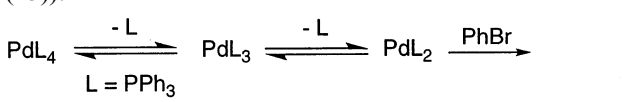



Scheme 57.

rmed that B-alkyl -9-BBN derivatives (**92**) are more reactive than the corresponding 9-oxa-10-borabicyclo[3.3.2]de-canes (**93**).

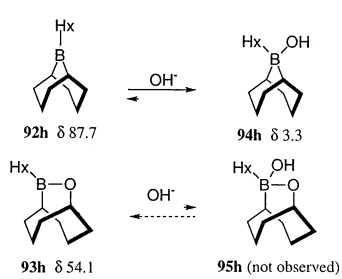
The role of base in the coupling process was observed by employing $^{11}$B-NMR. Namely, B-hexyl-9-BBN (**92h**) in THF exhibits its characteristic absorbance at $\delta$ 87.7 and at $\delta$ 3.3 upon the addition of NaOH (aq) (Scheme 58). These data clearly indicate a **92h**/**94h** equilibrium wherein the borane is mainly present as its hydroxyborate complex (**94h**). By contrast, the $^{11}$B-NMR of **93h** (R = hexyl in **93**) ($\delta$ 54.1), remains unchanged with added NaOH, indicating that no significant hydroxyborinate complex (**95h**) is formed under basic conditions.

Through $^{31}$P-NMR analysis, it was confirmed that the ligand-labile $Pd(PPh_3)_4$ (broad singlet, $\delta$ 18.0 (1:1 THF, $C_6D_6$), reacts cleanly with PhBr (1:1) at 67°C to produce a 1:2 ratio of *trans*-$BrPdPh(PPH_3)_2$ (**96**, $\delta$ 26.1, sharp singlet, THF) and $PPh_3$ ($\delta$ −3.2, broad) (Eq. (13)).

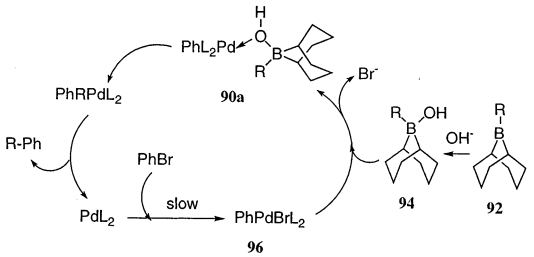



(13)

By the addition of two equivalents of NaOH (aq) to the **96**/$PPh_3$ mixture in THF, it was observed that **96** is partially hydrolyzed, giving the monomeric $HOPdPh(PPh_3)_2$ (**97**, $\delta$ 23.6 (ca. 33% of **96**, 2 h)). Heating this mixture at reflux temperature hastens the




Scheme 58.

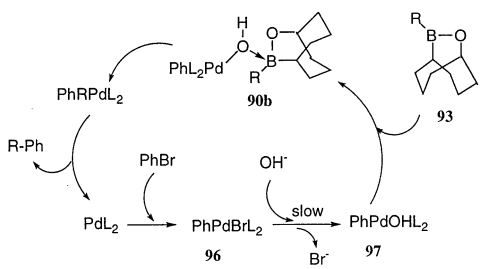



Scheme 59.

**96** to **97** conversion, which reaches about 90% after 2 h. These results demonstrate that the added base can hydrolyze Pd(II) halides producing monomeric hydroxypalladium(II) species (e.g. **97**) under these conditions.

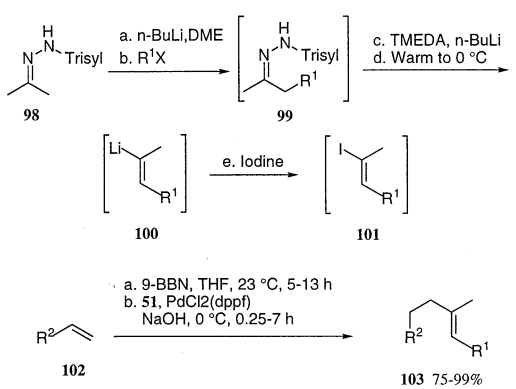
Kinetic studies reveal that the couplings are zero-order in the borane but for **92** exhibit a first-order dependence on [PhBr] (i.e. oxidative addition), while for **93** exhibit a first-order dependence on [$OH^-$] (i.e. Pd(II)X hydrolysis).

These data are interpreted in terms of attack of **96** by **94** to form a hydroxo $\mu_2$-bridged intermediate **90a**. This provides the precursor to transmetalation through a four-centered transition state **91**, as shown in Scheme 59 for the catalytic cycle of the coupling between the organoborane **92** and PhBr. On the other hand, for the coupling of 9-oxa-10-bora-bicyclo[3.3.2]decanes (**93**), because the analogous hydroxyborate complex (**95**) is absent, **96** is hydrolyzed by $OH^-$ forming **97** in a slower process, with this ultimately reacting with **93** to form a related intermediate **90b** which also collapses to products through **91** (Scheme 60).




Scheme 60.

An application of a Shapiro reaction-Suzuki coupling sequence to the stereoselective synthesis of *E*-trisubstituted olefins has been recently reported. Namely, double deprotonation of acetone trisylhydrazone (**98**) followed by alkylation with $R^1X$ produces unsymmetrical hydrazone **99**. Subsequent deprotonation followed by warming of the resulting dianion to 0°C provides *Z*-vinyllithium reagent **100**. Treatment of **100** with iodine affords *E*-trisubstituted vinyl iodide **101**. Suzuki cross-coupling of **101** and the alkyl borane derived from 9-BBN hydroboration of terminalolefin **102** produces trisubstituted olefin **103** [130] (Scheme 61).




Scheme 61.

## 5. Conclusions

The cross-coupling reactions of organoboron compounds with organic halides or related electrophiles provide one of the most straightforward methodologies for various carbon–carbon bond formations. Among such organoboron compounds, alkynylborane derivatives were not used in the Suzuki coupling, because they are stronger Lewis acids and easily hydrolyzed in the presence of bases. Fortunately, the difficulty has been overcome by using B-methoxy-9-borabicyclo[3.3.1]-nonane, This is a marked contribution in the study on the coupling reaction, which has been accomplished in the last few years. It has now confirmed that all kinds of carbon–boron bonds including ($sp^3$)C–B, ($sp^2$)C–B, and (sp)C–B bonds are employed as cross-coupling partners in the coupling reactions. In view of retrosynthetic analysis, the reaction is conceptually basic and important for construction of carbon framework of target molecules.

Further developments of this chemistry are expected in the near future.

## References

[1] N. Miyaura, A. Suzuki, Chem. Rev. 95 (1995) 2457.
[2] A. Suzuki, in: F. Diederich, P.J. Stang (Eds.), Metal-catalyzed Cross-Coupling Reactions, VCH, Weinheim, 1998, pp. 49–97.
[3] K.S. Chan, X. Zhou, M.T. Au, C.Y. Tam, Tetrahedron 51 (1995) 3129.
[4] X. Zhou, M.K. Tse, T.S.M. Wan, K.S. Chan, J. Org. Chem. 61 (1996) 3590.
[5] X. Zhou, K.S. Chan, J. Org. Chem. 63 (1998) 99.
[6] C.K. Chang, N. Bag, J. Org. Chem. 60 (1995) 7030.
[7] H. Zhang, K.S. Chan, Tetrahedron Lett. 37 (1996) 1043.
[8] S. Mikami, K. Sugiura, Y. Sakata, Chem. Lett. (1997) 833.
[9] G. Timari, T. Soos, G. Hajos, Synlett (1997) 1067.
[10] T. Watanabe, N. Miyaura, A. Suzuki, Synlett (1992) 207.
[11] J.M. Saa, G. Martorell, J. Org. Chem. 58 (1993) 1963.

[12] E.M. Cempi, W.R. Jackson, S.M. Maruccio, C.G.M. Naeslund, J. Chem. Soc. Chem. Commun. (1994) 2395.
[13] J.C. Anderson, H. Namli, Synlett (1995) 765.
[14] For instance, see: E. Cozzi, M. Cinquini, R. Annunziata, J.S. Siegel, J. Am. Chem. Soc. 115 (1993) 5330.
[15] A. Bahl, W. Grahn, S. Stadler, F. Feiner, G. Bourhill, C. Bräuchle, A. Reisner, P.G. Jones, Angew. Chem. Int. Ed. Engl. 34 (1995) 1485.
[16] M. Beller, H. Fischer, W.A. Herrmann, K. Öfele, C. Brossmer, Angew. Chem. Int. Ed. Engl. 34 (1995) 1848.
[17] M. Beller, J.G.E. Krauter, A. Zapf, Angew. Chem. Int. Ed. Engl. 36 (1997) 772.
[18] K. Jones, M. Keenan, F. Hibbert, Synlett (1996) 509.
[19] R. D'Alessio, A. Rossi, Synlett (1996) 513.
[20] S. Toyota, C.R. Woods, M. Benaglia, J.S. Siegel, Tetrahedron Lett. 39 (1998) 2697.
[21] I. Kawasaki, M. Yamashita, S. Ohta, Chem. Pharm. Bull. 44 (1996) 1831.
[22] C.J. Moody, K.J. Doyle, M.C. Elliott, T.J. Mowlem, J. Chem. Soc. Perkin Trans. 1 (1997) 2413.
[23] P. Deprez, J. Guillaume, R. Becker, A. Corbier, S. Didierlaurent, M. Fortin, D. Frechet, G. Hamon, B. Heckmann, H. Heitsch, H.-W. Kleeman, J.-P. Vevert, J.-C. Vincent, A. Wagner, J. Zhang, J. Med. Chem. 38 (1995) 2357.
[24] H. Heitsch, A. Wagner, N. Yadav-Bhatnagar, C. Griffoul-Marteau, Synthesis (1996) 1325.
[25] (a) A.S. Kende, L.S. Liebeskind, D.M. Braitsch, Tetrahedron Lett. 39 (1975) 3375. (b) J.E. Rice, Z.W. Cai, J. Org. Chem. 58 (1993) 1415. (c) V. Percec, J.Y. Bae, M. Zhao, D.L. Hill, J. Org. Chem. 60 (1995) 1066. (d) J. Lindley, Tetrahedron 40 (1984) 1433.
[26] A. Sekiya, N. Ishikawa, J. Organomet. Chem. 118 (1976) 349.
[27] J.W. Benbow, B.L. Maetinez, Tetrahedron Lett. 49 (1996) 8829.
[28] M. Moreno-Manas, M. Perez, R. Pleixats, J. Org. Chem. 61 (1996) 2346.
[29] N.G. Andersen, S.P. Maddaford, B.A. Keay, J. Org. Chem. 61 (1996) 9556.
[30] H. Zhang, F. Xue, T.C.W. Mark, K.S. Chang, J. Org. Chem. 61 (1996) 8002.
[31] Y. Satoh, C. Gude, K. Chan, F. Firooznia, Tetrahedron Lett. 38 (1997) 7645.
[32] A.O. Aliprantis, J.W. Canary, J. Am. Chem. Soc. 116 (1994) 6985.
[33] N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, J. Am. Chem. Soc. 107 (1985) 972.
[34] A.M. Gilbert, W.D. Wulff, J. Am. Chem. Soc. 116 (1994) 7449.
[35] (a) A.R. Martin, Y. Yang, Acta Chem. Scand. 47 (1993) 221. (b) K. Ritter, Synthesis (1993) 735. (c) L.S. Hegedus, J. Organomet. Chem. 457 (1993) 167.
[36] V. Percec, J.-Y. Bae, D.H. Hill, J. Org. Chem. 60 (1995) 1060.
[37] M. Rottländer, P. Knochel, J. Org. Chem. 63 (1998) 203.
[38] F. Firooznia, C. Gude, K. Chan, Y. Satoh, Tetrahedron Lett. 39 (1998) 3985.
[39] T. Ishiyama, M. Murata, N. Miyaura, J. Org. Chem. 60 (1995) 7508.
[40] S.R. Piettre, S. Baltzer, Tetrahedron Lett. 38 (1997) 1197.
[41] Y. Han, S.D. Walker, R.N. Young, Tetrahedron Lett. 37 (1996) 2703.
[42] J.W. Guiles, S.G. Johnson, W.V. Murray, J. Org. Chem. 61 (1996) 5169.
[43] (a) C.R. Strauss, R.W. Trainor, Aust. J. Chem. 48 (1995) 1665. (b) S. Caddick, Tetrahedron 51 (1995) 10403.
[44] M. Larhed, G. Linderberg, A. Hallberg, Tetrahedron Lett. 37 (1996) 8219.
[45] S.-B. Jang, Tetrahedron Lett. 38 (1997) 1793.
[46] E.W. Baxter, J.K. Rueter, S.O. Nortey, A.S.B. Beitz, Tetrahedron Lett. 39 (1998) 979.
[47] B.A. Lorsbach, J.T. Bagdanoff, R.B. Miller, M.J. Kurth, J. Org. Chem. 63 (1998) 2244.
[48] M.A. Lago, T.T. Nguyen, P. Bhatnagar, Tetrahedron Lett. 39 (1998) 3885.
[49] C.G. Blettner, W.A. König, W. Stenzel, T. Schotten, Synlett (1998) 295.
[50] P. Galda, M. Rehahn, Synthesis (1996) 614.
[51] N. Sakai, K.C. Brennan, L.A. Weiss, S. Matile, J. Am. Chem. Soc. 119 (1997) 8726.
[52] S. Setayesh, U.H.F. Bunz, Organometallics 15 (1996) 5470.
[53] K. Harre, V. Enkelmann, M. Schlze, U.H.F. Bunz, Chem. Ber. 129 (1996) 1323.
[54] B. Karakaya, W. Claussen, K. Gessler, W. Saenger, A.-D. Schlüter, J. Am. Chem. Soc. 119 (1997) 3296.
[55] Q.-S. Hu, W.-S. Huang, D. Vitharana, X.-F. Zheng, L. Pu, J. Am. Chem. Soc. 119 (1997) 12454.
[56] P.-K. Ng, X. Gong, W.-T. Wong, W.-K. Chan, Macromol. Rapid Commun. 18 (1997) 1009.
[57] C. Kowitz, G. Wegner, Tetrahedron 53 (1997) 15553.
[58] S.J. Gould, J. Chen, M.C. Cone, M.P. Gore, C.R. Melville, N. Tamaya, J. Org. Chem. 61 (1996) 5720.
[59] S.J. Gould, C.R. Melville, M.C. Cone, J. Chen, J.R. Carney, J. Org. Chem. 62 (1997) 320.
[60] H. Koyama, T. Kamikaya, Tetrahedron Lett. 38 (1997) 3973.
[61] P. Mattei, F. Diederich, Helv. Chim. Acta 80 (1997) 1555.
[62] A.M. Schoevaars, W. Kruizinga, R.W.J. Zijlstra, N. Veldman, A.L. Spek, B.L. Feringa, J. Org. Chem. 62 (1997) 4943.
[63] M.B. Goldfinger, K.B. Crawford, T.M. Swager, J. Am. Chem. Soc. 119 (1997) 4578.
[64] M.B. Goldfinger, K.B. Crawford, T.M. Swager, J. Org. Chem. 63 (1998) 1676.
[65] G. Bringmann, R. Götz, P.A. Keller, R. Walter, M.R. Boyd, F. Lang, A. Garcia, J.J. Walsh, I. Tellitu, K.V. Bhaskar, T.R. Kelly, J. Org. Chem. 63 (1998) 1090.
[66] P.D. Hobbs, V. Upender, M.I. Dawson, Synlett (1997) 965.
[67] K.C. Nicolaou, J.M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C.N.C. Boddy, F. Rübsam, Chem. Commun. (1997) 1899.
[68] T. Ishiyama, Y. Itoh, T. Kitano, N. Miyaura, Tetrahedron Lett. 38 (1997) 3447.
[69] N. Miyaura, A. Suzuki, Main Group Metal Chem. 10 (1987) 295.
[70] K.A. Smith, E.M. Campi, W.R. Jackson, S. Marcuccio, C.G.M. Naeslund, G.B. Deacon, Synlett (1997) 131.
[71] S. Yamaguchi, S. Ohno, K. Tamao, Synlett (1997) 1199.
[72] S.R. Piettre, C. Andre, M.-C. Chanal, J.-B. Ducep, B. Lesur, F. Piriou, P. Roboisson, J.-M. Rondeau, C. Schelcher, P. Zimmermann, A.J. Ganzhorn, J. Med. Chem. 40 (1997) 4208.
[73] X. Yue, F.-L. Qing, H. Sun, J. Fan, Tetrahedron Lett. 37 (1996) 8213.
[74] G.M. Boland, D.M.X. Dannelly, J.-P. Finet, M.D. Rea, J. Chem. Soc. Perkin Trans. I (1996) 2591.
[75] F.-L. Qing, J. Fan, Bioorg. Med. Chem. Lett. 7 (1997) 2117.
[76] M. Moreno-Manas, F. Pajuelo, R. Pleixats, J. Org. Chem. 60 (1995) 2396.
[77] F. Koch, W. Heitz, Macromol. Chem. Phys. 198 (1997) 1531.
[78] A. Pelter, K. Smith, H.C. Brown, Borane Reagents, Academic Press, London, 1988.
[79] (a) A. Suzuki, Pure Appl. Chem. 63 (1991) 419. (b) J.C. Colberg, A. Rane, J. Vaquer, J.A. Soderquist, J. Am. Chem. Soc. 115 (1993) 6065 and references cited therein.
[80] J.A. Soderquist, K. Matos, A. Rane, J. Ramos, Tetrahedron Lett. 36 (1995) 2401.
[80] J.A. Soderquist, K. Matos, A. Rane, J. Ramos, Tetrahedron Lett. 36 (1995) 2401.
[81] A. Fürstner, G. Seidel, Tetrahedron 51 (1995) 11165.
[82] (a) G.R. Pettit, S.B. Singh, M.R. Boyd, E. Hamel, R.K. Pettit, J.M. Schmidt, F. Hogan, J. Med. Chem. 38 (1995) 1666. (b)

J.A. Woods, J.A. Hadfield, G.R. Pettit, B.W. Fox, A.T. McGown, Br. J. Cancer 71 (1995) 705.
[83] A. Fürstner, K. Nikolakis, Liebigs Ann. (1996) 2101.
[84] G. Desurmont, R. Klein, S. Uhlenbrock, E. Laloë, L. Deloux, D.M. Giolando, Y.W. Kim, S. Pereira, M. Srebnik, Organometallics 15 (1996) 3323.
[85] G.M. Farinola, V. Fiandanese, L. Mazzone F. Naso, J. Chem. Soc. Chem. Commun. (1995) 2523.
[86] A. Tprrado, S. Lopez, R. Alvarez, A.R. de Lera, Synthesis (1995) 285.
[87] T. Sugai, M. Yokoyama, T. Yamazaki, H. Ohta, Chem. Lett. (1997) 797.
[88] M.J. Burk, J.G. Allen, W.F. Kiesman, J. Am. Chem. Soc. 120 (1998) 657.
[89] I.E. Marko, F. Murphy, S. Dolan, Tetrahedron Lett. 37 (1996) 2507.
[90] J. Uenishi, J.-M. Beau, R.W. Armstrong, Y. Kishi, J. Am. Chem. Soc. 109 (1987) 4756.
[91] (a) Y. Hoshino, N. Miyaura, A. Suzuki., Bull. Chem. Soc. Jpn. 61 (1988) 3008. (b) M. Sato, N. Miyaura, A. Suzuki, Chem. Lett. (1989) 1405.
[92] E. Negishi, Z. Owczarczyk, Tetrahedron Lett. 32 (1991) 6683.
[93] A. Torrado, B. Iglesias, S. Lopez, A.A. de Lera, Tetrahedron 51 (1995) 2435.
[94] J.P. Genet, E. Blart, M. Savignac, Synlett (1992) 715.
[95] J.P. Genet, A. Linquist, E. Blart, V. Mouries, M. Savignac, Tetrahedron Lett. 36 (1995) 1443.
[96] K.B. Wiberg, Acc. Chem. Res. 26 (1996) 229.
[97] A.B. Charette, A. Giroux, J. Org. Chem. 61 (1996) 8718.
[98] H.-U. Reissig, Angew. Chem. Int. Ed. Engl. 35 (1996) 971.
[99] A.B. Charette, J.-F. Marcoux, Synlett (1995) 1197.
[100] T. Ye, M.A. McKervey, Chem. Rev. 94 (1994) 1091.
[101] J.P. Hildebrand, S.P. Marsden, Synlett (1996) 893.
[102] S.-M. Zhou, Y.-L. Yan, M.-Z. Deng, Synlett (1998) 198.
[103] A.B. Charette, R.P. De Freitas-Gil, Tetrahedron Lett. 38 (1997) 2809.
[104] (a) T. Ishiyama, N. Matsuda, N. Miyaura, A. Suzuki., J. Am. Chem. Soc. (1993) 11018. (b) T. Ishiyama, N. Matsuda, M. Murata, F. Ozawa, N. Miyaura, A. Suzuki, Organometallics 15 (1996) 713.
[105] T. Ishiyama, M. Yamamoto, N. Miyaura, Chem. Lett. (1996) 1117.
[106] S.D. Brown, R.W. Armstrong, J. Am. Chem. Soc. 118 (1996) 6331.
[107] J.A. Soderquist, G. Leon, Tetrahedron Lett. 39 (1998) 3898.
[108] J. Uenishi, R. Kawahama, O. Yonemitsu, J. Org. Chem. 61 (1996) 5716.
[109] J. Uenishi, R. Kawahama, O. Yonemitsu, A. Wada, M. Ito, Angew. Chem. Int. Ed. 37 (1998) 320.
[110] W.R. Roush, K. Koyama, M.L. Curtin, K.J. Moriarty, J. Am. Chem. Soc. 118 (1996) 7502.
[111] J.D. White, T.-S. Kim, M. Nambu, J. Am. Chem. Soc. 119 (1997) 103.
[112] J.C. Muir, G. Pattenden, T. Ye, Tetrahedron Lett. 39 (1998) 2861.
[113] J.A. Soderquist, G. Leon, J.C. Colberg, L. Martinez, Tetrahedron Lett. 36 (1995) 3119.
[114] G. Esteban, M.A. Lopez-Sanchez, M.E. Martinez, J. Plumet, Tetrahedron 54 (1998) 197.
[115] J.A. Soderquist, I. Rosado, Y. Marrero, Tetrahedron Lett. 39 (1998) 3115.
[116] T.-H. Lee, C.-C. Liao, Tetrahedron Lett. 37 (1996) 6869.
[117] B.A. Johns, Y.T. Pan, A.D. Elbein, C.R. Johnson, J. Am. Chem. Soc. 119 (1997) 4856.
[118] B.A. Johns, C.R. Johnson, Tetrahedron Lett. 39 (1998) 749.
[119] D.-S. Su, D. Meng, P. Bertinato, A. Balog, E.J. Sorensen, S.J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S.B. Horwitz, Angew. Chem. Int. Ed. Engl. 36 (1997) 757.
[120] A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D. Su, E.J. Sorensen, S.J. Danishefsky, Angew. Chem. Int. Ed. Engl. 35 (1996) 2801.
[121] D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E.J. Sorensen, S.J. Danishefsky, J. Am. Chem. Soc 119 (1997) 10073.
[122] S.D. Rychnovsky, U.R. Khire, G. Yang, J. Am. Chem. Soc. 119 (1997) 2058.
[123] M. Ohba, N. Kawase, T. Fujii, J. Am. Chem. Soc. 118 (1996) 8250.
[124] J.F. Bower, D. Guillaneux, T. Nguyen, P.L. Wong, V. Snieckus, J. Org. Chem. 63 (1998) 1514.
[125] C.R. Johnson, B.A. Johns, Synlett (1997) 1406.
[126] A. Fürstner, G. Seidel, Synlett (1998) 161.
[127] A. Kojima, T. Takemoto, M. Sodeoka, M. Shibasaki, Synthesis (1998) 581.
[128] B.H. Ridgway, K.A. Woerpel, J. Org. Chem. 63 (1998) 458.
[129] K. Matos, J.A. Soderquist, J. Org. Chem. 63 (1998) 461.
[130] E.J. Corey, B.E. Roberts, Tetrahedron Lett. 38 (1997) 8919.