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Highly selective palladium-catalyzed Suzuki–Miyaura monocoupling reactions of ethene and arene derivatives bearing two or more electrophilic sites

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Abbreviations: Ac, acetyl; Ar, aryl; Bn, benzyl; 9-BBN, 9-borabicyclo(3.3.1)nonane; Boc, *tert*-butoxycarbonyl; Bs, benzenesulfonyl; *i*-Bu, *iso*-butyl; *n*-Bu, *n*-butyl; *t*-Bu, *tert*-butyl; Bz, benzoyl; Cbz, *N*-carbobenzoxy; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; dba, *trans*,*trans*-dibenzylideneacetone; DMA, *N*,*N*-dimetylacetamide; DMF, *N*,*N*-dimethylformamide; DME, dimethoxyethane; DMEDA, *N*,*N*′-dimethylethylene diamine; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone; DMSO, dimethylsulfoxide; DPEphos, 2,2′-oxybis(2,1-phenylene)bis(diphenylphosphine); dppf, 1,1′-bis(diphenylphosphino)ferrocene; dppp, 1,3-bis(diphenylphosphino)propane; Et, ethyl; (Het)Ar, (Hetero)aryl; Me, methyl; MOM, methoxymethyl; MPM, 4-methoxybenzyl; Ms, methylsulfonyl; NMP, *N*-methylpyrrolidinone; Ph, phenyl; Piv, pivaloyl; *i*-Pr, *iso*-propyl; PPD, 1,3-propanediol; TBAB, tetrabutylammonium bromide; TBS, *tert*-butyldimethylsilyl; Tf, trifluoromethylsulfonyl; THF, tetrahydrofuran; Ts, *p*-toluenesulfonyl.

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1. Introduction

In recent years, economic and environmental reasons have prompted the organic chemistry community to investigate and develop a number of catalytic methods not involving the use of stoichiometric amounts of organometallic reagents to form C–C bonds from organic halides or pseudohalides. Thus, in addition to the classical Mizoroki–Heck[1] and Sonogashira reactions,[2] at the present time synthetic organic chemists can use other very useful general transition metal-catalyzed methods that include α-arylation reactions of substrates with sp^3-hybridized C–H bonds,[3] direct arylation reactions of arenes and heteroarenes,[4] decarboxylative cross-coupling reactions,[5] oxidative coupling reactions of heteroarene Csp^2–H bonds with alkenes (Fujiwara–Moritani reaction),[6] and addition reactions of heteroarene Csp^2–H bonds to alkynes.[7]

Nevertheless, the Suzuki–Miyaura (S.–M.) Pd-catalyzed cross-coupling reaction of organoboron reagents with organic halides or pseudohalides can still be regarded as one of the most valuable transition metal-catalyzed methods for C–C bond formation. In fact, since the pioneering work published by Suzuki, Miyaura et al. in 1981,[8a] a huge number of studies aimed at the development and applications of this reaction have been accomplished and continue to be reported in international journals of organometallic, organic and polymer chemistry.[8b] In this regard, it is also worth mentioning that in October 2010 Professor Akira Suzuki, together with Professors Richard Heck and Ei-chi Negishi, were awarded the Nobel Prize in Chemistry for Pd-catalyzed cross couplings in organic synthesis.

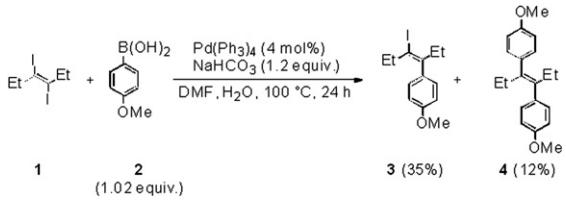
The relevant impact of the S.–M. reaction on both academic and industrial laboratories is due to several factors that include: (i) high tolerance to a wide range of functional groups; (ii) commercial availability and stability of organoboronic acids to heat, water and air; (iii) ease of separation of the boron-containing byproducts from the reaction mixtures; (iv) low toxicity of the boronic acids and their esters; and (v) ultimate degradation of the organoboron compounds into environmentally friendly boric acid. Moreover, during the last few decades, many catalyst systems have been developed that accelerate the reaction and/or make the cross-coupling reaction proceed with relatively inert electrophilic substrates such as aryl chlorides or extremely hindered aryl halides.[8c]

Several reviews on this reaction have been published[9] and significant examples of site-selective S.–M. reactions involving multiple halogenated compounds have been summarized and commented on in the reviews by Bach,[10] Manabe[11] and Chelucci.[12] However, no comprehensive review devoted to summarizing and discussing the updated literature data on selective S.–M. monocoupling reactions of dihalo- and polyhaloethenes and dihalo- and polyhaloarenes bearing different or identical halogen substituents has been published.

This review article, with 375 references, covering the literature up to the end of August 2010, is designed to bridge this gap and also illustrates selective Pd-catalyzed S.–M. monocoupling reactions of alkene and arene derivatives bearing halogen and pseudohalogen substituents or dipseudohalogen groups and the limitations they currently possess. Particular emphasis has been given to describing the catalysts systems and the reaction conditions that allow the efficient and selective preparation of functionalized stereodefined mono- and polyunsaturated aliphatic compounds, arene derivatives that include monohalo- and polyhalobiaryls, oligoarenes and heteroarenes. The use of highly selective S.–M. monocoupling reactions of alkenes and arene derivatives with two or more electrophilic sites as key steps in the synthesis of naturally-occurring compounds, bioactive substances including drugs, and liquid crystals is also reported. Moreover, the use of one-pot site-selective polycoupling reactions of polyhalogenated substrates that directly afford polysubstituted products is described. Finally, the reasons for the observed stereo-, site- and/or chemo-selectivities of the monocoupling reactions are mentioned and discussed.

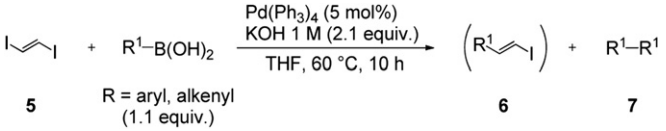
2. Monocoupling reactions of 1,2-dihalogenated- and polyhalogenated ethenes and 1,1-difluoro-2-*p*-toluenesulfonyloxyethene

A few attempts have been effected in the literature concerning S.–M. monocoupling reactions of (*E*)-1,2-diiodoethene derivatives with arylboronic acids[13,14] and it has been found that these reactions proceed in low yields and quite modest selectivity[13] or do not provide cross-coupled products.[14] Thus, the $Pd(PPh_3)_4$-catalyzed reaction of (*E*)-3,4-diiodo-3-hexene (**1**) with 4-methoxyphenylboronic acid (**2**) was found to give mono- and bis-cross-coupling products, **3** and **4**, in 35 and 12% yield, respectively (Scheme 1).[13]



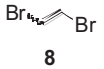
Scheme 1.

On the other hand, the $Pd(PPh_3)_4$-catalyzed S.–M. reaction of (*E*)-1,2-diiodoethene (**5**) with 1.1 equiv of aryl- or alkenylboronic acids in THF in the presence of KOH as base did not provide the anticipated monocoupling products **6** and the main reactions products proved to be compounds **7** derived from homocoupling of boronic acids (Scheme 2).[14]



Scheme 2.

Similar unsatisfactory results were obtained when a stereoisomeric mixture of (*E*)- and (*Z*)-1,2-dibromoethene (**8**) (Fig. 1) was reacted with 1 equiv of arylboronic acids under experimental conditions similar to those reported in Scheme 2.[14]

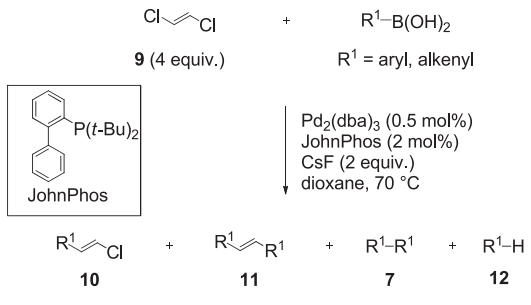


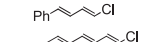
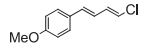
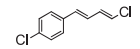
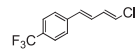
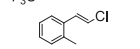
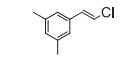
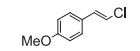
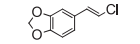
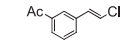
8

Fig. 1. Structure of compound **8**.

In stark contrast with these results, in 2006, Barluenga et al.[15] found that treatment of a large molar excess of (*E*)-1,2-dichloroethene (**9**) with electron-rich alkenylboronic acids and electron-rich arylboronic acids in dioxane at 70 °C in the presence of CsF as base and catalytic amounts of $Pd_2(dba)_3$ and JohnPhos stereoselectively provided the required monocoupling products **10a**–**i** in yields ranging from 14 to 82% (Scheme 3). However, some of the examined reactions, including those used to prepare compounds **10a**, **10d**, **10f** and **10i**, unexpectedly furnished significant amounts of double coupling products **11** as well as other undesired side products such as compounds **12** and **7**, derived from protodeboronation and homocoupling of boronic acids, respectively (Scheme 3).[15]

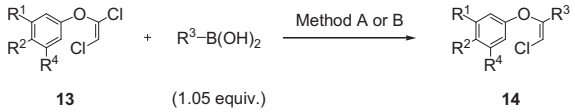
More recently, Geary and Hultin reported that (*E*)-1,2-dichlorovinyl ethers **13** participate in Pd-catalyzed monocoupling reactions with aryl-, heteroaryl- and alkenylboronic acids at the C-1



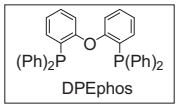
Compound **10**		Yield (%)	**10** : **11** : **12** : **7** molar ratio
	(**10a**)	44	65 : 31 : 0 : 0
	(**10b**)	65	79 : 0 : 21 : 0
	(**10c**)	60	100 : 0 : 0 : 0
	(**10d**)	33	56 :22 : 0 : 22
	(**10e**)	14	41 : 59 : 0 : 0
	(**10f**)	50	66 : 32 : 1 : 0
	(**10g**)	67	100 : 0 : 0 : 0
	(**10h**)	82	100 : 0: 0 : 0
	(**10i**)	31	44 : 12 : 44 : 0

Scheme 3.

position affording (*Z*)-1-aryloxy-1-substituted-2-chloroethenes **14a**–**g** (Scheme 4).[16] This site selectivity was consistent with the expectation that the C-1 position of compounds **13** is relatively electron poor, leading to preferential oxidative addition of Pd(0) at this position.[16c]



Method A : $Pd(Ph_3)_4$ (5 mol%); aq. KOH; THF (0.4 M); 65 °C; 1-22 h
Method B : $Pd_2(dba)_3$ (2.5 mol%); DPEphos (5 mol%); CsF (3 equiv.); Cs_2CO_3 (3 equiv.); THF (0.5 mol%); 65 °C; 16-24 h



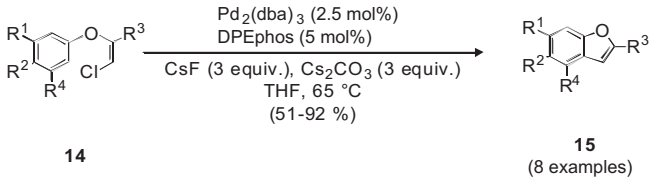
	Compound **14**				Method	Yield (%)
	R^1	R^2	R^3	R^4		
14a	H	H	H	4-MeOC_6H_4	A	82
14a	H	H	H	4-MeOC_6H_4	B	8
14b	H	MeO	H	4-MeOC_6H_4	A	57
14b	H	MeO	H	4-MeOC_6H_4	B	72
14c	MeO	H	H	4-MeOC_6H_4	B	63
14d	H	H	H	4-FC_6H_4	A	80
14d	H	H	H	4-FC_6H_4	B	81
14e	H	H	H	2-thienyl	A	73
14f	H	H	H	6-F, 3-pyridyl	A	54
14g	H	H	H	(*E*)-1-styryl	B	60

Scheme 4.

As shown in Scheme 4, the S.–M. reactions in THF at 65 °C catalyzed by either $Pd(PPh_3)_4$ or $Pd_2(dba)_3$/DPEphos could install aryl and heteroaryl groups or the styryl moiety at the C-1 position of **13**.

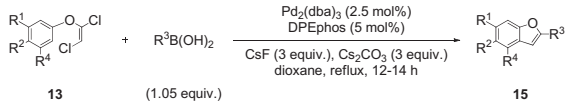
It is interesting to note that heteroarylboronic acids proved to be completely unreactive when the $Pd_2(dba)_3$/DPEphos catalyst system was used in the presence of CsF and Cs_2CO_3 (Method B). However, the reactions of heteroarylboronic acids with **13** were successfully effected in boiling THF by using $Pd(PPh_3)_4$ as catalyst in the presence of aqueous KOH (Method A).[16c]

Remarkably, when compounds **14** were treated with cesium bases in the presence of a $Pd_2(dba)_3$/DPEphos catalyst system, benzo[*b*]furans **15** proved to be the sole reactions products (Scheme 5).[16a] These heterocycles were probably formed via a direct arylation process involving the oxidative addition of Pd(0) onto the C–Cl bond of **14**, followed by arylation and reductive elimination.[16a]



Scheme 5.

Moreover, the site-selective S.–M. cross coupling and a direct arylation reaction could be combined in a one-pot procedure involving treatment of **13** with boronic acids in THF at 65 °C for 12–14 h in the presence of a $Pd_2(dba)_3$/DPEphos catalyst system and cesium bases.[16a,b] The synthesis of 2-substituted benzo[*b*]furans **15a**–**t** according to this protocol is illustrated in Scheme 6.

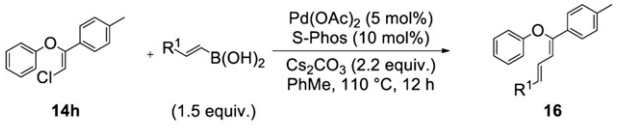


	Compound **15**				Yield %
	R^1	R^2	R^4	R^3	
15a	H	H	H	Ph	75
15b	H	H	H	4-FC_6H_4	53
15c	H	H	H	4-MeC_6H_4	51
15d	H	H	H	4-MeOC_6H_4	74
15e	H	H	H	3-AcC_6H_4	50
15f	H	H	H	(*E*)-Ph-CH=CH	71
15g	H	H	H	(*E*)-*c*-C_6H_{11}-CH=CH	59
15h	H	Me	H	4-MeOC_6H_4	87
15i	H	Me	H	4-FC_6H_4	76
15j	H	Me	H	3-$NO_2C_6H_4$	13
15k	H	Me	H	(*E*)-4-MeC_6H_4CH=CH	71
15l	H	MeO	H	4-MeOC_6H_4	82
15m	H	MeO	H	3,4-$(MeO)_2C_6H_3$	90
15n	H	MeO	H	4-MeC_6H_4	69
15o	MeO	H	MeO	2,4-$(MeO)_2C_6H_3$	80
15p	H	MeO	H	4-FC_6H_4	68
15q	H	MeO	H	3-AcC_6H_4	36
15r	H	CN	H	4-FC_6H_4	81
15s	H	CN	H	4-MeC_6H_4	85
15t	H	CN	H	3, 5-Me_2 ,4-EtOC_6H_2	87

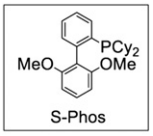
Scheme 6. One-pot preparation of benzo[*b*]furans **15** from (*E*)-1,2-dichlorovinylethers **13**.

Geary and Hultin also reported that the reaction of compound **14h** with 1-alkenylboronic acids in boiling toluene in the presence of Cs_2CO_3 as base and a $Pd(OAc)_2$/*S*-Phos catalyst system provided 1,3-butadienes **16a**–**c** in low-to-high yields (Scheme 7).[16c]

Interestingly, the method employed for the synthesis of compounds **15** was extendable to the preparation of indoles **18** from 1,2-dichlorovinyl amides **17** (Fig. 2).[16a,b]



16	R^1	Yield (%)
16a	4-FC_6H_4	15
16b	Ph	65
16c	*t*-Bu	87



Scheme 7.

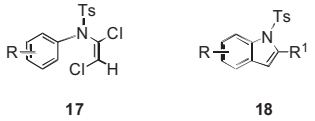
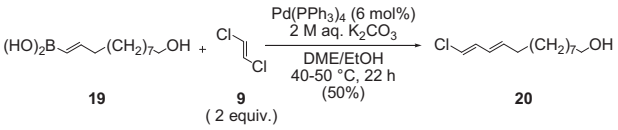


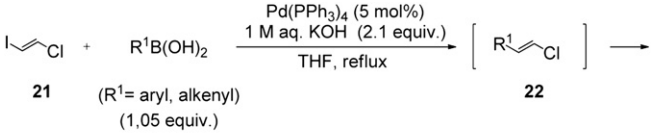
Fig. 2. Structures of compounds **17** and **18**.

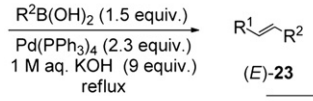
Some years before this study, Chen and Millar[17] prepared stereoisomerically pure (10*E*,12*E*)-13-chlorotrideca-10,12-dien-1-ol (**20**) in 50% yield by the $Pd(PPh_3)_4$-catalyzed reaction of (*E*)-alkenylboronic acid **19** with 2 equiv of **9** in the presence of 2 M K_2CO_3 in a mixture of DME and EtOH at 40–50 °C (Scheme 8).



Scheme 8.

In the last decade, several examples of highly chemoselective S.–M. monocoupling reactions of ethene substrates bearing two (or more) different electrophilic sites have also been reported in the literature.[18–25] In 2000, Organ et al.[18] described that (*E*)-1-chloro-1-alkenes **22**, obtained in high conversions by the $Pd(PPh_3)_4$-catalyzed reaction of (*E*)-1-chloro-2-iodoethene (**21**) with 1.05 equiv of aryl- or alkenylboronic acids in THF under reflux in the presence of 1 M KOH, are able to react with 1.5 equiv of aryl- or alkenylboronic acids and additional KOH and $Pd(PPh_3)_4$ to give 1,2-disubstituted ethenes (*E*)-**23** in good overall yields (Scheme 9).



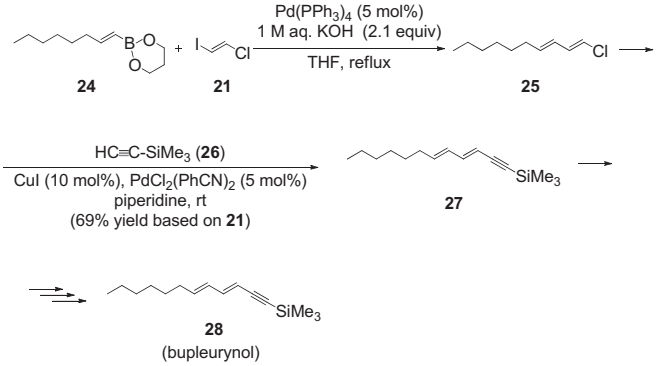


(*E*)-**23**

R^1	R^2	Yield (%)
Ph	4-$MeOC_6H_4$	50
4-$MeOC_6H_4$	Ph	52
(*E*)-*n*C_6H_{13}CH=CH	Ph	65
Ph	(*E*)-*n*C_6H_{13}CH=CH	52
(*E*)-*n*C_6H_{13}CH=CH	4-$MeOC_6H_4$	74

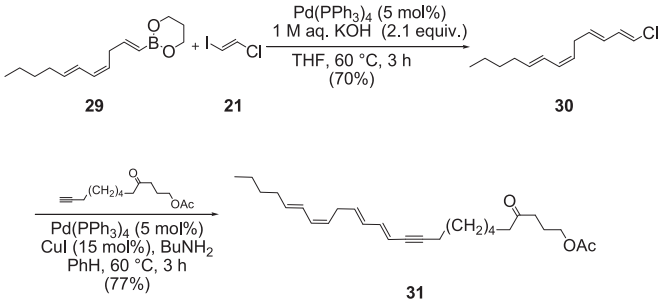
Scheme 9.

In 2003, Antunes and Organ[19] reported that boronic ester **24** couples cleanly at the C–I bond of **21** in the presence of 1 M KOH and 5 mol % $Pd(PPh_3)_4$ and that the resulting (*E*)-1-chloro-1,3-diene **25** undergo a Sonogashira reaction with trimethylsilylacetylene (**26**) to give enediyne **27** in 69% overall yield (Scheme 10). This compound was then used as a precursor to the naturally occurring polyacetylene, bupleurynol (**28**) (Scheme 10).[19]



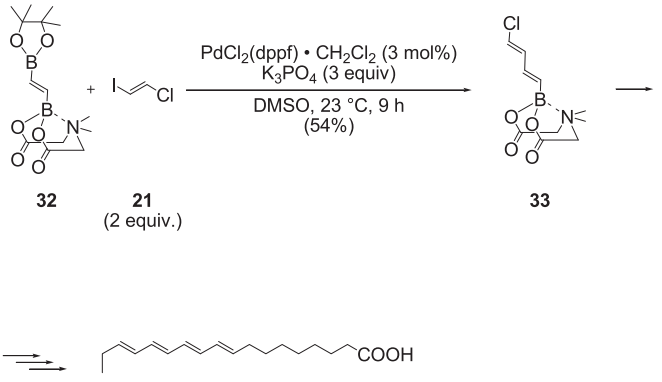
Scheme 10.

One year later, Organ and Ghasemi[20] synthesized (1*E*,3*E*,6*Z*,8*Z*)-1-chlorotrideca-1,3,6,8-tetraene (**30**) in 70% yield by the $Pd(PPh_3)_4$-catalyzed reaction of **21** with 2-[(1*E*,4*Z*,6*Z*)-1,4,6-undecatrien]-1,3,2-dioxaborane (**29**) in THF at 60 °C in the presence of 1 M KOH (Scheme 11). Compound **30** was then used as a precursor to (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacosa-13,15,18,20-tetraen-1-yn-4-one-1-acetate (**31**), a naturally occurring ant venom.[20]



Scheme 11.

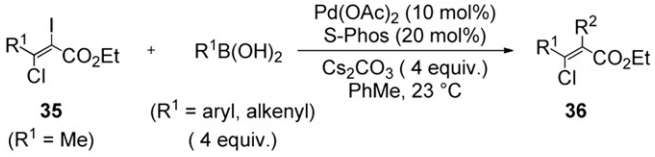
In 2008, Burke et al.[21a] described the synthesis of the *B*-protected 4-chloro-1,3-butadienylboronate **33** in 54% yield via the chemo- and stereoselective $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed reaction of the (*E*)-(2-pinacolethenyl)boronate ester **32** with 2 equiv of **21** in DMSO at 23 °C in the presence of 3 equiv of anhydrous K_3PO_4 (Scheme 12).



Scheme 12.

Compound **33** was then used as a precursor to β-parinaric acid (**34**),[21a] a fluorescent substance used to determine characteristic temperatures of membrane and membrane lipids from cultured animal cells.[21b]

In the same year, Ogilvie et al.[22a] prepared a wide variety of stereoisomerically pure (*Z*)-2-aryl- and (*Z*)-2-(1-alkenyl)-3-chloro-2-butenoates **36** in good-to-excellent yields by the S.–M. reaction of ethyl (*E*)-3-chloro-2-iodo-2-butenoate (**35**; R^1=Me) with a large molar excess of aryl- and alkenylboronic acids in toluene at room temperature in the presence of Cs_2CO_3 and a $Pd(OAc)_2$/*S*-Phos catalyst system (Scheme 13). Selective coupling at the α-position of **35** (R^1=Me) was observed for all examples, demonstrating that this position is more activated towards the oxidative addition of Pd(0) than the β-position.



R^2	Yield (%)
4-MeC_6H_4	81
Ph	100
4-$MeOC_6H_4$	84
2-$MeOC_6H_4$	93
3-$MeOC_6H_4$	65
4-FC_6H_4	82
1-naphthyl	94
2-naphthyl	95
2-thiophenyl	64
(*E*)-PhCH=CH	85
(*E*)-1-octenyl	75

Scheme 13.

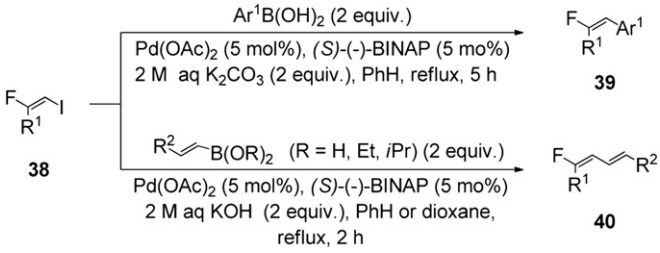
Interestingly, compounds **36** could be converted into stereoisomerically pure tetrasubstituted alkenes by S.–M. couplings with aryl- and alkenylboronic acids in dioxane at 23 °C in the presence of Cs_2CO_3 as base and a $Pd(OAc)_2/PMe_3\cdot HBF_4$ catalyst system.[22a]

During a recent investigation, Ogilvie et al.[22b] found that the $Pd(OAc)_2$/*S*-Phos-catalyzed reaction of ethyl (*E*)-3-chloro-2-iodo-2-alkenoates **35** with 3 equiv of 9-alkyl-9-BBN derivatives and 3 equiv of $K_3PO_4\cdot H_2O$ in THF at 23 °C for 18 h occurred site- and stereoselectively to give trisubstituted olefins **37** (Fig. 3) as single isomers.

Fig. 3. Structures of compounds **35** and **37**.

Mechanistic investigations were consistent with a process in which a proton transfer from water to the α-position of the substrate occurs, and then an alkyl group is introduced into the β-position of the intermediate template while replacing a chloride.[22b]

Hara et al.[23] had previously used a $Pd(OAc)_2$/(*S*)(−)-BINAP catalyst system for the synthesis of (*E*)-fluoroalkenes **39** and (*E*,*E*)-fluoroalkadienes **40** by treatment of (*E*)-2-fluoro-1-iodo-1-alkenes **38** with aryl- and (*E*)-1-alkenylboronates, respectively (Scheme 14). The S.–M. reactions leading to compounds **39** were performed in refluxing benzene in the presence of 2 M K_2CO_3, but the cross-couplings leading to **40** were carried out in refluxing benzene or dioxane in the presence of 2 M KOH as the base (Scheme 14).[23]

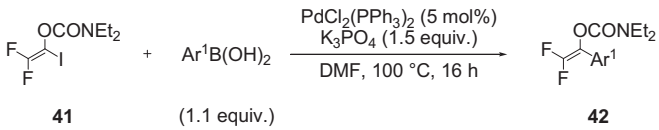


39	Ar^1	R^1	Yield (%)
a	Ph	*n*-$C_{10}H_{21}$	85
b	2-MeC_6H_4	*n*-$C_{10}H_{21}$	92
c	1-naphthyl	*n*-$C_{10}H_{21}$	94
d	Ph	$MeOOC(CH_2)_8$	93
e	Ph	*t*-$BuCO(CH_2)_8$	77
f	Ph	$AcO(CH_2)_9$	90
g	Ph	$HO(CH_2)_9$	74

40	R^2	R^1	Yield (%)
a	Bu	*n*-$C_{10}H_{21}$	87
b	Et	*n*-$C_{10}H_{21}$	67
c	$EtO_2CC(Me)_2CH_2$	*n*-$C_{10}H_{21}$	82
d	*n*-Bu	$EtO_2CC(Me)_2CH_2$	85
e	Et	$HO(CH_2)_9$	67
f	Bu	$Cl(CH_2)_9$	90

Scheme 14.

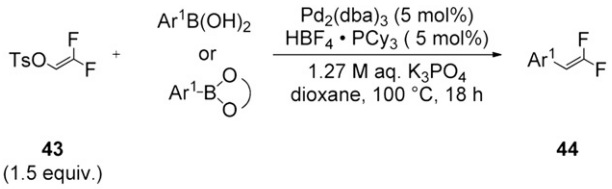
In 2000, 2-aryl-1-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoroethenes **42a**–**h** were synthesized by Percy et al.[25] in yields ranging from 36 to 85% by the site- and stereoselective S.–M. reaction of 1-(*N*,*N*-diethoxycarbamoyloxy)-2,2-difluoro-1-iodoethene (**41**) with 1.1 equiv of arylboronic acids in DMF at 100 °C in the presence of K_3PO_4 as base and a catalytic quantity of $PdCl_2(PPh_3)_2$ (Scheme 15). However, the reaction between **41** and 2-formylboronic acid, known to be sensitive to hydrolytic deboronation, did not produce the required cross-coupling product **42i** (Scheme 15). Moreover, all attempts to use alkenyl- or alkylboronic derivatives in cross-coupling reactions with **41** resulted in the recovery of unreacted **41** or in its reduction to 1-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoroethene.[25]



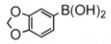
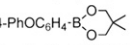
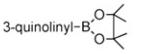
42	Ar^1	Yield (%)
a	4-$MeOC_6H_4$	50
b	Ph	77
c	2-naphthyl	85
d	4-ClC_6H_4	63
e	3-$MeOC_6H_4$	50
f	3-$NO_2C_6H_4$	50
g	2-MeC_6H_4	85
h	2-BrC_6H_4	36
i	2-$CHOC_6H_4$	0

Scheme 15.

Recently, Skrydstrup et al.[24] developed general reaction conditions for the site- and chemoselective synthesis of 2,2-difluorostyrenes **44** from 2,2-difluorovinyl tosylate (**43**) that involved the reaction of 1.5 equiv of this substrate with arylboronic acids or esters in dioxane at 100 °C in the presence of 1.27 M K_3PO_4 and a $Pd_2(dba)_3/PCy_3 \cdot HBF_4$ catalyst system. Compounds **44** were obtained in good-to-excellent yields (Scheme 16).



43 (1.5 equiv.) **44**

Organoboron compound	Yield (%)
4-CNC_6H_4-$B(OH)_2$	90
4-PhC_6H_4-$B(OH)_2$	98
2-naphthyl-$B(OH)_2$	81
6-MeO-2-naphthyl-$B(OH)_2$	50
	46
4-dibenzofuryl-$B(OH)_2$	76
3-$AcNHC_6H_4$-$B(OH)_2$	75
	94
4-AcC_6H_4-$B(OH)_2$	85
	75
	69

Scheme 16.

3. Monocoupling reactions of 1,1-dihalogenated-1-alkenes

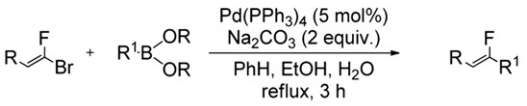
3.1. Monocoupling reactions of 1-bromo-1-fluoro- and 1-chloro-1-fluoro-1-alkenes

In most cases, the oxidative addition of Pd(0) to the organic halides in S.–M. reactions is the selectivity-determing step and the observed reactivity for Csp^2-hybridized electrophiles in these cross-couplings is: I>OTf>Br>>Cl>>F.[26] This electronic preference has been reported to parallel the rate of nucleophilic aromatic substitution in the same polyaromatics.[27]

Thus, in 1999, McCarthy et al.[28a,b] found that the coupling of (*E*)-1-bromo-1-fluoro-2-phenylethene ((*E*)-**45**; R=Ph) with arylboronic acids proceeds in the presence of 5 mol % $Pd(PPh_3)_4$ and 2 M NaOH in a mixture of benzene and EtOH under reflux and gave compounds (*Z*)-**46** (R=Ph) exclusively in excellent yields (Scheme 17). Excellent results were also obtained when (*E*)-**45** (R=Ph) was reacted with an (*E*)-alkenylboronic acid or an arylboronic ester (Scheme 17).[28a]

Interestingly, the coupling of (*Z*)-**45** (R=Ph) with arylboronic acids also proceeded stereoselectively to give stilbenes (*E*)-**46** (R=Ph) in high yields (Scheme 18).[28a]

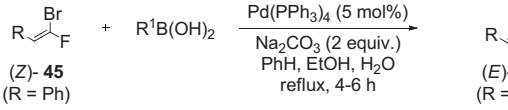
High yielding monocoupling reactions were also found to occur when stereoisomeric mixtures of 1-chloro-1-fluoro-1-alkenes **47** were reacted with phenylboronic acid (**48**) in the presence of aqueous Na_2CO_3 and a catalytic quantity of $Pd(PPh_3)_4$ (Method A) or $PdCl_2(PPh_3)_2$ (Method B) (Scheme 19).[28a] The (*Z*)- and (*E*)-stereoisomers of the resulting products **49** could be separated by chromatography.



(*E*)- **45** (R = Ph) (R^1 = H, alkyl) (*Z*)- **46** (R = Ph)

Organoboron compound	Yield %
$PhB(OH)_2$	86
4-$ClC_6H_4B(OH)_2$	89
4-$MeOC_6H_4B(OH)_2$	91
2-benzofurylB$(OH)_2$	83
(*E*)-*n*-Bu-CH=CHB$(OH)_2$	81
	94

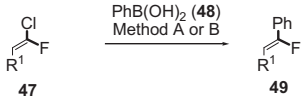
Scheme 17.



(*Z*)- **45** (R = Ph) (*E*)- **46** (R = Ph)

R^1	Yield (%)
Ph	92
4-ClC_6H_4	90
4-$MeOC_6H_4$	85
1-naphthyl	78

Scheme 18.



47 **49**

Method A: $Pd(PPh_3)_4$ (5 mol%); Na_2CO_3 (2 equiv.); PhH/ EtOH/ H_2O; reflux; 4-8 h
Method B: $PdCl_2(PPh_3)_2$ (cat.); Na_2CO_3; dioxane/ H_2O; reflux; 24 h

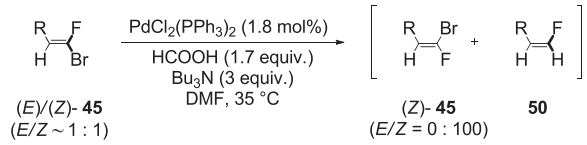
Method	R^1	Yield %
A	Ph	92
A	4-MeOC6H4	80
B	PhCH2CH2	83

Scheme 19.

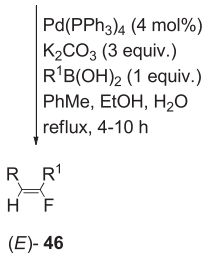
More recently, Xu and Burton[29] reported that (*Z*)-1-bromo-1-fluoro-1-alkenes (*Z*)-**45**, which were prepared by the kinetic reduction method involving treatment of stereoisomeric mixtures of 1-bromo-1-fluoro-1-alkenes (*E*)/(*Z*)-**45** with formic acid and Bu_3N in DMF at 35 °C in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$,[30] undergo $Pd(PPh_3)_4$-catalyzed reaction with arylboronic acids to give (*E*)-α-fluorostilbenes (*E*)-**46** having high stereoisomeric purity in good yields (Scheme 20). In most cases, compounds (*Z*)-**45** were not separated from the corresponding reduced products **50** and mixtures of (*Z*)-**45** and **50** were directly subjected to S.–M. reaction with arylboronic acids.[29]

3.2. Monocoupling reactions of 1,1-dibromo- and 1,1-dichloro-1-alkenes

As far as is known, examples of Pd-catalyzed S.–M. monocoupling reactions of 1,1-diiodo-1-alkenes **51** or 2,2-disubstituted 1,1-dihaloethenes **52** (Fig. 4) have not yet been reported in the literature.



R	R^1	Yield (% (*E*)- **46**)	*E*/*Z* molar ratio
Ph	3-AcC_6H_4	83	100 : 0
2-ClC_6H_4	Ph	82	100 : 0
2-ClC_6H_4	3-AcC_6H_4	90	89 : 11
2-ClC_6H_4	3-AcC_6H_4	90	95 : 5
1-naphthyl	Ph	85	96 : 4
PhCH(Me)	3-AcC_6H_4	92	100 : 0
PhCH(Me)	3-AcC_6H_4	93	100 : 0



Scheme 20.

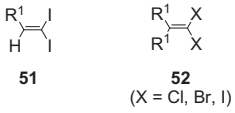
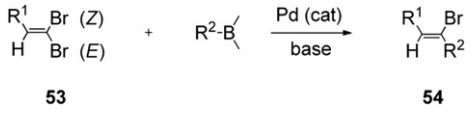


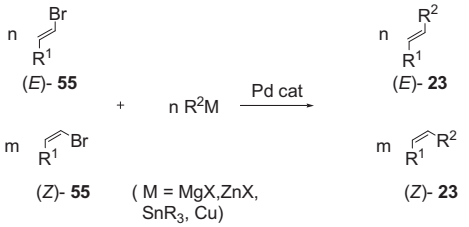
Fig. 4. Structures of compounds **51** and **52**.

On the contrary, since 1988, a very large number of site- and stereoselective Pd-catalyzed S.–M. monocouplings, illustrating that the two C–Br bonds of 1,1-dibromo-1-alkenes **53** exhibit different reactivities towards organoboron reagents, providing compounds **54** with very high stereoisomeric purity, have been described[31–48] (Scheme 21).



Scheme 21.

The high selectivities of these reactions, which occur at the C–Br bond in the *E*-position of compounds **53**, could be anticipated taking into account that the rates of Pd-catalyzed cross-coupling reactions of (*E*)- and (*Z*)-1-bromo-1-alkenes **55** are substantially different and that bromides (*E*)-**55** undergo preferentially intermolecular Pd-catalyzed cross-coupling reactions with organometallic reagents to give compounds (*E*)-**23** having high stereoisomeric purity (Scheme 22).[49,50]

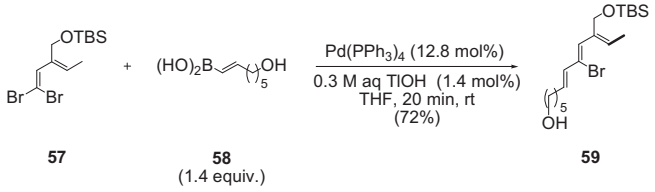


Scheme 22.

Very recently, Chelucci[12] summarized and commented on several Pd-catalyzed monocoupling reactions of compounds **53** with organoboron reagents.[31–38,40,41,43–46,49] This section provides an overview of the Pd-catalyzed S.-M. monocouplings of compounds **53** and 1,1-dichloro-1-alkenes **56** (Fig. 5) not included in the review by Chelucci, which have been reported in the literature by the end of August 2010.

Fig. 5. Structure of 1,1-dichloroalkenes **56**.

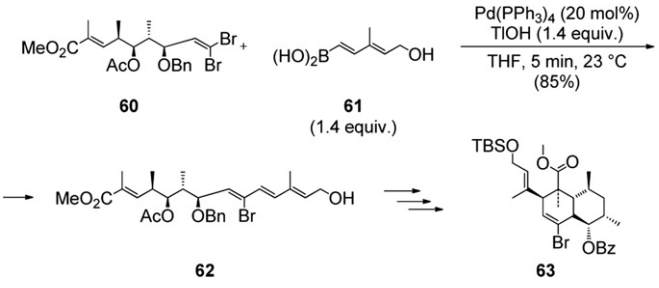
In 1998, Roush and Sciotti,[48] in the contest of their studies on the synthesis of the aglycon of spirotetronate antibiotic chlorothricin, found that the $Pd(PPh_3)_4$-catalyzed cross-coupling reaction of (*Z*)-1,1-dibromo-3-[(*tert*-butyldiphenylsilyloxy)methyl]penta-1,3-diene (**57**) with alkenylboronic acid **58** by using Kishi's modification of the S.–M. protocol,[51] provides (6*E*,8*Z*,10*Z*)-bromotriene **59** in 72% yield (Scheme 23). Surprisingly, this compound proved to be contaminated by 20–25% of the corresponding (6*E*,8*Z*,10*E*)-stereoisomer.[48]



Scheme 23.

Ten years earlier, Roush et al. had first utilized reaction conditions similar to those reported in Scheme 23 for the synthesis of the octahydronaphthalene subunit **63**.[31]

In particular, they prepared stereoisomerically pure compound **62** in 85% yield by the $Pd(PPh_3)_4$-catalyzed reaction of 1,1-dibromo-1-alkene **60** with 1.4 equiv of boronic acid **61** and 1.4 equiv of TlOH in THF at room temperature for 5 min (Scheme 24).[31]

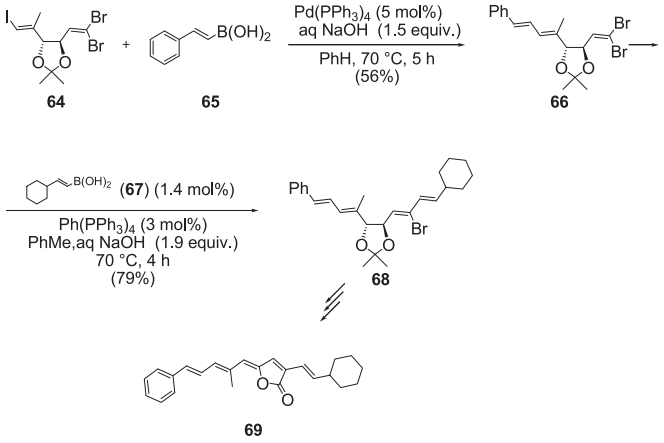


Scheme 24.

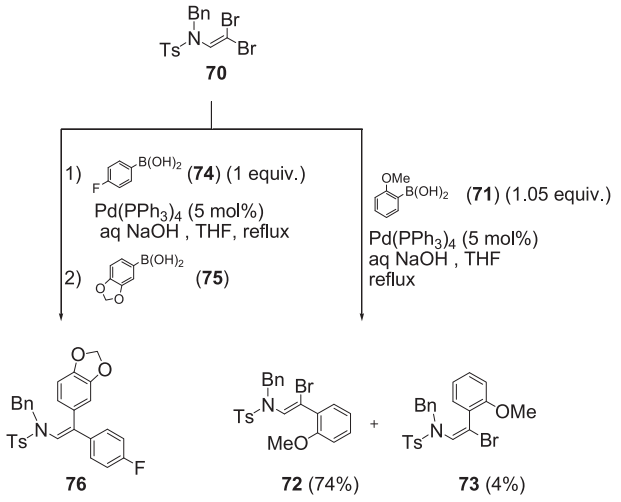
In 2000, Hanisch and Bruckner[39] reported that 1,1-dibromo-1-alkene **66**, which was prepared in 56% yield by the chemoselective $Pd(PPh_3)_4$-catalyzed reaction of dibromoiododiene **64** with boronic acid **65**, underwent a stereoselective $Pd(PPh_3)_4$-catalyzed monocoupling reaction with boronic acid **67** in toluene at 70 °C in the presence of aqueous NaOH to give the (*Z*)-configured monobromo-1-alkene **68** in 79% yield (Scheme 25).

This substance was then transformed into the stereoisomerically pure α-alkylidene-γ-butenolide **69** in three steps.[39]

In 2005, Cossy et al.[42] found that β,β-dibromoenamide **70** undergoes $Pd(PPh_3)_4$-catalyzed stereoselective monoarylation by treatment with 1.05 equiv of boronic acid **71** to give (*Z*)-bromoenamide **72** and β,β-diarylenamide **73** in 74 and 4% yield, respectively (Scheme 26). Remarkably, compound **70** proved also to be able to undergo a $Pd(PPh_3)_4$-catalyzed sequential stereoselective disubstitution in a one-pot process involving sequential addition of boronic acids **74** and **75**, which gave the trisubstituted ethene derivative **76** in 70% yield (Scheme 26).[42]

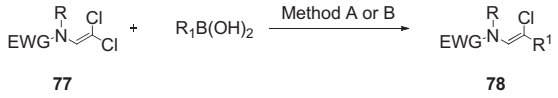


Scheme 25.



Scheme 26.

Cossy et al. also found that β,β-dichloroenamides **77** could be converted stereoselectively and in high yields into (*Z*)-chloroenamides **78** by $Pd(PPh_3)_4$-catalyzed monocouplings with boronic acids (Scheme 27).[42]

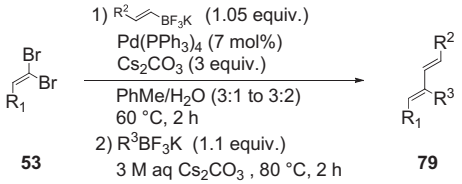


Method A : $Pd(PPh_3)_4$ (5 mol%); $Ba(OH)_2 \cdot H_2O$; THF/MeOH/H_2O (4 : 1: 1); reflux.
Method B : $Pd(PPh_3)_4$ (5 mol%); 1 M $NaOH_{aq}$; THF; reflux.

Method	EWG	R	R^1	Yield (%)
A	Ts	CH_2=CH-$(CH_2)_2$	Ph	76
A	Ts	CH_2=CH-$(CH_2)_2$	2-$MeOC_6H_4$	81
B	Ts	CH_2=CH-$(CH_2)_2$	4-FC_6H_4	89
B	Ts	Bn	Ph	98
B	Ts	Bn	2-$MeOC_6H_4$	91
B	Ts	Bn	3,4-$Cl_2C_6H_3$	88
B	Ts	Bn	*(E)*-*n*-Bu-CH=CH	65
B	Ts	4-$MeOC_6H_4$	Ph	94
B	Bz	$(MeO)_2$CH-CH_2	Ph	73

Scheme 27.

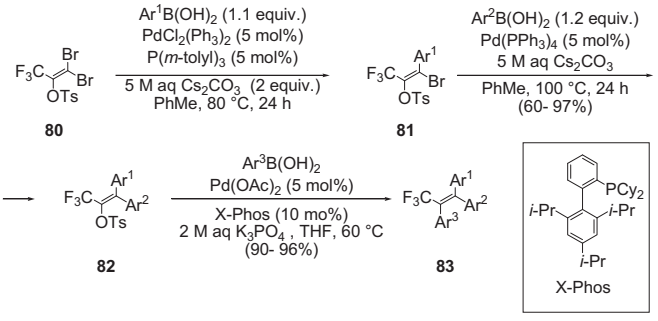
In 2006, Molander and Yokoyama[43] designed an efficient method for the one-pot synthesis of conjugated dienes **79** via sequential stereoselective disubstitution of 1,1-dibromo-1-alkenes **53** by using alkenyltrifluoroborates followed by alkyltrifluoroborates in the presence of a catalytic amount of $Pd(PPh_3)_4$ (Scheme 28). Compounds **79** were obtained in excellent yields and their stereoisomeric purity was generally quite high, although dependent upon the steric properties of the dibromides **53**.[43]



R^1	R^2	R^3	Yield (%)	Stereoisomeric purity
n-C_7H_{15}	$(CH_2)_3CO_2Me$	$(CH_2)_4OPiv$	85	92
$PhCH_2$	$(CH_2)_3CO_2Me$	$(CH_2)_4OPiv$	87	94
	$(CH_2)_3CO_2Me$	$(CH_2)_4OPiv$	86	92
	$(CH_2)_3CO_2Me$	$(CH_2)_4OPiv$	90	100

Scheme 28.

More recently, Shimizu et al.[46] developed a straightforward stereocontrolled synthesis of trifluoromethyl-substituted triarylethenes **83** that involved a threefold Pd-catalyzed reaction of 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene (**80**) with three kinds of arylboronic acids (Scheme 29). The first step of the reaction sequence leading to compounds **83** consisted of the stereo-, chemo- and site-selective synthesis of compounds **81** by the $PdCl_2(PPh_3)_2$-catalyzed reaction of **80** with 1.1 equiv of arylboronic acids $Ar^1B(OH)_2$ in the presence of P(*m*-tolyl)$_3$ and 5 M Cs_2CO_3 as base in toluene at 80 °C.



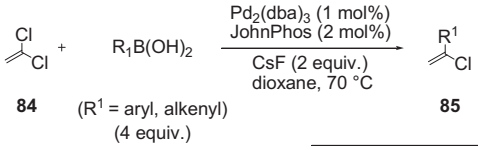
Scheme 29.

As shown in Table 1, which lists the yields and stereoisomeric purities of compounds **81** prepared according to this protocol, the *Z*/*E* selectivity of the reactions ranged from 87/13 to 92/8. However, the stereoisomers of compounds **81** could be easily separated by chromatography.[46] The $Pd(PPh_3)_4$-catalyzed cross-coupling reactions of **81** with 1.2 equiv of $Ar^2B(OH)_2$ in toluene at 100 °C in the presence of 5 M Cs_2CO_3 as base also proceeded chemoselectively, providing compounds **82** as single diastereoisomers in yields ranging from 60 to 97% (Scheme 29). On the other hand, the final cross-coupling reactions of the reaction sequence illustrated in Scheme 29 were effected by using the conditions developed by Buchwald et al.[47] to give stereoisomerically pure compounds **83** in excellent yields.[46]

Table 1
Synthesis of compounds **81** by coupling of **80** with $Ar^1B(OH)_2$

Ar^1	Yield of **81** (%)	(*Z*)/(*E*) molar ratio
Ph	94	92/8
4-$MeOC_6H_4$	74	90/10
4-Me C_6H_4	73	89/11
4-$CF_3C_6H_4$	89	87/13
4-BrC_6H_4	85	88/12
4-PhC_6H_4	86	88/12
2-Naphthyl	78	89/11
3-FC_6H_4	87	89/11
3-Thienyl	80	90/10

In 2006, Barluenga et al.[15] investigated the S.–M. monocoupling reactions of 1,1-dichloroethene (**84**) with aryl- and alkenylboronic acids and found that the reaction of these organometallic reagents with 4 equiv of **84** in dioxane at 70 °C in the presence of 2 equiv of CsF, 2 mol% JohnPhos and 1 mol% $Pd_2(dba)_3$ provides α-chlorostyrenes and 2-chloro-1,3-butadienes **85** as the sole reaction products (Scheme 30). However, the instability of these compounds towards chromatography gave rise, in some cases, to relatively reduced yields.[15]



R^1	Yield (%)
(*E*)-PhCH=CH	76
(*E*)-4-$MeOC_6H_3$CH=CH	72
(*E*)-4-ClC_6H_3CH=CH	49
2-MeC_6H_4	64
3,5-$Me_2C_6H_3$	87
4-$MeOC_6H_4$	66
	83
3-AcC_6H_4	21

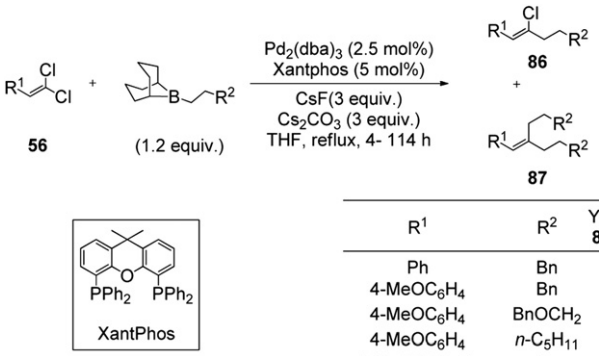
Scheme 30.

In 2007, Roulland et al.[52] described the synthesis of (*Z*)-chloroalkenes **86** via $Pd_2(dba)_3$/XantPhos-catalyzed S.–M. cross coupling of 1,1-dichloro-1-alkenes **56** with 9-alkyl-9-BBN derivatives (Scheme 31). Stereoisomerically pure compounds **86**, which were obtained together with 2–10% of the bis-coupling derivatives **87**, were isolated in modest to good yields (Scheme 31).[52] Interestingly, the use of the KF–K_3PO_4 couple in place of the CsF–Cs_2CO_3 couple as base for the $Pd_2(dba)_3$/XantPhos-catalyzed reactions also allowed the synthesis of compounds **86** in high yields.[52]

Roulland et al. also investigated the $Pd_2(dba)_3$/XantPhos-catalyzed reaction of trichloroethene (**88**) with the organoboron compound **89** in refluxing THF in the presence of the KF–K_3PO_4 couple as base, but found that the reaction was not selective and produced compounds **90** and **91** in 29 and 21% yield, respectively (Scheme 32).[52]

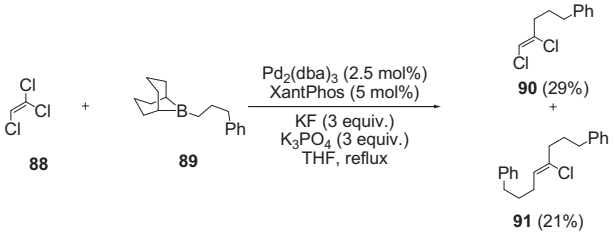
More recently, Roulland synthesized chemo-, stereo- and site-selectively compound **94** in 87% yield by the $Pd_2(dba)_3$/DPEphos-catalyzed reaction of 1,1-dichloro-1-alkene **92** with 9-alkyl-9-BBN **93** (Scheme 33).[53] Compound **94** was then used as a key intermediate in the total synthesis of (+)-oocydin A (**95**),[53] a compound extracted from the bacterium *Serratia marcescens*.[54]

In concluding this section, it seems important to point out that, as far as we know, no successful protocols for double cross-coupling reactions of 1,1-dichloro-1-alkenes with two different organoboron derivatives have been described to date.

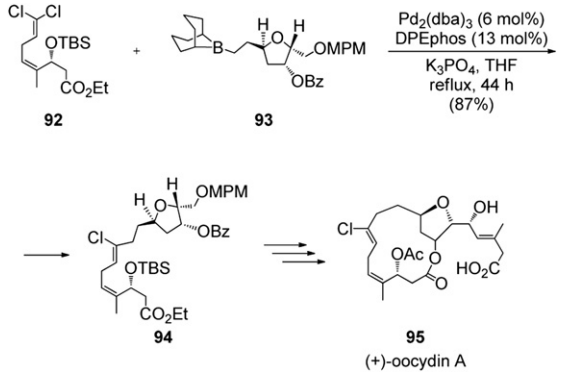


R^1	R^2	Yield of **86** (%)
Ph	Bn	80
4-$MeOC_6H_4$	Bn	88
4-$MeOC_6H_4$	$BnOCH_2$	79
4-$MeOC_6H_4$	*n*-C_5H_{11}	61
4-$MeOOCC_6H_4$	Bn	73
4-FC_6H_4	Bn	68
2,3-$(MeO)_2C_6H_3$	*n*-C_5H_{11}	79
4-FC_6H_4	*n*-C_5H_{11}	87
	Bn	79
	$BnOCH_2$	65
	*n*-C_5H_{11}	70
n-C_5H_{11}	$BnOCH_2$	46
n-C_5H_{11}	*n*-C_5H_{11}	65

Scheme 31.



Scheme 32.

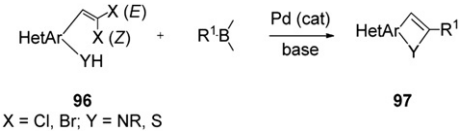


Scheme 33.

3.3. Pd-catalyzed tandem processes of 1,1-dihalogenated-1-alkenes involving S.–M. monocoupling reactions

In recent years, significant attention has been devoted to the synthesis of heterocycle derivatives of general formula 97 from 1,1-dihalo-1-alkenes **96** via tandem processes involving intramolecular carbon–heteroatom bond-forming reactions and intermolecular S.–M. reactions (Scheme 34). In these processes, the (*Z*)-bromide of

compounds **96** is involved in the cyclization reaction and the (*E*)-bromide participates to the intermolecular S.–M. reaction.

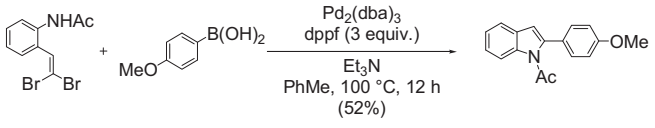


96
X = Cl, Br; Y = NR, S

97

Scheme 34.

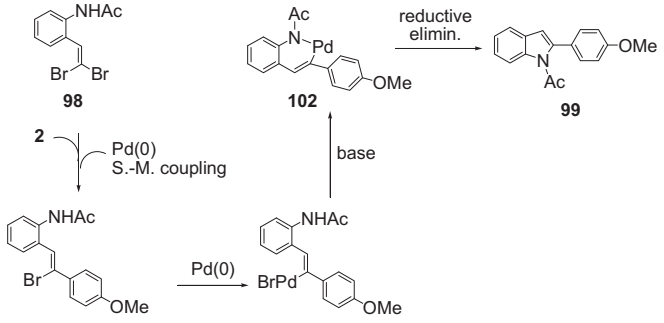
In 2004, this strategy was applied by Bisseret et al.[55a] to the synthesis of 2-(4-anisyl)-*N*-acetylindole (**99**) in 52% yield by the $Pd_2(dba)_3$/dppf-catalyzed reaction of 2-(2-acetamidophenyl)-1,1-dibromoethene (**98**) with 4-methoxyphenylboronic acid (**2**) in a mixture of Et_3N and toluene at 100 °C (Scheme 35).



98 **2** **99**

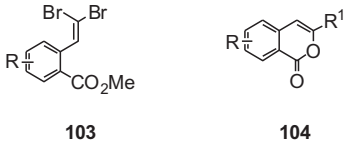
Scheme 35.

A possible simplified mechanism that accounts for the formation of **99** via intermediates **100**, **101** and **102** is shown in Scheme 36.



Scheme 36.

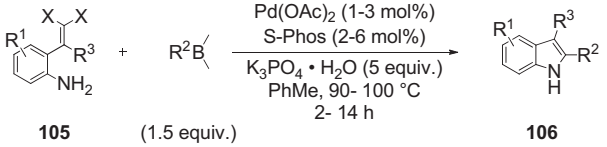
It is based on the known higher reactivity of the C–Br bond in the *E*-position of 1,1-dibromo-1-alkenes relative to the C–Br bond in the *Z*-position towards oxidative addition of Pd(0) as well as on the mechanism proposed by Wang and Shen[55b] for the related synthesis of 3-substituted isocoumarins **104** via Pd-catalyzed coupling of methyl 2-(2′,2′-dibromovinyl)benzoates **103** (Fig. 6) with organostannanes.



103 **104**

Fig. 6. Structures of compounds **103** and **104**.

In 2005, Fang and Lautens synthesized in high yields a wide variety of 2-substituted free (NH)-indoles **106** via the Pd-catalyzed reaction of *ortho-gem*-dihalovinylanilines **105** with organoboron reagents (Scheme 37).[56] The tandem process, involving a Buchwald–Hartwig C–N bond-forming reaction[57] and an S.–M. chemo-, site- and stereoselective intermolecular cross coupling, was performed in toluene at 90–100 °C in the presence of $K_3PO_4 \cdot H_2O$ and a low loading of a $Pd(OAc)_2$/*S*-Phos catalyst system.



105
(X = Br, Cl)

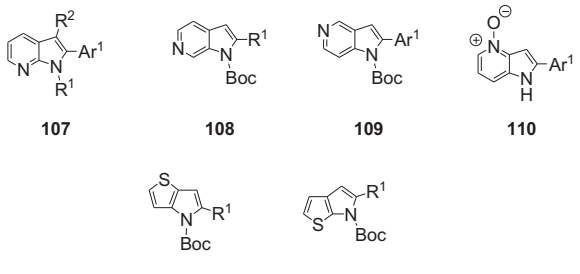
(1.5 equiv.)

106

X	R^1	R^3	R^2B	Yield (%)
Br	H	H	$PhB(OH)_2$	84
Br	H	H	$4\text{-}MeOC_6H_4B(OH)_2$	83
Br	H	H	$2\text{-}MeC_6H_4B(OH)_2$	82
Br	H	H	$4\text{-}CF_3C_6H_4B(OH)_2$	75
Br	H	H	2-thienylB$(OH)_2$	86
Br	H	H	(*E*)-*n*-BuCH=CHB$(OH)_2$	80
Br	H	H		73
Br	H	H	Et_3B	73
Br	H	H	*n*-C_6H_{13}-9-BBN	79
Br	H	H	BnO-$(CH_2)_4$-9-BBN	78
Br	6-Me	H	$PhB(OH)_2$	77
Br	6-F	H	$PhB(OH)_2$	88
Br	5-F	H	$PhB(OH)_2$	87
Br	4-F	H	$PhB(OH)_2$	80
Br	4-CF_3	H	$PhB(OH)_2$	90
Br	4-MeO_2C	H	$PhB(OH)_2$	90
Br	6-BnO,5-MeO	H	$PhB(OH)_2$	72
Br	5-BnO	H	$PhB(OH)_2$	79
Cl	H	H	$PhB(OH)_2$	95
Cl	H	Me	$PhB(OH)_2$	96

Scheme 37.

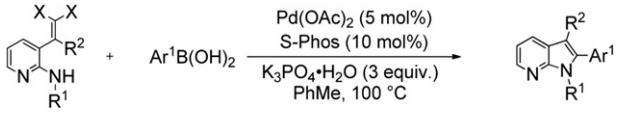
Two years later, Lautens et al. extended the methodology concerning tandem Buchwald–Hartwig C–N bond-forming reactions/S.–M. cross couplings to the synthesis of 7-, 6-, 5- and 4-azaindole derivatives, **107**, **108**, **109** and **110**, respectively, as well as of thienopyrroles **111** and **112** (Fig. 7).[58] In particular, several compounds **107** were synthesized in good-to-excellent yields by the reaction of substrates **113** with electron-neutral, electron-rich and electron-deficient arylboronic acids in toluene at 100 °C in the presence of $K_3PO_4 \cdot H_2O$ and a $Pd(OAc)_2$/*S*-Phos catalyst system (Scheme 38).[58]



107 **108** **109** **110**

111 **112**

Fig. 7. Structures of compounds **107**–**112**.

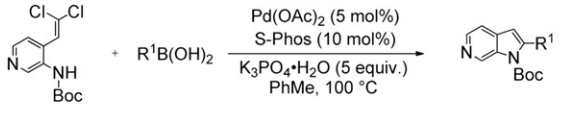


113 107

X	R^1	R^2	Ar^1	Yield (%)
Br	Bn	H	Ph	74
Cl	Bn	H	Ph	90
Br	Bn	H	Ph	84
Cl	Me	H	Ph	96
Cl	Me	H	4-$CF_3C_6H_4$	87
Cl	Me	H	4-$MeOC_6H_4$	83
Cl	Boc	H	Ph	62
Cl	Boc	Me	Ph	40 (R^1 = Boc) + 57 (R^1 = H)

Scheme 38.

Several 6-azaindoles **108** were similarly synthesized from 1.5 equiv of boronic acids and [4-(2,2-dichlorovinyl)pyridin-3-yl] carbamic acid *t*-butyl ester (**114**) (Scheme 39).[58]

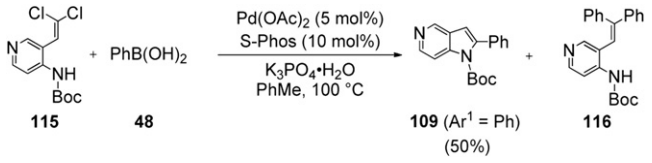


114 108

R^1	Yield (%)
Ph	87
2-Me-C_6H_4	73
4-$CF_3C_6H_4$	72
4-$MeOC_6H_4$	81
2-naphthyl	70
3-thienyl	55
(*E*)-1-pentenyl	79
2-MeO-quinolin-3-yl	91

Scheme 39.

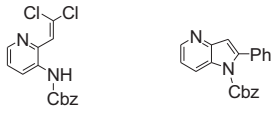
However, the reaction between [3-(2,2-dichlorovinyl)pyridin-3-yl]carbamic acid *tert*-butyl ester (**115**) and phenylboronic acid (**48**), carried out under experimental conditions similar to those employed for the synthesis of compounds **107** and **108**, provided a mixture of the required 5-azaindole **109** (Ar^1=Ph) and the bis-S.–M. coupling product **116** (Scheme 40).[58]



115 48 109 (Ar^1 = Ph) (50%) 116

Scheme 40.

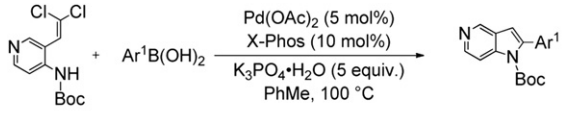
Remarkably, these experimental conditions proved unsuitable for the synthesis of 4-azaindole **118** from phenylboronic acid and substrate **117** (Fig. 8).[58]



117 118

Fig. 8. Structures of compounds **117** and **118**.

Nevertheless, when X-Phos was used as the ligand for the Pd-catalyzed reaction of **115** with arylboronic acids, 5-azaindoles **109** were cleanly obtained in high yields (Scheme 41).[58]

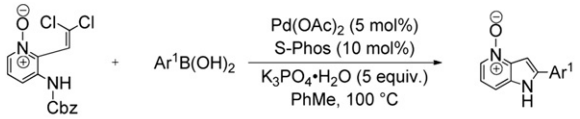


115 109

Ar^1	Yield (%)
Ph	87
4-FC_6H_4	88
4-$MeOC_6H_4$	68
2-MeC_6H_4	75

Scheme 41.

It was also found that *N*-oxide **119**, prepared by the oxidation of **117** with *m*-chloroperbenzoic acid, undergoes a $Pd(OAc)_2$/*S*-Phos-catalyzed tandem coupling with arylboronic acids to give *N*-oxy-4-azaindoles **110** in high yields (Scheme 42).[58]

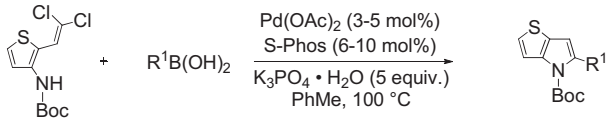


119 110

Ar^1	Yield (%)
Ph	75
4-$MeOC_6H_4$	97

Scheme 42.

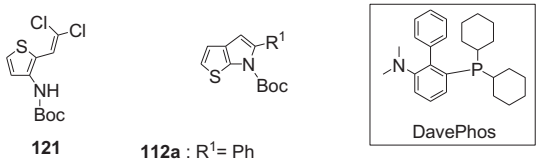
A $Pd(OAc)_2$/*S*-Phos catalyst system also allowed the high-yielding synthesis of 5-substituted thieno[3,2-*b*]pyrrole-4-carboxylic acid *t*-butyl esters **111** from [2-(2,2-dichlorovinyl)thiophen-3-yl]carbamic acid *tert*-butyl ester (**120**) and boronic acids (Scheme 43) as well as of 5-phenylthieno[2.3-*b*]pyrrole-6-carboxylic acid *t*-butyl ester (**112a**) in 76% yield from substrate **121** (Fig. 9) and phenylboronic acid.[58]



120 111

R^1	Yield (%)
Ph	73
4-FC_6H_4	74
4-$CF_3C_6H_4$	66
4-$MeO_2CC_6H_4$	74
(*E*)-1-pentenyl	80
3-thienyl	73

Scheme 43.



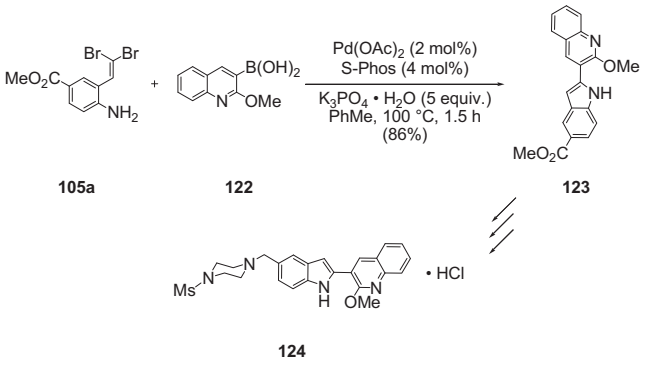
121

112a : R^1= Ph
112b : R^1= 4-FC_6H_4
112c : R^1= (*E*)-PhCH=CH

Fig. 9. Structures of compounds **112a–c**, **121** and Davephos.

However, a $Pd(OAc)_2$/Dave-Phos catalyst system was employed for the regioselective synthesis of compounds **112b** and **112c** (Fig. 9) in 81 and 71% yield, respectively, from **121** and the required boronic acids.

In 2007, Lautens and Fang applied their newly developed indole-synthesis methodology[56] for the preparation of compound **123**, a key intermediate in the synthesis of the potent KDR kinase inhibitor **124**, from 1,1-dibromo-1-alkene **105a** and heteroarylboronic acid **122** (Scheme 44).[59a]

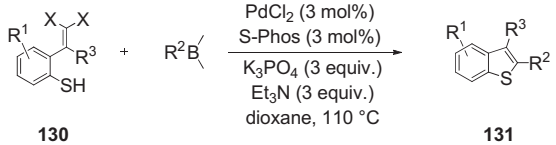


105a 122 123 124

Scheme 44.

In 2008, Fang and Lautens[59b] investigated the mechanism of the Pd-catalyzed tandem process leading to indoles **106a** from the deuterium labelled *ortho-gem*-dibromovinylaniline **105b** and proposed that the dominant process was a direct Buchwald–Hartwig C–N coupling[57] through the intermediates **128** and **129** (Scheme 45, path A) accompanied by a minor pathway involving the formation of the 1-bromo-1-alkyne intermediates **126** from **125** (Scheme 45, path B). A Pd(II)-mediated 5-*endo-dig* cyclization of **126** would then give **127** and, after the reductive elimination of palladium, the bromoindole derivatives **129**. This last compound finally would undergo S.–M. coupling with the arylboronic acids to give indoles **106a**. Proton exchange of DPdBr with a proton source such as **105b** or the boronic acids would then be responsible for the observed deuterium leaching (Scheme 45).[59b]

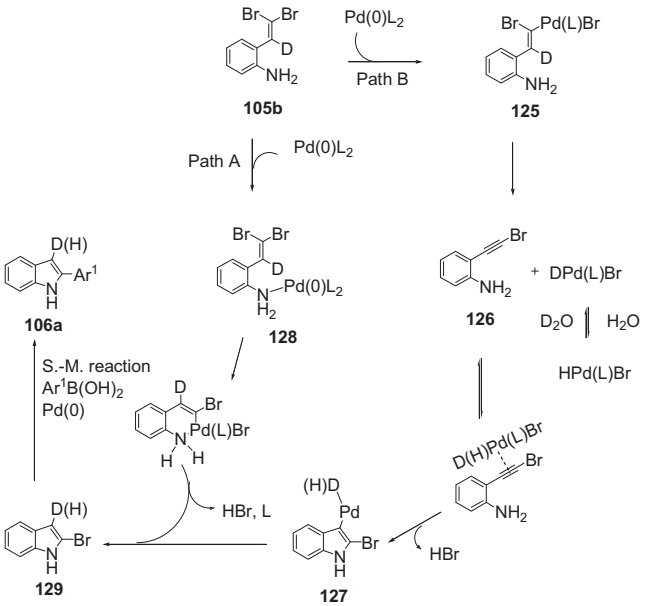
In 2009, Lautens et al. developed a general and efficient method for the synthesis of diversely functionalized benzothiophenes **131** from *gem*-dihalovinylthiophenols **130** and organoboron compounds including aryl- and alkenylboronic acids, aryl boronates, trialkylboranes, and potassium organotrifluoroborates (Scheme 46).[60] The reactions, which represent the first example of a tandem catalytic process involving a C–S bond-forming reaction and an S.–M. coupling, were performed by using a $PdCl_2$/*S*-Phos catalyst system, 3 equiv of Et_3N, and 3 equiv of K_3PO_4 in dioxane at 100 °C and gave compounds **131** in high yields.[60]



130 131

X	R^1	R^3	R^2B	Yield (%)
Br	H	H	4-$FC_6H_4B(OH)_2$	91
Br	H	H	3-$ClC_6H_4B(OH)_2$	83
Br	H	H	4-$AcC_6H_4B(OH)_2$	84
Br	H	H	3-$HO_2CC_6H_4B(OH)_2$	76
Br	H	H	2-$MeC_6H_4B(OH)_2$	82
Br	H	H	3-thienylB$(OH)_2$	99
Br	H	H	3-furylB$(OH)_2$	96
Br	H	H	2-MeO-quinolin-3-ylB$(OH)_2$	83
Br	H	H	(*E*)-PhCH=CHB$(OH)_2$	87
Br	H	H		80
Br	H	H	$PhBF_3K$	84
Br	H	H	CH_2=$CHBF_3K$	85
Br	H	H	Et_3B	80
Br	4-F	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	78
Br	3-Cl	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	76
Br	4-Br	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	84
Br	5-Br	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	75
Br	4-Me	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	84
Br	3,4-CH_2(O–)(O–)	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	64
Br	6-CF_3	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	45
Br	4-NO_2	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	46
Cl	H	H	3,4-$(MeO)_2C_6H_3B(OH)_2$	77
Cl	H	Me	3,4-$(MeO)_2C_6H_3B(OH)_2$	81

Scheme 46.

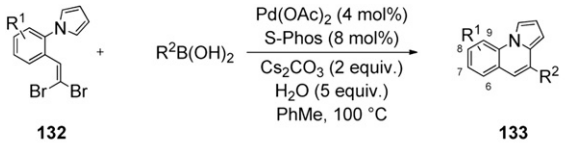


Scheme 45.

Again in 2009, Chai and Lautens described a new process for the highly efficient synthesis of 4-substituted pyrrolo[1,2-*a*]quinolines **133** from 1-[2-(2,2-dibromovinyl)-5-aryl]-1*H*-pyrroles **132** and boronic acids that involved a water-accelerated Pd-catalyzed S.-M. coupling and a direct arylation reaction (Scheme 47).[61] Interestingly, a wide range of aryl-, alkenyl- and alkylboronic acids could be used and a variety of substitution patterns on the phenyl ring of compounds **132** were tolerated. Mechanistic studies conducted to ascertain the order of the couplings allowed the authors to establish that the S.–M. reaction occurs prior to the direct arylation reaction.[61] The dramatic effect of water on both the reactivity of **132** and the reduction of the reaction byproducts was also evidenced.[61]

Examples of Pd-catalyzed tandem processes of *gem*-dihaloolefins involving a selective S.–M. reaction and a 5-*exo-dig*-cyclization[62] have also been described.[63–65]

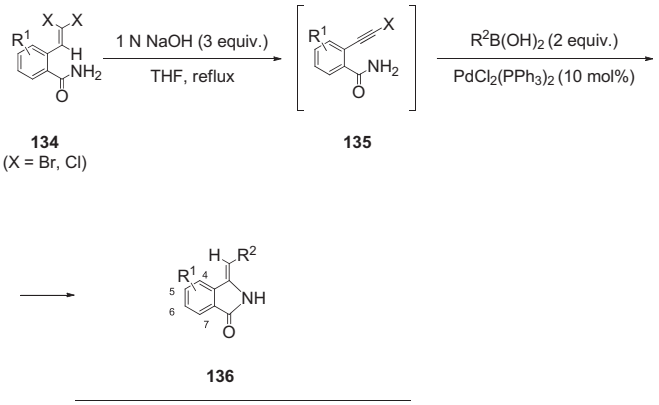
In 2008, Sun and Xu[63] developed a novel one-pot process for the efficient synthesis of (*Z*)-3-(arylmethylidene)isoindolin-1-ones **136**



132 133

R^1	R^2	Yield (%)
H	Ph	90
H	4-$MeOC_6H_4$	76
H	2-MeO_6H_4	75
H	3,4-$(MeO)_2C_6H_3$	55
H	4-ClC_6H_4	71
H	3-ClC_6H_4	62
H	4-$CF_3C_6H_4$	62
H	2-FC_6H_4	46
H	4-F_6H_4	86
H	2,6-$F_2C_6H_3$	0
H	3-thienyl	67
H	1-naphthyl	64
H	*(E)*-PhCH=CH	85
H	2-F,4-MeC_6H_3	74
H	3-$SiMe_3$	87
H	$PhCH_2CH_2$	87
H	2-MeC_6H_4	45
H	4-$BocNHC_6H_4$	74
H	4-F,2-$MeOC_6H_4$	56
7-MeO_2C	Ph	70
8-F	Ph	88
9-MeO	Ph	93
8-BnO	Ph	52
8-Cl	Ph	83
8,9 =CH-CH=CH-CH=	Ph	72

Scheme 47.



134 (X = Br, Cl) 135 136

X	R^1	R^2	Yield (%)
Br	H	Ph	84
Br	H	2-MeC_6H_4	86
Br	H	2-$MeOC_6H_4$	87
Br	H	3-$H_2NC_6H_4$	87
Br	H	3-$MeOC_6H_4$	84
Br	N	3-FC_6H_4	85
Br	H	3-$NO_2C_6H_4$	63-72
Br	H	4-MeC_6H_4	96
Br	H	4-HOC_6H_4	96
Br	H	4-$MeOC_6H_4$	94
Br	H	4-ClC_6H_4	91
Br	H	4-$TsOC_6H_4$	77
Br	H	4-$CF_3C_6H_4$	55-68
Br	H	2-naphthyl	78
Br	H	2-thienyl	76-91
Br	H	CH_2=CH	91
Br	6-F	4-MeC_6H_4	87
Br	6-F	4-$CF_3C_6H_4$	80
Br	7-Cl	4-MeC_6H_4	70
Br	5-Br	4-MeC_6H_4	0
Cl	H	4-MeC_6H_4	92

Scheme 48.

from *ortho-gem*-dihalovinylbenzamides **134** and organoboronic acids or esters, which consisted of a tandem elimination–cyclization–S.–M. coupling approach (Scheme 48). The synthetic procedure, which could be performed in the open air, involved treatment of compounds **134** with 1 M NaOH in THF under reflux, followed by the reaction of the resulting 1-bromo-1-alkynes **135** with the organoboron compounds in the presence of 1 mol % $PdCl_2(PPh_3)_2$.[63] In the mechanism proposed to rationalize the process (Scheme 49) compounds **135**, formed by dehydrohalogenation of **134**, would undergo a base-catalyzed, site-selective 5-*exo-dig*-cyclization reaction[66] to give the (*Z*)-3-(halomethylidene)isoindolin-1-ones **137**. Finally, a conventional S.–M. cross-coupling reaction of **137** with the organoboron compounds would produce compounds **136** (Scheme 49).[63]

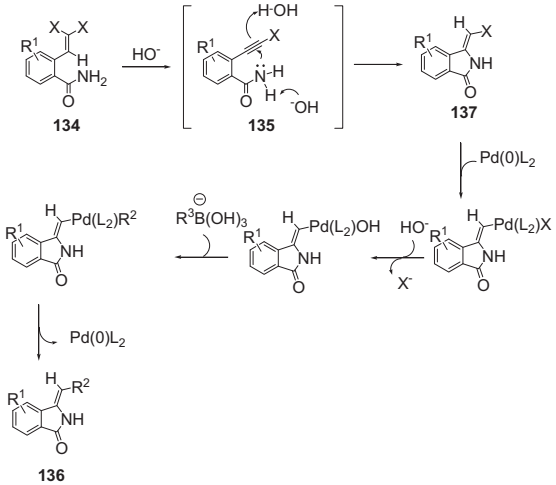
In 2010, (*E*)-1-methylidene-1*H*-indenes **139** were synthesized by Bryan and Lautens[64] from readily available (*E*)-*gem*-dibromoolefins **138** and arylboronic acids by using an efficient $Pd_2(dba)_3$/P(2-furyl)$_3$-catalyzed tandem intermolecular S.–M.-intramolecular Heck reaction (Scheme 50).

It was also observed that the reaction conditions used to prepare compounds **139** were unsuitable for the S.–M. cross-coupling reaction of bromides **140** (Fig. 10) with arylboronic acids[64] and it was therefore ruled out that compounds **140** were intermediates of the tandem process leading to (*E*)-1-methylidene-1*H*-indenes **139**.

In 2010, compounds **139** were also synthesized in high yields by Wu et al.[65] via the reaction of (*E*)-*gem*-dibromoolefins **138** with 1.5 equiv of arylboronic acids in toluene at 100 °C in the presence of 3 equiv of KOH, 2.5 mol % $Pd(OAc)_2$, and 5 mol % PPh_3.

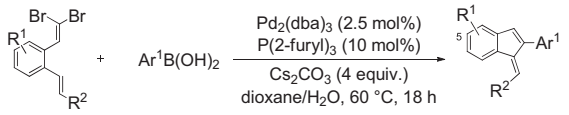
Lautens[64] and Wu[65] independently proposed that the synthesis of compounds **139** occurs via oxidative addition of Pd(0) to the (*E*)-bromide of compounds **138**, followed by a transmetalation reaction with a boronate and a reductive elimination (Scheme 51).

The resulting intermediates **141**, obtained alongside Pd(0), would then undergo an E2 elimination reaction to give the byproducts **142**[64] or re-enter the catalytic cycle via an oxidative addition



134 135 137 136

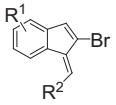
Scheme 49.



138 139

R^1	R^2	Ar^1	Yield (%)
H	CO_2Me	Ph	82
H	CO_2Me	3,4-$(MeO)_2C_6H_3$	77
H	CO_2Me	2-MeC_6H_4	80
H	CO_2Me	4-$MeO_2CC_6H_4$	87
H	CO_2Me	4-$CHOC_6H_4$	65
H	CO_2Me	4-$BocNHC_6H_4$	79
H	CO_2Me	3-$NO_2C_6H_4$	70
H	CO_2Me	3-furyl	79
H	CO_2t-Bu	Ph	62
H		Ph	91
H	CN	Ph	26
H	Ph	Ph	85
H	4-$MeOC_6H_4$	Ph	72
H	2,4-$Me_2C_6H_3$	Ph	92
H	4-pyridyl	Ph	71
5-MeO	CO_2Me	Ph	83
5-F	CO_2Me	Ph	64
5-Cl	CO_2Me	Ph	71
5-CF_3	CO_2Me	Ph	50

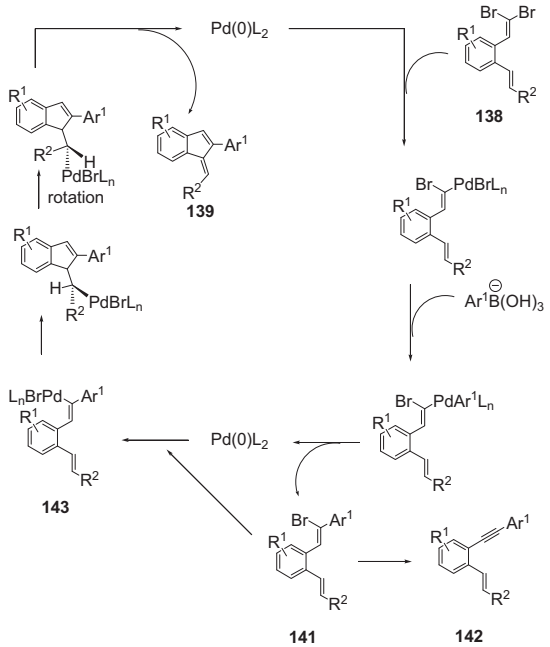
Scheme 50.



140

Fig. 10. Structure of compound **140**.

reaction to the remaining alkenyl bromide[64,65] (Scheme 51). In the latter case, the resulting alkenylpalladium(II) species **143** would undergo carbopalladation, followed by bond rotation and β-hydride elimination to give compounds **139** (Scheme 51).[64,65]

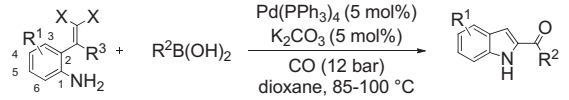


138 139 141 142 143

Scheme 51.

Bryan and Lautens[64] also found that, when the Pd-catalyzed reactions between **138** and arylboronic acids were performed by using an electron-rich sterically crowded ligand such as *S*-Phos or P(*t*-Bu)$_3$ instead of P(2-furyl)$_3$ or PPh_3, a different reaction mechanism was operating, which gave rise to compounds **140**.

One year before these studies, Florent et al.[67] employed a domino Pd-catalyzed C–N coupling/carbonylation/C–C coupling sequence to prepare a wide variety of highly functionalized 2-aroyl-1*H*-indoles **144** from *gem*-dibromovinylanilines **105**, arylboronic acids, and carbon monoxide (Scheme 52). Their synthetic procedure involved the treatment of **105** with 1.1 equiv of arylboronic acids, 5 equiv of K_2CO_3, and 5 mol % $Pd(PPh_3)_4$ in dioxane at 85–100 °C in an autoclave pressurized with 10 bar of CO.[67] Compounds **144**, which represent a class of tubulin polymerization inhibitors,[68] were prepared in moderate-to-good yields.



105 (X = Br; R^3 = H) 144

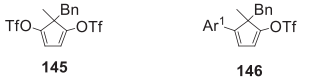
R^1	R^2	Yield (%)
3-Cl	Ph	68
4-CO_2Me	Ph	50
4,5 - H_2C(O)(O)	Ph	56
4,5-$(MeO)_2$	Ph	55
4-BnO	Ph	73
3,4,5-$(MeO)_3$	Ph	65
H	4-$MeOC_6H_4$	61
H	3,4,5-$(MeO)_3C_6H_2$	63
H	2-$MeOC_6H_4$	40
H	2,6-$Me_2C_6H_3$	--
H	4-$CF_3C_6H_4$	73
H	4-ClC_6H_4	70
H	4-$MeNHCOC_6H_4$	29
H	styryl	67
H	3-thienyl	67
H	benzofuran-2-yl	58
H	dibenzofuran-4-yl	71
H	isoquinolin-3-yl	21
H	naphthalen-2-yl	70

Scheme 52.

4. Monocoupling reactions of cyclic 1,3-dione derived bis(triflates)

In the past few years, the research group of Willis has performed studies on Pd-catalyzed S.–M. monocoupling reactions of cyclic 1,3-dione derived bis(triflates) with organoboron reagents.[69–71] In 2001, it was found that compound **145** undergoes a facile $Pd(OAc)_2$/PPh_3-catalyzed reaction with 4-methoxyphenylboronic acid (**2**) in THF at room temperature in the presence of aqueous KOH to give the monocoupling derivative **146** (Ar^1=4-$MeOC_6H_4$) as the sole arylation product in 71% yield (Fig. 11).[69]

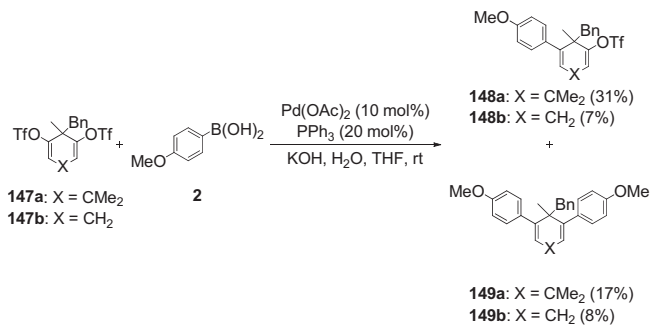
Nevertheless, the six-membered bis(triflates) **147a** and **147b** proved to react with **2** to give mixtures of the monoarylated



145 146 (Ar^1 = 4-$MeOC_6H_4$)

Fig. 11. Structures of compounds **145** and **146**.

derivatives, **148a** and **148b**, respectively, alongside low yields of compounds **149a** and **149b**, respectively (Scheme 53).[69] Unfortunately, the reason for the poor selectivity of these reactions was not elucidated.



Scheme 53.

In 2002, it was found that, when **147a** was treated with 1 equiv of arylboronic acid **150** under standard conditions [$Pd(OAc)_2/PPh_3$ as catalyst, KOH as base], the expected mono- and bis-coupling products **151** and **152**, respectively (Fig. 12), were formed together with compound **153a**, which was produced at the expense of **151** via an intramolecular arene–alkenyl triflate coupling.[70]

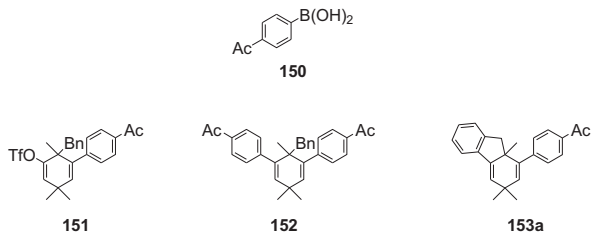
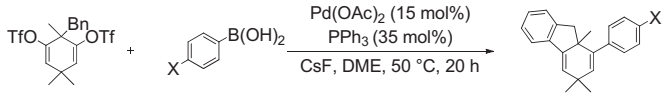


Fig. 12. Structures of compounds **150**, **151**, **152** and **153a**.

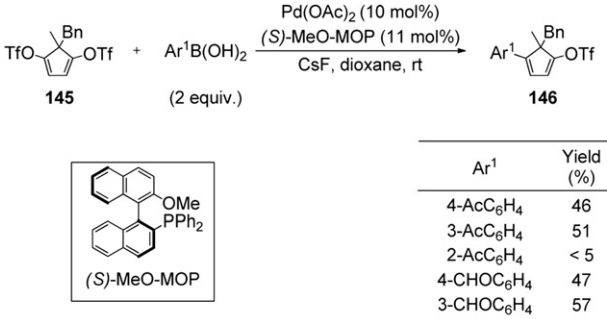
Optimized conditions for the selective synthesis of tricyclic carbocycles **153** from **147a**, involving the use of 1.8 equiv of arylboronic acids, a $Pd(OAc)_2/PPh_3$ catalyst system, DME as solvent and CsF as base, were then developed (Scheme 54).[70] The reactions, which were carried out at 50 °C for 20 h, provided compounds **153a–e** in yields ranging from 65 to 88%.



153	X	Yield (%)
153a	Ac	88
153b	CN	82
153c	OMe	80
153d	Ph	72
153e	H	65

Scheme 54.

Two years later, Willis et al. reported that the S.–M. reaction between bis(triflate) **145** and 2 equiv of arylboronic acids in dioxane at room temperature, in the presence of CsF as base and a $Pd(OAc)_2$/(*S*)-MeO-MOP catalyst system gave enantioselectively compounds **146** in satisfactory yields (Scheme 55).[71]



Ar^1	Yield (%)	ee (%)
4-AcC_6H_4	46	77
3-AcC_6H_4	51	86
2-AcC_6H_4	< 5	-
4-$CHOC_6H_4$	47	73
3-$CHOC_6H_4$	57	80
2-$CHOC_6H_4$	41	82
4-HOC_6H_4	43	74
3-furyl	53	72
N-Bn-indol-3-yl	66	85

Scheme 55.

5. Monocoupling reactions of arene derivatives bearing two or more electrophilic sites

5.1. Monocoupling reactions of arene derivatives bearing two (or more) different carbon–(pseudo)halogen bonds

The oxidative addition of aryl halides to Pd(0) species[72] is generally considered to be the selectivity-determining step of the S.–M. reactions. For these cross couplings, the relative order of reactivity of the aryl halides ArI>ArBr>ArCl>ArF has commonly been observed. This order relates to the Ar–X bond strength, which increases as follows Ar–I<Ar–Br<Ar–Cl<Ar–F and makes the oxidative addition step increasingly difficult.

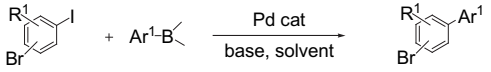
Taking advantage of the different reactivity of aryl halides bearing different halogen atoms, a very large number of chemoselective monofunctionalization reactions of polyhalogenated arenes bearing different halogen atoms via S.–M. reactions have been accomplished.

5.1.1. Monocoupling reactions of bromoiodoarenes. Table 2 summarizes the catalyst systems and the reaction conditions used for the chemoselective synthesis of bromobiphenyls **155a–c**, **155f–k** and **155q**, bromoquaterphenyl **155d**, dibromoiodobiphenyl **155r**, bromooligophenylenes **155e** and **155l**, and bromophenylpyridines **155m–p** by Pd-catalyzed S.–M. monocoupling reactions of the required bromoiodoarenes **154**. Compounds **155** were generally obtained in satisfactory or excellent yields,[73–86] but the degree of selectivity of the reactions used for their preparation was rarely mentioned.

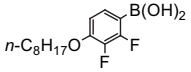
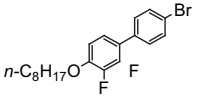
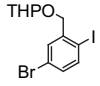
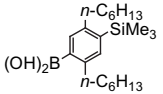
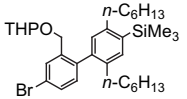
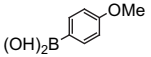
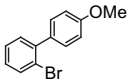
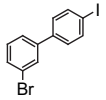
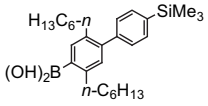
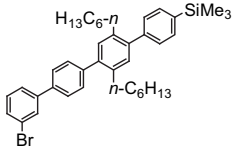
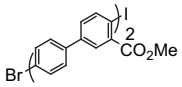
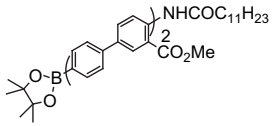
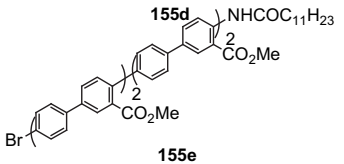
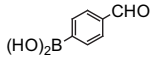
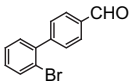
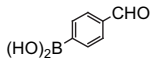
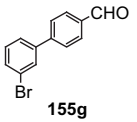
Examples have also been reported in the literature showing that the higher reactivity of aryl iodides, compared to the corresponding aryl bromides, can be used for the efficient synthesis of unsymmetrical terphenyls through one-pot sequential double S.–M. reactions of bromoiodobenzenes with two different arylboronic acids.[87–89] On the other hand, *o*-, *m*- and *p*-terphenyl compounds have attracted a great deal of attention, because they include biologically active substances with potential therapeutic value,[79,90] naturally occurring derivatives,[91] and compounds possessing unique photophysical properties that can be exploited in the design of liquid-crystalline materials[92] and organic electroluminescent devices.[93]

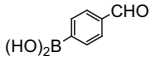
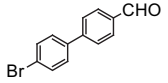
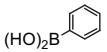
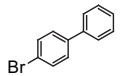
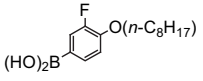
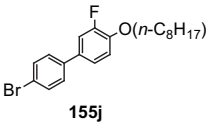
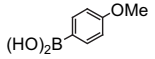
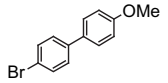
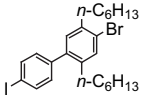
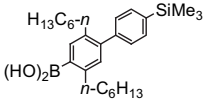
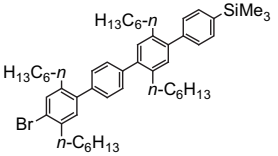
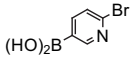
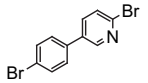
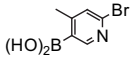
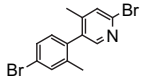
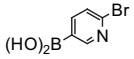
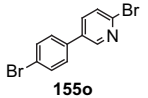
In 1992, Snieckus et al.[87] prepared unsymmetrical *m*-teraryls **156a** and **156b** as single isomers in 77 and 61% yield, respectively, by the $Pd(PPh_3)_4$-catalyzed coupling reaction of

Table 2
Chemoselective S.–M. monocoupling reactions of bromoiodoarenes **154** with boronic acids or esters



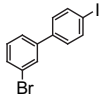
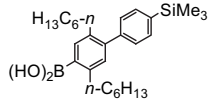
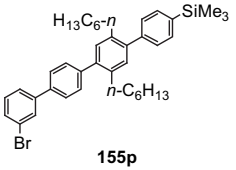
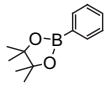
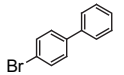
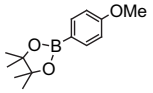
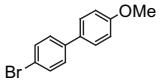
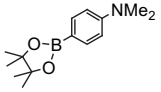
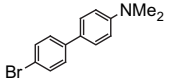
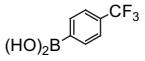
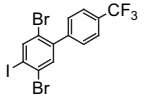
154 **155**

Entry	Reagents		Ar^1-B/**154** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product **155**	Yield (%)	Ref.
	154	Ar^1-B								
1	 **154a**		1.25	$Pd(PPh_3)_4$ (5)	$NaHCO_3$	EtOH/H_2O	Reflux/2.25	 **155a**	84	73
2	 **154b**		1.0	$Pd(PPh_3)_4$ (0.5)	$Ba(OH)_2$	PhMe/H_2O	Reflux/48	 **155b**	97	74
3	 **154c**		Not reported	$Pd(PPh_3)_4$ (3)	$Ba(OH)_2$	DME/H_2O	Reflux[a]	 **155c**	77	75
4	 **154d**		1.0	$Pd(PPh_3)_4$ (10)	$Ba(OH)_2$	PhMe/H_2O	Reflux[a]	 **155d**	81	76
5	 **154d**		1.21	$Pd(PPh_3)_4$ (4.3)	K_2CO_3	DMF	60/12	 **155e**	42.5	77
6	 **154c**		1.57	$Pd(PPh_3)_4$ (3–5)	Na_2CO_3	PhMe/EtOH/H_2O	Reflux/3	 **155f**	52	78
7	 **154f**		1.57	$Pd(PPh_3)_4$ (3–5)	Na_2CO_3	PhMe/EtOH/H_2O	Reflux/3	 **155g**	85 50	78 79

8	 **154a**		1.57	$Pd(PPh_3)_4$ (3–5)	Na_2CO_3	PhMe/EtOH/H_2O	Reflux/3	 **155h**	64 62	78 79
9	 **154a**		1.1	PdTN[b,c]	KF	THF	20/15	 **155i**	70	80
10	 **154a**		1.1	$Pd(PPh_3)_4$ (not reported)	Na_2CO_3	Dioxane/H_2O	Reflux/12	 **155j**	47.2	87
11	 **154a**		1.2	$Pd(OAc)_2/Ph_2C{=}CMePCy_2$	KF	PhMe	80/35	 **155k**	84	82
12	 **154g**		1.07	$Pd(PPh_3)_4$ (0.5)	Na_2CO_3	PhMe/H_2O	Reflux/48	 **155l**	32	83
13	 **154a**		1.1	$Pd(PPh_3)_4$ (5)	Na_2CO_3	Dioxane	Reflux[a]	 **155m**	60	84
14	 **154n**		1.1	$Pd(PPh_3)_4$ (5)	Na_2CO_3	Dioxane	Reflux[a]	 **155n**	30	84
15	 **154a**		1.1	$Pd(PPh_3)_4$ (4)	Na_2CO_3	Dioxane/H_2O	Reflux/24	 **155o**	60	84

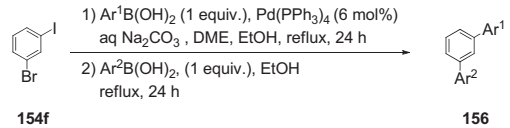
(*continued on next page*)

Table 2 (*continued*)

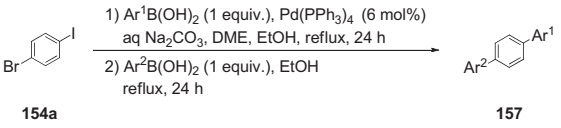
Entry	Reagents		Ar^1–B< /**154** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product **155**	Yield (%)	Ref.
	154	Ar^1–B<								
16	 **154d**		1.0	$Pd(PPh_3)_4$ (1)	$Ba(OH)_2$	PhMe/H_2O	Reflux/72	 **155p**	81	76
17	 **154a**		Not reported	$PdCl_2(PPh_3)_2$ (not reported)	Na_2CO_3	THF/H_2O	80[a,d]	 **155i**	82	85
18	 **154a**		Not reported	$PdCl_2(PPh_3)_2$ (not reported)	Na_2CO_3	THF/H_2O	80[d]	 **155k**	84	85
19	 **154a**		Not reported	$PdCl_2(PPh_3)_2$ (not reported)	Na_2CO_3	THF/H_2O	80[d]	 **155q**	91	85
20	 **154i**		0.07	$Pd(PPh_3)_4$ (5)	K_2CO_3	DME/H_2O	75/16	 **155r**	48	86

[a] The reaction was maintained at reflux until complete consumption of the aryl halide.
[b] PdTN=palladium-dodecanethiolate nanoparticles.
[c] PdTN (12 mg) was used for the reaction of 1 mmol of 4-bromo-1-iodobenzene.
[d] The reaction was maintained at 80 °C until completion.

3-bromoiodobenzene (**154f**) with two different arylboronic acids according to the sequential regimen shown in Scheme 56. A similar protocol was then used for the synthesis of functionalized unsymmetrical *p*-teraryls **157a** and **157b** from 4-bromoiodobenzene (**154a**) (Scheme 56).[87]



	Ar^1	Ar^2	Yield (%)
156a	3-MeC_6H_4	Ph	77
156b	2-(*i*-Pr)$_2$NCOC_6H_4	3-$MeOCH_2C_6H_4$	61

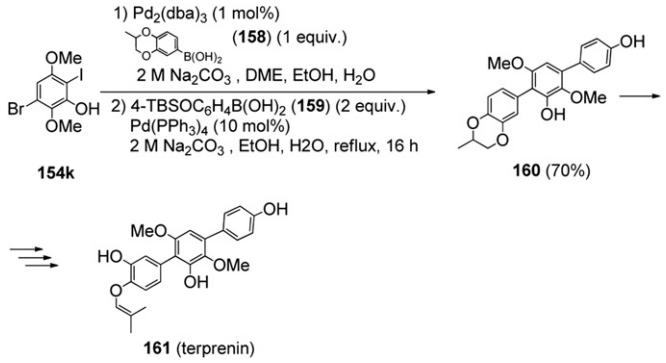


	Ar^1	Ar^2	Yield (%)
157a	3-MeC_6H_4	Ph	74
157b	2-(*i*-Pr)$_2$NCOC_6H_4	3-$MeOCH_2C_6H_4$	55

Scheme 56.

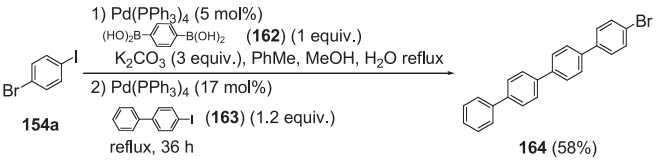
In 2005, Ohtani et al.[88] found that compound **154k**, which has a different halogen functionality at the C-1 and C-4 positions, reacted preferentially with boronic acid **158** at the iodo-substituted position in the presence of a catalytic amount of $Pd_2(dba)_3$ under ligandless conditions.

Without isolation of the resulting bromobiphenyl compound, the phenol-type boronic acid **159** and 10 mol% $Pd(PPh_3)_4$ were added to the reaction mixture and the expected terphenyl derivative **160** was obtained in 70% yield (Scheme 57).[88] This compound was then used as a key intermediate in the synthesis of terprenin (**161**), a compound discovered in the fermentation broth of Aspergillus candidus RF-5672.[94]



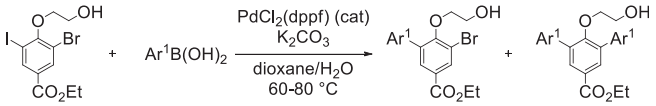
Scheme 57.

More recently, Lutzen at al.[89] synthesized 4-bromo-1,1′:4′:1″:4″:1‴-quaterphenyl (**164**) by the reaction of **154a** with 1 equiv of benzene-1,4-diylboronic acid (**162**) in a mixture of toluene, methanol and water under reflux in the presence of K_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$, followed by treatment of the resulting crude biphenylboronic acid with 4-iodobiphenyl (**163**) and an additional portion of $Pd(PPh_3)_4$ (Scheme 58). Compound **164** was obtained in 58% yield.[89]



Scheme 58.

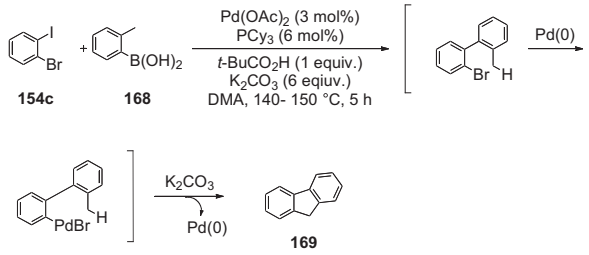
Greenfield et al.[95] had previously observed that the $PdCl_2$(dppf)-catalyzed reactions of the bromoiodobenzene derivative **165** with arylboronic acids in a 5/1 to 10/1 mixtures of dioxane and water in the presence of K_2CO_3 as base disappointingly occurred with selectivities of 2/1 to 4/1 of monoarylated versus biarylated compounds, **166** and **167**, respectively (Scheme 59). However, pure compounds **166** were isolated in 60–70% yield by HPLC of the reaction mixtures on silica columns.[95]



[Ar^1 = 2-FC_6H_4; 3-$CF_3C_6H_4$; 3-ClC_6H_4; 4-$MeOC_6H_4$]

Scheme 59.

Finally, Hu et al.[96] recently synthesized fluorene (**169**) in 78% yield by a $Pd(OAc)_2/PCy_3$-catalyzed tandem process involving the S.–M. coupling reaction of 2-bromoiodobenzene (**154c**) with *o*-tolylboronic acid (**168**) and a cyclization reaction proceeding through Csp^3–H bond activation (Scheme 60). This process was carried out by using 1 equiv of pivalic acid as an additive. In fact, it is known that this carboxylic acid in combination with a Pd compound and a ligand is able to generate a highly active catalyst for direct arylation reactions.[97]

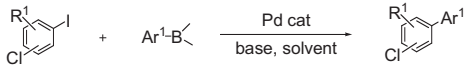


Scheme 60.

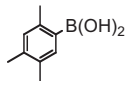
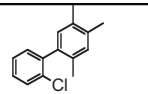
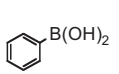
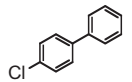
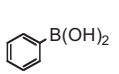
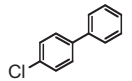
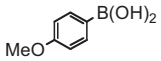
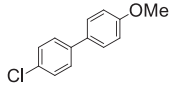
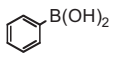
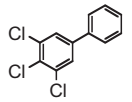
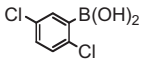
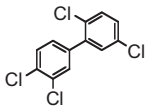
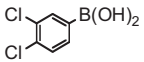
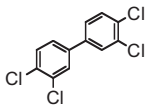
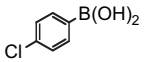
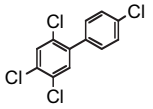
5.1.2. Monocoupling reactions of chloroiodo- and bromochloroarenes. Since 1992, significant attention has been directed to the synthesis of monochlorinated- and polychlorinated biphenyls via Pd-catalyzed halogen-selective S.–M. reactions of monochloro- and polychloroiodobenzene derivatives, respectively.[98–108] In fact, it is well known that polychlorinated biphenyls are persistent organic pollutants that are implicated in a number of human diseases, such as reproductive and neurological deficiencies and cancer of the digestive system.[109]

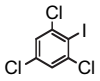
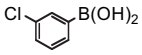
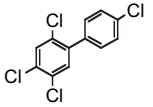
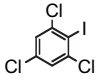
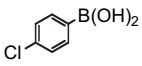
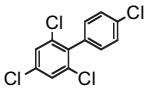
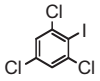
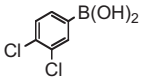
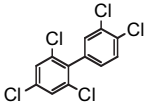
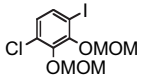
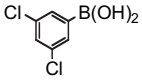
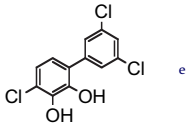
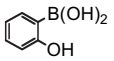
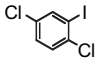
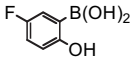
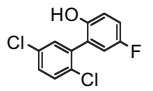
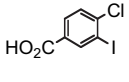
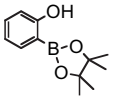
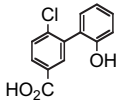
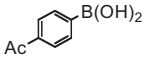
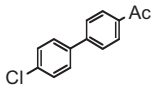
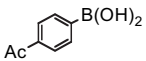
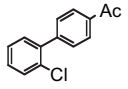
Table 3 lists the catalyst systems and the reaction conditions used for the synthesis of monochlorinated biphenyls **171a**–**c** (entries 1–4 and 19),[98–101,106] **171l** (entry 13),[104] **171n**–**p** (entries 15–17),[104,105] **171r** (entry 20)[107] and **171s** (entry 21),[107] and polychlorinated biphenyls **171d**–**k** (entries 5–12),[102,103] **171m** (entry 14)[104] and **171q** (entry 18)[105] from chloroiodoarenes **170** and arylboronic acids or esters. As shown in this table, 4-chlorobiphenyl (**171b**) was prepared in high yields from 4-chloroiodobenzene

Table 3
Chemoselective S.–M. monocoupling reactions of chloroiodoarenes **170** with arylboronic acids or esters



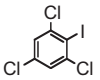
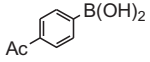
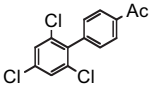
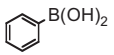
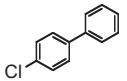
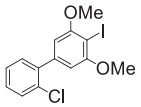
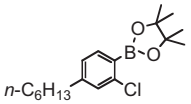
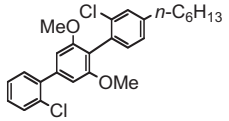
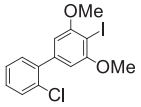
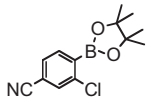
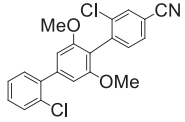
170 **171**

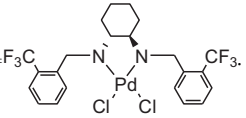
Entry	Reagents		Ar^1–B</ **170** molar ratio	Pd Catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product **171**	Yield (%)	Ref.
	170	Ar^1–B</								
1	 **170a**		1.1	$Pd(PPh_3)_4$	$Ba(OH)_2$	DME/H_2O	80[a]	 **171a**	94	98
2	 **170b**		1.0	$Pd_2(dba)_3$ (0.5) $P(t\text{-}Bu)_3$ (1.2)	KF	THF	rt[a]	 **171b**	98	99
3[b]	 **170b**		1.0	$Pd(OAc)_2$ (3.7)	AcONa	MeOH+[BMIm][BF_4]	30/50	 **171b**	82	100
4	 **170b**		1.1	$Pd_2(dba)_3{\cdot}CHCl_3$ (1)	K_3PO_4	PhMe/H_2O/THPC[c]	50/1	 **171c**	90	101
5	 **170c**		Not reported	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux[d]	 **171d**	52	102
6	 **170d**		Not reported	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux[d]	 **171e**	68	102
7	 **170d**		Not reported	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux[d]	 **171f**	69	102
8	 **170e**		Not reported	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux[d]	 **171g**	16	102

9	 **170f**		Not reported	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux[d]	 **171g**	11	102
10	 **170f**		Not reported	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux[d]	 **171i**	64	102
11	 **170f**		Not reported	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux[d]	 **171j**	77	102
12	 **170g**		1.5	$Pd(PPh_3)_4$ (%)	K_3PO_4	DMF	110/18	 **171k** (e)	32	103
13	 **170a**		105	$Pd(OAc)_2$ (5) PPh_3 (10)	K_3PO_4	MeCN/H_2O	50/20	 **171l**	90	104
14	 **170h**		1.5	$Pd(OAc)_2$ (5) PPh_3 (10)	K_3PO_4	MeCN/H_2O	50/20	 **171m**	83	104
15	 **170i**		1.5	$Pd(OAc)_2$ (5) PPh_3 (5)	K_3PO_4	MeCN/H_2O	50/20	 **171n**	98	104
16[f]	 **170b**		1.3	Complex A[g] (1)	K_2CO_3	DMF	120/24	 **171o**	83	105
17[f]	 **170a**		1.3	Complex A[g] (1)	K_2CO_3	DMF	120/24	 **171p**	69	105

(*continued on next page*)

Table 3 (*continued*)

Entry	Reagents		Ar^1-B</>/**170** molar ratio	Pd Catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product **171**	Yield (%)	Ref.
	170	Ar^1-B</>								
18[f]	 **170f**		1.3	Complex A[g] (1)	K_2CO_3	DMF	120/24	 **171q**	23	105
19	 **170b**		2.0	PVC–EDA–SA–Pd[h] (1)	K_2CO_3	95% EtOH	Reflux/0.5	 **171b**	88	106
20	 **170j**		2.0	$Pd(PPh_3)_4$ (5)	Na_2CO_3	PhMe/EtOH/H_2O	90/48	 **171r**	92	107
21	 **170j**		2.0	$Pd(PPh_3)_4$ (5)	Na_2CO_3	PhMe/EtOH/H_2O	90/48	 **171s**	88	107

[a] The reaction was maintained at room temperature until completion.
[b] [BMIm][BF_4]=1-*n*-butyl-3-methylimidazolium tetrafluoroborate.
[c] THPC=tetradecylhexylphosphonium chloride.
[d] The reaction was maintained under reflux until completion.
[e] Compound obtained after acidic hydrolysis of the cross-coupling product.
[f] The reaction was carried out under argon or in the open air.
[g] Complex A=  .
[h] PVC-EDA-SA-Pd=nanoparticles of palladium immobilized on a matrix of poly(vinylchloride)-(PVC)-supported Schiff base.

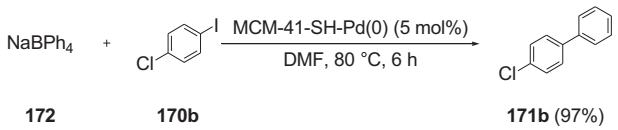
(**170b**) by using three different protocols. In 2000, Fu et al. carried out the S.–M. reaction in THF at room temperature in the presence of an expensive and air unstable $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system (entry 2, Table 3).[99] In 2002, Srinivasan et al.[100] performed the cross-coupling reaction under ultrasonic irradiation at 30 °C in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]BF_4, with methanol as cosolvent in the presence of a catalytic amount of $Pd(OAc)_2$, but in the absence of a phosphine ligand (entry 3, Table 3). More recently, Liu et al.[106a] conducted the S.–M. reaction in 95% EtOH under reflux for 0.5 h by using a more exotic catalyst system, i.e., nanoparticles of Pd immobilized on a matrix of poly(vinyl chloride)-supported Schiff base (entry 19, Table 3). Schiff bases derived from substituted benzaldehydes had previously been reported as effective ligands for Pd-catalyzed S.–M. reactions of phenylboronic acid with aryl, benzyl and allyl bromides under mild conditions.[106b]

The phosphonium salt ionic liquid, tetradecylphosphonium chloride (THPC), had previously been used as the solvent for the synthesis of 4-methoxy-4′-chlorobiphenyl (**171c**) from **170b** and 4-methoxyphenylboronic acid at 50 °C in the presence of K_3PO_4 as base and a catalytic amount of $Pd_2(dba)_3\cdot CHCl_3$ (entry 4, Table 3).[101]

In 2008, Kylmälä et al. employed 1 mol % of a complex obtained from $PdCl_2$ and a reduced Salen-type ligand to catalyze the synthesis of compounds **171o**, **171p** and **171q** from chloroiodobenzenes **170b**, **170a** and **170f**, respectively, according to the S.–M. cross-coupling protocol (entries 16–18, Table 3).[105]

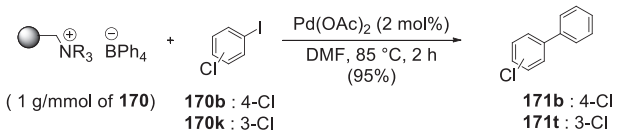
The remaining reactions listed in Table 3 were carried out by using catalysts consisting of conventional Pd complexes that included $Pd(PPh_3)_4$ (entries 1,[98] 12,[103] 20 and 21[107]), $PdCl_2$(dppf) (entries 5–9),[102] or a mixture of $Pd(OAc)_2$ and PPh_3 (entries 13–15).[104]

It should be noted that chlorinated biphenyls have also been synthesized by S.–M.-type monocoupling reactions that do not require the use of a base. In fact, in 2007, Cai et al. prepared compound **171b** in 97% yield by the heterogeneous coupling reaction of sodium tetraphenylborate (**172**) with 4-chloroiodobenzene (**170b**) in DMF at 80 °C in the presence of 5 mol % mercapto-functionalized MCM-41-supported sulfur Pd(0) complex (Scheme 61).[110]



Scheme 61.

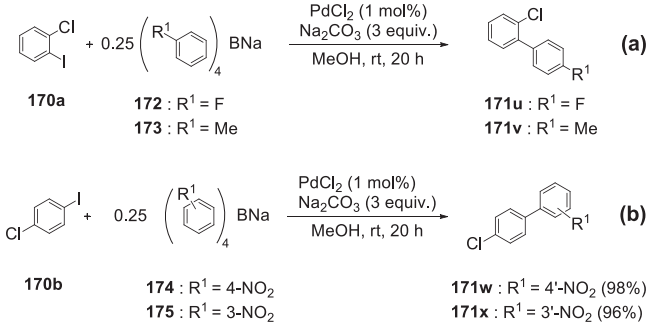
In 2008, Basu et al.[111] described the synthesis of 4-chlorobiphenyl (**171b**) and 3-chlorobiphenyl (**171t**) in 95% yield by the $Pd(OAc)_2$-catalyzed reaction of 4-chloroiodobenzene (**170b**) and 3-chloroiodobenzene (**170k**), respectively, with tetraphenylborate immobilized on Amberlite® resin (Scheme 62).



Scheme 62.

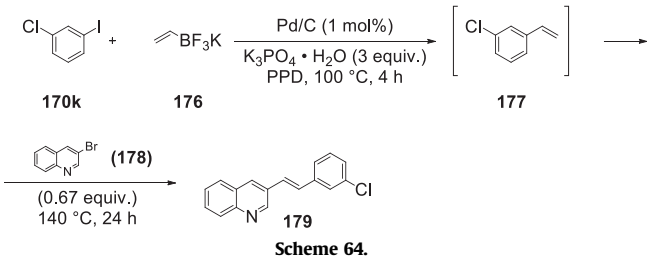
On the other hand, recently, chlorinated biphenyl derivatives have also been synthesized by highly atom-efficient Pd-catalyzed S.–M. reactions involving the use of sodium tetraarylborates in the presence of a base.[108]

In particular, compounds **171u** and **171v** were prepared in excellent yields by the $PdCl_2$-catalyzed reaction of 2-chloroiodobenzene (**170a**) with 0.25 equiv of sodium tetra(4-fluorophenyl)borate (**172**) and sodium tetra(4-tolyl)borate (**173**), respectively, in methanol at room temperature in the open air, in the presence of 3 equiv of Na_2CO_3 (Scheme 63, Eq. a). An analogous protocol was used for the synthesis of chlorobiphenyls **171w** and **171x** in 98 and 96% yield from **170b** and sodium tetraarylborates **174** and **175**, respectively (Scheme 63, Eq. b).[108]



Scheme 63.

On the other hand, (*E*)-stilbene **179** was recently prepared from chloroiodobenzene **170k** via an efficient one-pot S.–M./Heck sequence involving treatment of this substrate with 1.1 equiv of potassium vinyltrifluoroborate (**176**) in 1,3-propanediol (PPD) in the presence of 1 mol % Pd/C and 3 equiv of $K_3PO_4\cdot H_2O$ (Scheme 64).[112] The crude resulting compound **177** was then reacted with 0.07 equiv of 3-bromoquinoline (**178**) at 140 °C for 48 h to give compound **179** in 62% yield (Scheme 64).[112]



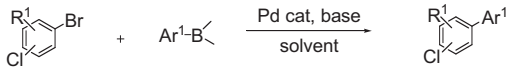
Scheme 64.

Interestingly, compound **179** was also obtained in 80% yield by mixing all reactants **170m**, **176** and **178** in NMP in the presence of Pd/SiO_2 and 3 equiv of $K_3PO_4\cdot H_2O$ at 140 °C for 4 h and subsequently at 140 °C for 24 h.[112]

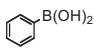
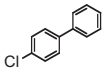
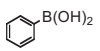
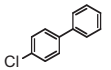
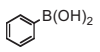
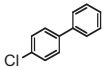
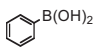
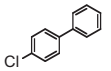
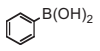
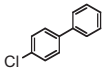
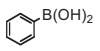
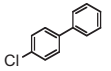
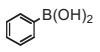
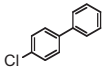
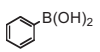
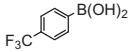
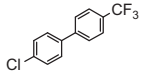
Numerous chlorinated biphenyls **171** have also been synthesized via chemoselective Pd-catalyzed S.–M. reactions of arylboronic acids or esters with bromochlorobenzenes **180**.[99,102–105] The catalyst systems and the reaction conditions employed to prepare compounds **171b**, **171c**, **171t** and **171aa**–**au** according to this strategy are listed in Table 4 (entries 1–37). In particular, in 2000, Fu et al. synthesized compound **171b** in 97% yield from 4-chlorobromobenzene (**180a**) and phenylboronic acid through the use of a catalyst system consisting of 0.5 mol % $Pd_2(dba)_3$ and 1.2 mol % $P(t\text{-}Bu)_3$ (entry 1, Table 4).[99]

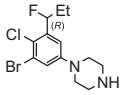
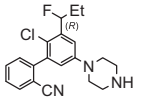
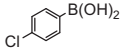
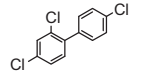
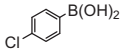
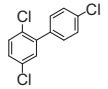
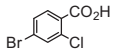
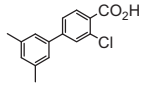
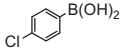
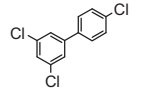
On the other hand, reaction conditions similar to those employed in entry 6 of Table 4 allowed the synthesis of 4-chloro-4′-trifluoromethylbiphenyl (**171z**) in 91% yield from **180a** and 4-trifluoromethylboronic acid (entry 9, Table 4).[117]

Table 4
Chemoselective S.–M. monocoupling reactions of bromochlorobenzenes **180** with arylboronic acids or esters



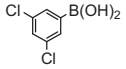
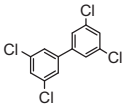
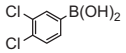
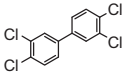
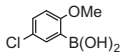
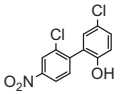
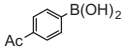
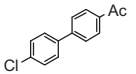
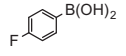
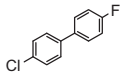
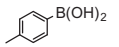
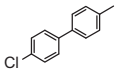
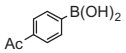
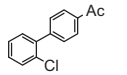
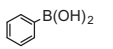
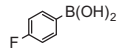
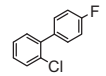
180 **171**

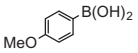
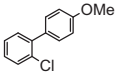
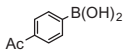
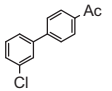
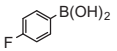
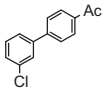
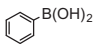
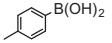
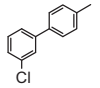
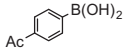
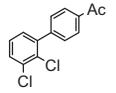
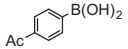
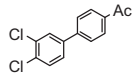
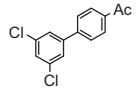
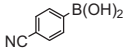
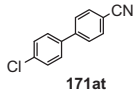
Entry	Reagents		Ar^1–B/**180** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product		Ref.
	180	Ar^1–B						**171**	Yield (%)	
1	 **180a**		1.0	$Pd_2(dba)_3$ (0.5) $P(t\text{-}Bu)_3$ (1.2)	KF	THF	rt[a]	 **171b**	97	99
2	 **180a**		1.1	$Pd(OAc)_2$ (1) **L1**[b] (3)	Na_2CO_3	PhMe/EtOH/H_2O	70/3	 **171b**	84	113
3	 **180a**		1.5	$Pd(OAc)_2$ (4) **L2**[c] (4)	Cs_2CO_3	PhMe	80[a]	 **171b**	90	114
4	 **180a**		1.4	NDEP–Al_2O_3–$Pd(OAc)_2$[d] (5.4)	K_2CO_3	EtOH/H_2O	rt/1.5	 **171b**	97	115
5	 **180a**		1.0	PdCl[3-(η-$C_{12}H_{25}$)C_6H_2-2,6-(=PPh_2)]$_2$[e] (0.1)	Na_2CO_3	DMF	110/8	 **171b**	71	116
6	 **180a**		1.5	$Pd(OAc)_2$ (0.5)	Na_2CO_3	Acetone/H_2O	35/0.5 in air	 **171b**	98	117
7	 **180a**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171b**	100	121
8	 **180b**		1.1	$Pd(OAc)_2$ (1) $P(i\text{-}BuNCH_2CH_2)_3N$[f] (3)	Na_2CO_3	PhMe/EtOH/H_2O	70/3	 **171y**	97	113
9	 **180a**		1.5	$Pd(OAc)_2$ (0.5)	Na_2CO_3	Acetone/H_2O	35/0.75 in air	 **171z**	91	117

10	 **180c**		1.5	$Pd(OAc)_2$ **L4**[g] (Pd/**L4**=1)	Cs_2CO_3	Dioxane	90/6	 **171t**	98	118
11	 **180d**		1.5	$PdCl_2(PPh_3)_2$ (1)	$K_3PO_4 \cdot nH_2O$	PhMe	Reflux/1.5	 **171aa**	87	119
12	 **180e**		1.0	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux/16	 **171ab**	36	102
13	 **180f**		1.0	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux/16	 **171ac**	42	102
14	 **180g**		1.0	$PdCl_2$(dppf) (0.004)	Na_2CO_3	EtOH/dioxane/H_2O	Reflux/16	 **171ad**	61	102
15	 **180h**		1.0	$Pd(PPh_3)_4$ (1)	Na_2CO_3	H_2O/TBAB	130/0.33 μW	 **171ae**	96	120
16	 **180e**		1.03	$Pd(PPh_3)_4$ (3.4)	Na_2CO_3	DMF/H_2O	Reflux/48	 **171ab**	90	103
17	 **180i**		1.03	$Pd(PPh_3)_4$ (3.4)	Na_2CO_3	DMF/H_2O	Reflux/48	 **171af**	78	103

(*continued on next page*)

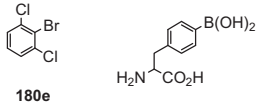
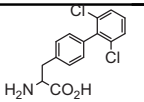
Table 4 (*continued*)

Entry	Reagents		Ar^1–B/**180** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product		Ref.
	180	Ar^1–B						**171**	Yield (%)	
18	 **180i**		1.03	$Pd(PPh_3)_4$ (3.4)	Na_2CO_3	DMF/H_2O	Reflux/48	 **171ag**	44	103
19	 **180j**		1.03	$Pd(PPh_3)_4$ (3.4)	Na_2CO_3	DMF/H_2O	Reflux/48	 **171af**	51	103
20	 **180k**		1.1–1.5	$Pd(OAc)_2$ (5) PPh_3 (10)	K_3PO_4	MeCN/H_2O	80[a]	 **171ah**	72[h]	104
21	 **180a**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171o**	100	121
22	 **180a**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171ai**	100	121
23	 **180a**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171aj**	100	121
24	 **180b**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171p**	93	121
25	 **180b**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171ak**	100	121
26	 **180b**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171v**	100	121

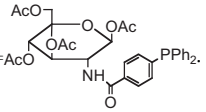
27	 **180b**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171l**	100	121
28	 **180c**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171n**	100	121
29	 **180c**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171n**	100	121
30	 **180c**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171t**	100	121
31	 **180c**		1.1	$Pd(OAc)_2$ (1.5)	K_3PO_4	DMF/H_2O	rt/3	 **171ap**	100	121
32	 **180l**		1.3	Complex **B**[i] (1)	K_2CO_3	DMF	120/24 in air	 **171aq**	72	105
33	 **180j**		1.3	Complex **B**[i] (1)	K_2CO_3	DMF	120/24 in air	 **171ar**	86	105
34	 **180i**	 **180i**	1.3	Complex **B**[i] (1)	K_2CO_3	DMF	120/24 in air	 **171as**	71	105
35	 **180a**		1.1	$Pd_2(dba)_3$ (0.5) $[HP(t\text{-}Bu)_3][BF_4]$ (1.2)	KF·H_2O	THF	rt[a]	 **171at**	98	122

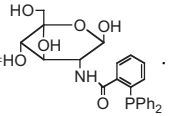
(*continued on next page*)

Table 4 (*continued*)

Entry	Reagents		Ar^1–B/**180** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product		Ref.
	180	Ar^1–B						**171**	Yield (%)	
36	 **180e**		1.0	$PdCl_2(PPh_3)_2$ (5)	Na_2CO_3	MeCN/H_2O	150/0.08 μW	 **171au**	75	123
37	 **180c**		1.1–1.2	$PdCl_2(PCy_2NC_5H_{10})_2$[j] (0.2)	K_3PO_4	PhMe	80/0.1 in air	 **171t**	84	124

[a] The reaction was maintained at this temperature until completion.

[b] **L1**=  .

[c] **L2**=  .

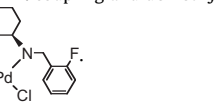
[d] NDEP–Al_2O_3–$Pd(OAc)_2$=$Pd(OAc)_2$ immobilized on amorphous *N*,*N*-diethylaminoalumina.

[e] PdCl[3-(η-$C_{12}H_{25}$)C_6H_2-2,6-($OPPh_2$)]$_2$=Pd phosphinite POCOP pincer complex derived from 4-*n*-dodecylresorcinol.

[f] A bicyclic triaminophosphine.

[g] **L4**=2-(Diphenylphosphino)benzaldoxime ligand.

[h] Overall yield after S.–M. coupling and demethylation by treatment with BBr_3 in CH_2Cl_2.

[i] Complex **B**=  .

[j] $PdCl_2(PCyNC_5H_{10})_2$=dichloro bis[1-(diyclohexylphosphanyl)piperidine]Pd.

In 2005, Wan et al.[118] employed a 1/1 mixture of $Pd(OAc)_2$ and 2-(diphenylphosphino)benzaldoxime as catalyst for the synthesis of 3-chlorobiphenyl (**171t**) from 3-bromochlorobenzene (**180c**) and phenylboronic acid (**48**).

Souda et al.[119] had previously reported that 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(*R*)-fluoropropyl]}phenyl-piperazine (**171aa**), an intermediate for the synthesis of a potent antagonist of D_3/D_2/5-HT_2 receptors, could be obtained in 87% yield by the S.–M. reaction of 1-{3-bromo-4-chloro-5-[1-(*R*)-fluoropropyl]}phenyl-piperazine (**180d**) and the thermally unstable pinacol ester of (*o*-cyanophenyl)boronic acid in refluxing toluene in the presence of K_3PO_4 as base and 1 mol % $PdCl_2(PPh_3)_2$ (entry 11, Table 4).

In 2006, Wolf et al.[120] showed that the microwave-promoted $Pd(PPh_3)_4$-catalyzed cross-coupling reaction of 4-bromo-2-chlorobenzoic acid (**180h**) with 3,5-dimethylphenylboronic acid in water at 130 °C for 20 min in the presence of *n*-Bu_4NBr as additive and Na_2CO_3 as base provided 4-(3′,5′-dimethylphenyl)-2-chlorobenzoic acid (**171ae**) in 96% yield (entry 15, Table 4).

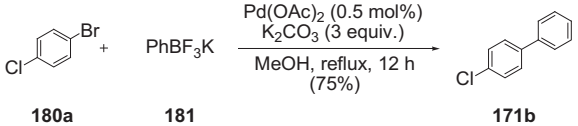
One year later, conventional reaction conditions, involving the use of $Pd(PPh_3)_4$ as the catalyst and aqueous Na_2CO_3 as the base, were used by Snieckus et al. for the synthesis of polychlorinated biphenyls **171ab**, **171af**, **171ag** and **171ah** from dichlorobromobenzenes **180e**, **180i** and **180j** and the required chlorinated phenylboronic acids (entries 16–19, Table 4).[103]

Gong and He[123] had previously employed a $PdCl_2(PPh_3)_2$-catalyzed S.–M. reaction under microwave irradiation for the synthesis of 4-arylphenylalanine **171au**, a *o*,*o*,*o*′-trisubstituted biphenyl derivative, in 75% yield from 1-bromo-2,6-dichlorobenzene (**180e**) and 4-boronophenylalanine (entry 36, Table 4).

In 2010, Lousand and Fu[122] synthesized chemoselectively 4-chloro-4′-cyanobiphenyl (**171at**) in excellent yield through a user-friendly method involving a $Pd_2(dba)_3$/[HP(*t*-Bu)$_3$][BF_4]-catalyzed reaction between 4-bromochlorobenzene (**180a**) and 4-cyanophenylboronic acid at room temperature in the presence of KF·$2H_2O$ as base (entry 35, Table 4).

Again in 2010, Bolliger and Frech[124] reported the synthesis of 3-chlorobiphenyl (**171t**) in 86% yield by the reaction of 3-bromochlorobenzene (**181c**) with phenylboronic acid in toluene at 80 °C in the open air in the presence of K_3PO_4 as base and a catalytic quantity of dichlorobis[1-(dicyclohexylphosphanyl)piperidine]Pd (entry 37, Table 4).

In concluding this section, it should be noted that procedures different from those illustrated in entries 1–7 of Table 3 have also been used for the synthesis of 4-chlorobiphenyl (**171b**), a compound used as a model substrate to investigate the microbial aerobic biodegradation of polychlorinated biphenyls.[125] In 2002, Molander and Biolatto[126] prepared **171b** in 75% yield by the reaction of **180a** with potassium phenyltrifluoroborate (**181**) in refluxing methanol in the presence of 3 equiv of K_2CO_3 and 0.5 mol % $Pd(OAc)_2$ (Scheme 65).

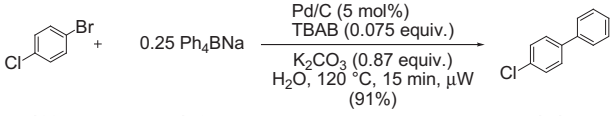


180a **181** **171b**

Scheme 65.

In 2007, the synthesis of **171b** was performed in 88% yield by the coupling reaction of **180a** with 1 equiv of sodium tetraphenylborate (**172**) in water by using the MCM-supported sulfur Pd(0) complex as catalyst.[110a]

Two years later, **171b** was synthesized in 91% yield via the heterogeneous Pd/C-catalyzed atom-efficient phenylation of **180a** with 0.25 equiv of **172** in water under focused microwave irradiation (Scheme 66).[127]



180a **172** **171b**

Scheme 66.

More recently, the operationally simple, atom-efficient cross-coupling reaction of 2-bromochlorobenzene (**170b**) with 0.25 equiv of **172** in the presence of 3 equiv of Na_2CO_3 and 3 mol % $PdCl_2$ in methanol at room temperature in open-air conditions was found to give 2-chlorobiphenyl (**171y**) in 91% yield.[108]

5.1.3. Monocoupling reactions of fluoroiodo-, bromofluoro- and chlorofluoroarenes and polyfluoronitrobenzenes. Fluorinated biphenyl derivatives **183** include naturally-occurring compounds,[128] synthetic precursors to luminophores[129] and compounds that are fundamental building blocks in fluorinated liquid crystals.[130] The synthesis of numerous compounds **183** has frequently been achieved via Pd-catalyzed S.–M. chemoselective monocoupling reactions of fluoroiodobenzenes **182** with arylboronic acids or esters.[124,131–134] Entries 1–23 of Table 5 list the reaction conditions and the catalyst systems employed for the synthesis of compounds **183a**–**w** from the required fluoroiodobenzenes **182**.

It should be noted that, unlike the cross-coupling reactions used to prepare compounds **183c**–**w** (entries 3–23, Table 5), which were generally accomplished by treatment of the organoboron compounds with a molar excess of iodofluorobenzenes, the $PdCl_2$(dppf)-catalyzed reactions employed for the synthesis of optically active compounds **183a** and **183b** (entries 1 and 2, Table 5) were performed by the reaction of a molar excess of 4-fluoroiodobenzene (**182a**) with the pinacol esters of the required arylboronic acids.[131]

In 2003, solventless S.–M. microwave-promoted reactions, which utilized a commercially available KF–Al_2O_3 mixture and a high loading of Pd powder, allowed Kabalka et al.[133] to synthesize compounds **183e** and **183f** from 4-tolylboronic acid and fluoroiodobenzenes **182b** and **182c**, respectively (entries 5 and 6, Table 5).

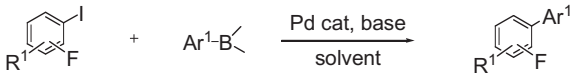
Interestingly, the Pd catalyst could be recycled without loss of catalytic activity by using a simple filtration and washing sequence.[133]

In 2006, Steiniger and Wuest[135] directed their attention towards the synthesis of ^{18}F-labelled biphenyls bearing different functional groups and found that the optimized conditions to prepare compounds **183g**–**t** in radiochemical yields up to 94% involved treatment of a molar excess of the required arylboronic acids with 4-[^{18}F]-fluoroiodobenzene (**182d**) in acetonitrile at 60 °C for 5 min in the presence of 5 mol % $Pd_2(dba)_3$ and 1.98 equiv of Cs_2CO_3 (entries 7–20, Table 5).

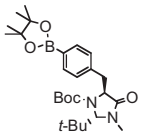
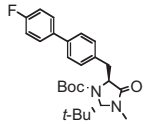
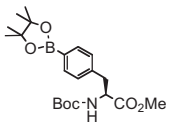
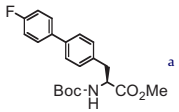
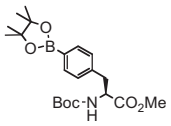
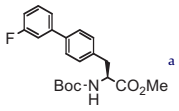
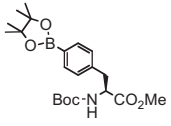
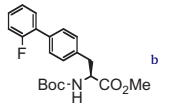
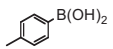
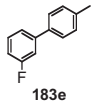
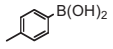
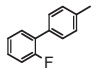
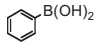
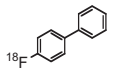
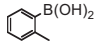
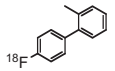
Some years earlier, Hird et al.[134] had described the chemoselective synthesis of compounds **183v** and **183w** containing alkoxy, cyano, bromo and fluoro groups by the $Pd(PPh_3)_4$-catalyzed reaction of 4-*n*-octyloxyphenylboronic acid with bromofluoroiodobenzonitriles **182e** and **182f**, respectively (entries 22 and 23, respectively, Table 5).

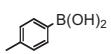
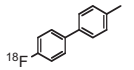
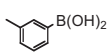
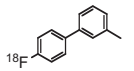
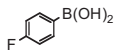
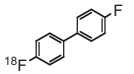
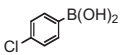
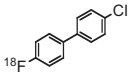
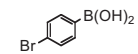
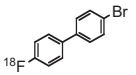
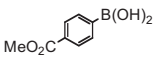
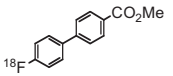
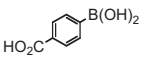
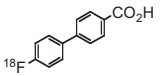
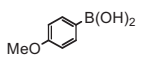
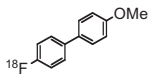
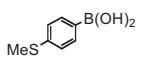
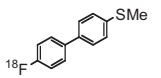
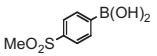
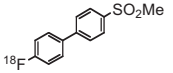
In 2006, Wang and Li[136a] synthesized 3-fluoro-4′-methylbiphenyl (**183x**) and 2-fluoro-4′-methylbiphenyl (**183y**) in 93 and 90% yield, respectively, by the reaction of potassium 4-tolyltrifluoroborate (**184**) with fluoroiodobenzenes **182b** and **182c** and 1 mol % palladium nanoparticles on poly(vinylpyrrolidone) (PVP) in water under reflux for 4 h in the presence of K_2CO_3 as base in the absence of any ligand (Scheme 67). Palladium(0) on PVP was prepared from $Pd(OAc)_2$ and a methanol solution of PVP, according to the Bradley procedure.[136b]

Table 5
Chemoselective S.–M. monocoupling reactions of fluoroiodobenzenes **182** with arylboronic acids or esters



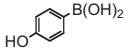
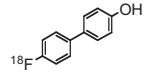
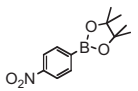
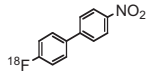
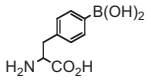
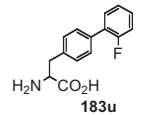
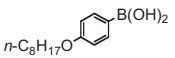
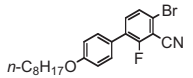
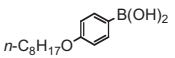
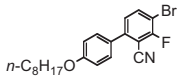
182 **183**

Entry	Reagents		Ar^1–B / **182** molar ratio	Pd catalyst (mol%)	Base	Solvent	Reaction condition (°C/h)	Product		Ref
	182	Ar^1–B						**183**	Yield (%)	
1	 **182a**		0.66	$PdCl_2$(dppf) (3)	$Ba(OH)_2 \cdot 8H_2O$	DME/H_2O	Reflux/16	 **183a**	90	131
2	 **182a**		0.83	$PdCl_2$(dppf) (7)	K_2CO_3	DME	80/18	 [a] **183b**	82	132
3	 **182b**		1.2	$PdCl_2$(dppf)	K_2CO_3	DMF	80/18	 [a] **183c**	90	132
4	 **182c**		1.2	$PdCl_2$(dppf)	K_2CO_3	DMF	80/18	 [b] **183d**	87	132
5	 **182b**		1.1	Pd black (42.7)	40% KF/Al_2O_3	—	70/2 μW	 **183e**	84	133
6	 **182c**		1.1	Pd black (42.7)	40% KF/Al_2O_3	—	70/2 μW	 **183f**	79	133
7	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183g**	90[c]	195
8	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183h**	91[c]	135

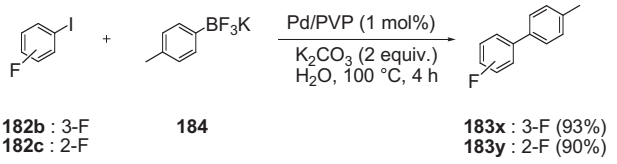
9	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183i**	90[c]	135
10	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183j**	90[c]	135
11	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183k**	82[c]	135
12	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183l**	77[c]	135
13	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183m**	30[c]	135
14	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183n**	89[c]	135
15	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183o**	37[c]	135
16	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183p**	82[c]	135
17	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183q**	94[c]	135
18	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183r**	84[c]	135

(*continued on next page*)

Table 5 (*continued*)

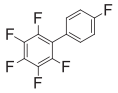
Entry	Reagents		Ar^1–B / **182** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction condition (°C/h)	Product		Ref
	182	Ar^1–B						**183**	Yield (%)	
19	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183s**	93[c]	135
20	 **182d**		1.3	$Pd_2(dba)_3$ (5)	Cs_2CO_3	MeCN	60/0.08	 **183t**	88[c]	135
21	 **182c**		1.0	$PdCl_2(PPh_3)_2$ (5)	Na_2CO_3	MeCN/H_2O	150/0.08 μW	 **183u**	86	124
22	 **182e**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	DME/H_2O	Reflux/4	 **183v**	56	134
23	 **182f**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	DME/H_2O	Reflux/4	 **183w**	65	134

[a] This compound was obtained in 99% ee.
[b] This compound was obtained in 92% ee.
[c] Radiochemical yield determined by radio-TLC referring to the percentage of the radioactivity area of the ^{18}F-labelled diphenyl related to the total radioactivity area.



Scheme 67.

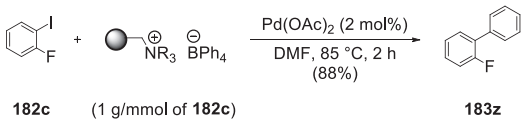
More recently, the Pd-catalyzed cross coupling of 4-fluoroiodobenzene (**182a**) with $K[C_6F_5BF_3]$ in the presence of *N*-heterocyclic carbene ligands was studied and it was found that, when the reaction was performed in the presence of an equimolar amount of Ag_2O, 5 mol % $PdCl_2(PPh_3)_2$ and 5 mol % 1,3-dimesitylimidazoline-2-ylidene·HCl in toluene at 100 °C for 8 h, 2,3,4,5,6-pentafluoro-4′-fluorobiphenyl (**183-F$_6$**) (Fig. 13) was obtained in 90% isolated yield.[136c]



183-F$_6$

Fig. 13. Structure of compound **183-F$_6$**.

On the other hand, Basu et al.[111] performed the synthesis of 2-fluorobiphenyl (**183z**) in 88% yield by the $Pd(OAc)_2$-catalyzed arylation of a DMF solution of 2-fluoroiodobenzene (**182c**) with tetraphenylborate immobilized on Amberlite® resin (Scheme 68).



Scheme 68.

Bromofluorobenzenes **185** have also been used as electrophiles for the chemoselective synthesis of fluorinated biphenyls **183** via Pd-catalyzed S.–M. monocoupling reactions with arylboronic acids or esters.[136–145] The catalyst systems and the reaction conditions used for the synthesis of compounds **183f**, **183aa**–**az** and **183aaa**–**aae** from the required fluorinated bromobenzenes **185** are listed in Table 6 (entries 1–33).

Thus, an air- and moisture-stable resin bound catalyst, which was prepared by treating wet Deloxan® resin with a methanol solution of $Pd(OAc)_2$, was found to enable the synthesis of 2-fluoro-2′-methylbiphenyl (**183f**) in 78% yield from 2-bromofluorobenzene (**185a**) and *o*-tolylboronic acid (entry 1, Table 6).[137]

In 2005, 4-fluorobiphenyl (**183aa**) and **183ab** were synthesized in excellent yields by S.–M. reactions involving 4-bromofluorobenzene (**185b**), which were carried out in the presence of 1 mol % of an alkoxo–Pd(II) complex $[Pd(Ph_2PCH_2CH_2O)_2]$ (entries 2 and 3, Table 6).[138]

In the same year, Leadbeater et al. reported the synthesis of 4-fluorostilbene (**183ac**) in 17% yield by the microwave-promoted reaction of **185b** with (*E*)-2-phenylvinylboronic acid, which was run in the presence of Na_2CO_3 as base with no addition of Pd (entry 4, Table 6).[139] However, it was discovered that Pd contaminants down to a level of 50 ppb, present in commercially available Na_2CO_3, were responsible for the generation of **183ac**.[139]

Again in 2005, Gauthier et al.[140] found that the reaction of 2-bromo-3-fluorobenzonitrile (**185c**) with 2-fluorophenylboronic acid in a mixture of THF, acetonitrile and water at 45–50 °C for 2 h, in the presence of K_3PO_4 as base and catalytic quantities of $[\eta^3\text{-}C_3H_5PdCl]_2$ and P(*t*-Bu)$_3$, gave 2′,6-difluoro-1,1′-biphenyl-2-carbonitrile (**183ad**) in 85% yield (entry 5, Table 6).

One year later, Ley et al.[141] employed a commercially available polyurea microencapsulated Pd catalyst (Pd EnCat™) for the microwave-assisted reaction of **185b** with 4-methoxyphenylboronic acid in MeCN in the presence of 3 equiv of *n*-Bu_4NOAc, which gave compound **183ae** in 92% yield (entry 6, Table 6).

In 2008, Ahn et al.[142] reported that the S.–M. reaction of **185b** with phenylboronic acid, by using KF as base and $[Pd(NH_3)_4]^{2+}$-modified nanopore silica as catalyst under solvent-free conditions, provided compound **183aa** in 82% yield (entry 7, Table 6).

In 2010, Langer et al.[143] synthesized chemo- and site-selectively 2-bromo-3,5-difluorobiphenyls **183af**–**al** in satisfactory yields by $Pd(PPh_3)_4$-catalyzed reaction of 1,2-dibromo-3,5-difluorobenzene (**185d**) with 1 equiv of the required arylboronic acids in dioxane at 90 °C in the presence of Cs_2CO_3 as base (entries 8–14, Table 6). It was also found that the $Pd(PPh_3)_4$-catalyzed one-pot reaction of **185d** with two different, sequentially added arylboronic acids provides difluorinated *o*-terphenyls **186a**–**d** bearing two different terminal aryl groups (Fig. 14) in yields ranging from 45 to 62%.[143]

In the same year, Fabis et al.[144] prepared 2′-fluorobiphenyl-2-carbonitriles **183am**–**ar** in good yields via the $Pd(PPh_3)_4$-catalyzed reaction of commercially available 2-bromofluorobenzenes **185a** and **185e**–**h** with pinacol esters of the required 2-cyanophenylboronic acids (entries 15–20, Table 6). The base used in the synthesis of **183am** and **183an** was K_3PO_4 (entries 15 and 16, Table 6), but the microwave-promoted reactions leading to compounds **183ao**–**ar** (entries 17–20, Table 6) were carried out by using Cs_2CO_3 as base.[144]

In 2010, Cs_2CO_3 was also used as base by Langer et al. in the site-selective $Pd(PPh_3)_4$-catalyzed high-yielding synthesis of 4-bromo-3-fluorobiphenyls **183as**–**ay** involving treatment of 1,4-dibromo-2-fluorobenzene (**185i**) with 1 equiv of the required arylboronic acids in dioxane at 90 °C (entries 21–27, Table 6).[145]

Some years earlier, liquid crystalline terphenyls **185az** and **183aaa**–**aae**, containing a lateral fluoro substituent in the *ortho* position to a lateral cyano group, had been synthesized in satisfactory yields by $Pd(PPh_3)_4$-catalyzed chemoselective S.–M. cross couplings of bromofluoroarenes **185j**–**o** with the required biphenylboronic acids in a refluxing mixture of DME and water in the presence of Na_2CO_3 as base (entries 28–33).[134]

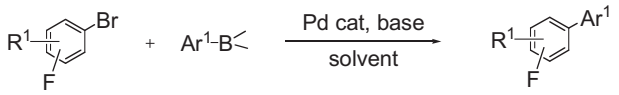
On the other hand, in 2010, the unsymmetrical fluorinated *p*-terphenyls **187a**–**e** were synthesized site selectively in satisfactory yields by a one-pot process involving a sequential addition of two different arylboronic acids to a mixture containing Cs_2CO_3, compound **185i** and a catalytic amount of $Pd(PPh_3)_4$ in dioxane (Scheme 69).[145]

In 2010, it was also found that the microwave-promoted $Pd(PPh_3)_4$-catalyzed reaction of fluorinated methyl 2-bromobenzoates **185p** and **185q** with 2-hydroxyarylboronic acids **189a**–**d** proceeded chemoselectively and was followed by spontaneous lactonization of the resulting cross-coupling products to give the fluorinated 6*H*-benzo[*c*]chromen-6-ones **190a**–**d** in yields ranging from 71 to 96% (Scheme 70).[146]

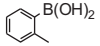
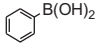
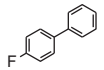
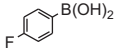
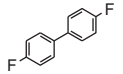
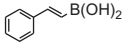
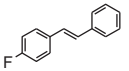
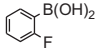
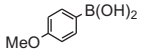
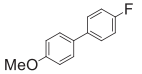
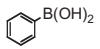
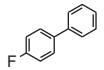
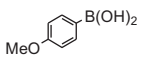
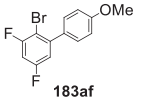
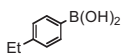
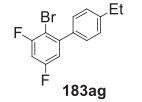
Previously, it had been reported that the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed reaction of potassium (*E*)-1-decenyl trifluoroborate (**191**) with 1-bromo-4-fluorobenzene (**185b**) in a mixture of *i*-PrOH and water under reflux in the presence of Et_3N as base gave chemoselectively (*E*)-1-(1-decenyl)-4-fluorobenzene (**192**) in 59% yield (Scheme 71).[147]

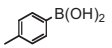
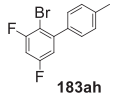
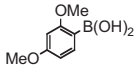
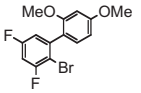
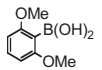
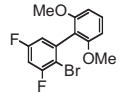
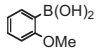
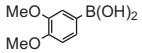
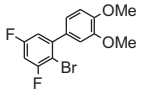
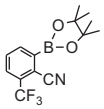
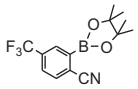
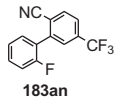
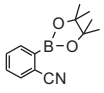
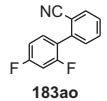
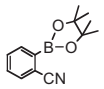
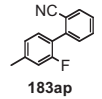
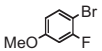
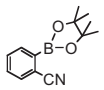
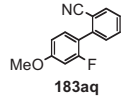
To conclude the discussion of the S.–M. chemoselective monocoupling reaction of bromofluorobenzene derivatives, it should be mentioned that, in 2006, racemic flurbiprofen (**193**), a non-steroidal anti-inflammatory and analgesic drug, was synthesized via the heterogeneous Pd/C-catalyzed atom-efficient arylation of racemic 4-bromo-3-fluoro-α-methylphenylacetic acid (**185r**) with sodium tetraphenylborate (**172**) in water under reflux in the open air in the presence of Na_2CO_3 as the base (Scheme 72).[148] Compound **193** was obtained in 98% yield.

Table 6
Selective S.–M. monocoupling reactions of bromofluorobenzenes **185** with arylboronic acids or esters



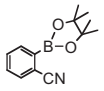
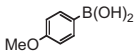
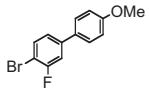
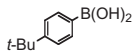
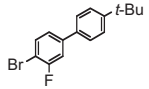
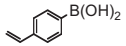
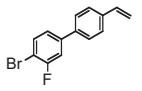
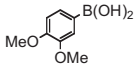
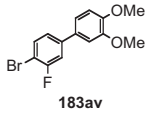
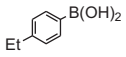
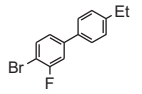
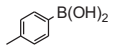
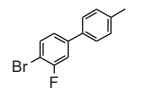
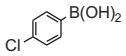
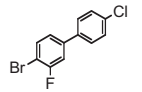
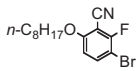
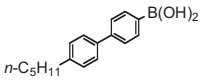
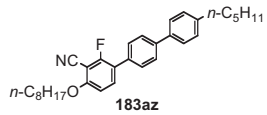
185 **183**

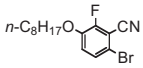
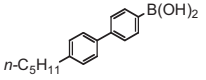
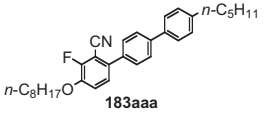
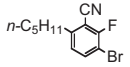
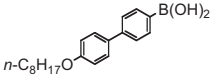
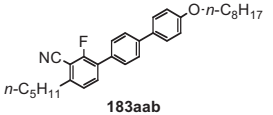
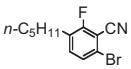
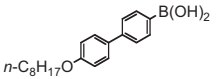
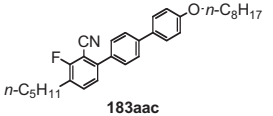
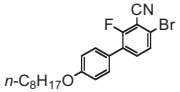
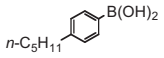
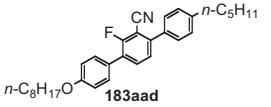
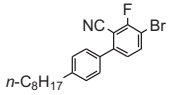
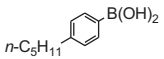
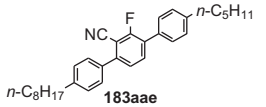
Entry	Reagents		Ar^1-B</ **185** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product		Ref.
	185	Ar^1-B</						**183**	Yield (%)	
1	 **185a**		1.0	Resin-Pd[a] (1.5)	K_2CO_3	H_2O	Reflux/4	 **183f**	78	137
2	 **185b**		1.5	$Pd[Ph_2PCH_2CH(Me)O]_2$[b] (1.0)	$K_3PO_4·3H_2O$	THF	rt/9	 **183aa**	98	138
3	 **185b**		1.5	$Pd[Ph_2PCH_2CH(Me)O]_2$[b] (1.0)	$K_3PO_4·3H_2O$	THF	rt/9	 **183ab**	99	138
4	 **185b**		1.3	—[c]	Na_2CO_3	H_2O+TBAB	150/0.08 μW	 **183ac**	17	139
5[d]	 **185c**		1.26	$(\eta^3\text{-}C_3H_5PdCl)_2$/P(*t*-Bu)$_3$ (2.5)	K_3PO_4	THF/MeCN/H_2O	45–50/2	 **183ad**	85	140
6	 **185b**		1.05	Pd EnCat™ (5)	Bu_4NOAc	MeCN	140/0.25 μW	 **183ae**	92	141
7	 **185b**		1.0	$[Pd(NH_3)_4]^{2+}$-modified nanopore silice (50 mg/mmol of **185b**)	KF	—	90–100/3	 **183aa**	82	142
8	 **185d**		1.5	$Pd(PPh_3)_4$ (3.0)	Cs_2CO_3	Dioxane	90/9	 **183af**	60	143
9	 **185d**		1.5	$Pd(PPh_3)_4$ (3.0)	Cs_2CO_3	Dioxane	90/9	 **183ag**	65	143

10	 **185d**		1.5	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/9	 **183ah**	45	143
11	 **185d**		1.5	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/9	 **183ai**	67	143
12	 **185d**		1.5	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/9	 **183aj**	68	143
13	 **185d**		1.5	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/9	 **183ak**	60	143
14	 **185d**		1.5	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/9	 **183al**	60	143
15	 **185a**		1.2	$Pd(PPh_3)_4$ (5)	K_3PO_4	DMF	150/1.25 μW	 **183am**	78	144
16	 **185a**		1.2	$Pd(PPh_3)_4$ (5)	K_3PO_4	DMF	105/16	 **183an**	63	144
17	 **185e**		1.2	$Pd(PPh_3)_4$ (5)	Cs_2CO_3	EtOH/PhMe	125/1.25 μW	 **183ao**	81	144
18	 **185f**		1.2	$Pd(PPh_3)_4$ (5)	Cs_2CO_3	EtOH/PhMe	150/1.25 μW	 **183ap**	67	144
19	 **185g**		1.2	$Pd(PPh_3)_4$ (5)	Cs_2CO_3	EtOH/PhMe	125/2 μW	 **183aq**	65	144

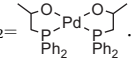
(*continued on next page*)

Table 6 (*continued*)

Entry	Reagents		Ar^1-B</ **185** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product		Ref.
	185	Ar^1-B</						**183**	Yield (%)	
20	 **185h**		1.2	$Pd(PPh_3)_4$ (5)	Cs_2CO_3	EtOH/PhMe	130/1.75 μW	 **183ar**	78	144
21	 **185i**		1.0	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/6–8	 **183as**	60	145
22	 **185i**		1.0	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/6–8	 **183at**	58	145
23	 **185i**		1.0	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/6–8	 **183au**	45	145
24	 **185i**		1.0	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/6–8	 **183av**	67	145
25	 **185i**		1.0	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/6–8	 **183aw**	68	145
26	 **185i**		1.0	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/6–8	 **183ax**	60	145
27	 **185i**		1.0	$Pd(PPh_3)_4$ (3)	Cs_2CO_3	Dioxane	90/6–8	 **183ay**	60	145
28	 **185j**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	H_2O/DME	Reflux/4	 **183az**	67	134

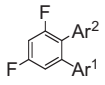
29	 **185k**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	H_2O/DME	Reflux/4	 **183aaa**	61	134
30	 **185l**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	H_2O/DME	Reflux/4	 **183aab**	63	134
31	 **185m**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	H_2O/DME	Reflux/4	 **183aac**	58	134
32	 **185n**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	H_2O/DME	Reflux/4	 **183aad**	66	134
33	 **185o**		1.2	$Pd(PPh_3)_4$ (3.3)	Na_2CO_3	H_2O/DME	Reflux/4	 **183aae**	57	134

[a] Resin–Pd=resin-bound catalyst prepared by treating the wet Deloxan® resin with a MeOH solution of $Pd(OAc)_2$.

[b] $Pd[Ph_2PCH_2CH(Me)O]_2$=  .

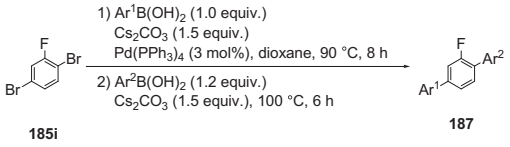
[c] The reaction was run with the need for addition of a Pd catalyst.

[d] The reaction was performed on a multikilogram scale.



186a : Ar^1= 2, 4-$(MeO)_2C_6H_3$; Ar^2 = 4-MeC_6H_4 (48%)
186b : Ar^1 = 2, 6-$(MeO)_2C_6H_3$; Ar^2 = 4-MeC_6H_4 (60%)
186c : Ar^1 = 4-FC_6H_4; Ar^2 = 4-ClC_6H_4 (45%)
186d : Ar^1 = 2-$MeOC_6H_4$; Ar^2 = 4-MeC_6H_4 (62%)

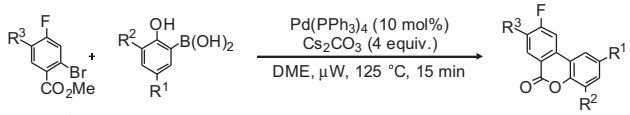
Fig. 14. Structures of compounds **186a**–**d**.



185i **187**

187	Ar^1	Ar^2	yield (%)
a	4-AcC_6H_4	4-$MeOC_6H_4$	60
b	4-$MeOC_6H_4$	2-$MeOC_6H_4$	67
c	4-MeC_6H_4	4-$MeOC_6H_4$	48
d	4-MeC_6H_4	4-AcC_6H_4	42
e	3, 4-$(MeO)_2C_6H_3$	2-thienyl	53

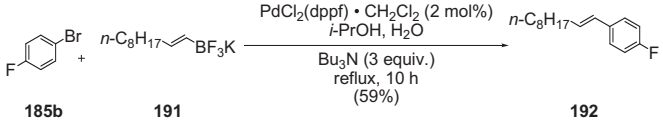
Scheme 69.



185p : R^3= H
185q : R^3= F
189a-d **190a-d**

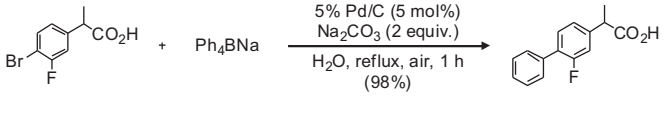
190	R^1	R^2	R^3	yield (%)
a	H	H	H	96
b	F	H	H	94
c	H	Cl	H	71
d	H	H	F	86

Scheme 70.



185b **191** **192**

Scheme 71.



185r **172** (0.27 equiv.) **193**

Scheme 72.

In numerous papers published in recent years, it has been demonstrated that chlorofluoroarenes **194** are also useful electrophiles for highly halogen-selective Pd-catalyzed S.–M. mono-coupling reactions with arylboronic acids.[149–155]

Table 7 lists the catalyst systems and the reaction conditions used so far for performing these reactions. Thus, 4-fluorobiphenyl (**183aa**) was obtained in 76% yield by the microwave-promoted reaction of 4-chlorofluorobenzene (**194a**) with phenylboronic acid in a mixture of DMF and water in the presence of *n*-Bu_4NI as additive and a catalytic amount of air- and moisture-stable dihydrogen-di-μ-chlorodichlorobis(di-*tert*-butylphosphinito-*k*P) dipalladate (POPd2) (entry 1, Table 7).[149,156] Analogous reaction conditions were used to prepare 5-(4-fluorophenyl)indole (**183aaf**) in 78% yield from **194a** and 5-indolylboronic acid (entry 2, Table 7).[149]

However, standard reaction conditions involving the use of $Pd(PPh_3)_4$ as catalyst, aqueous Na_2CO_3 as base and toluene as solvent, allowed the synthesis of 4-fluoro-2-nitrobiphenyl (**183aag**) in 55% yield from phenylboronic acid and 1-chloro-4-fluoro-2-nitrobenzene (**194b**) (entry 3, Table 7).[150]

In 2005, Jensen et al.[151] unexpectedly obtained two products, which differed in substitution on the imidazole ring, from the $Pd_2(dba)_3$/P(*t*-Bu)$_3$-catalyzed reaction between 3-pyridylboronic acid (**195**) and chlorofluoroarene **194c** and in THF and water at 70 °C in the presence of Na_2CO_3 as base. The two compounds corresponded to the cross-coupling derivative **183aah** and the rearranged substance **196** (Scheme 73).

The authors found that during the S.–M. reaction compounds **194c** and **183aah** underwent a Dimroth rearrangement[157] producing compounds **196** and **197** (Scheme 73). However, under the optimized reaction conditions reported in entry 4 of Table 7, a 102/1 mixture of **183aah** and **196** was formed from which crystalline **183aah**, a GABA $\alpha_{2,3}$-selective allosteric modulator, was isolated in 96% yield.[151]

In 2007, Fleckenstein and Plenio[152] tested a variety of 9-fluorenylphosphines as ligands for Pd-catalyzed reactions and found that a combination of phosphine EtFluPCy$_2$ (Fig. 15) and Na_2PdCl_4 catalyzed the reaction of 2-chlorofluorobenzene (**194d**) with *p*-tolylboronic acid to give 2-fluoro-4′-methylbiphenyl (**183y**) in almost quantitative yield (entry 5, Table 7).

In 2010, a combination of $Pd(OAc)_2$ and IPr·HCl [IPr=1,3-bis(2,6-diisopropylphenyl)imidazolylidene] was used by Chen et al.[154] as the catalyst for the synthesis of ethyl (*E*)-3-(4-trifluoromethyl-3″-fluoro-[1,1′:4′:1″]terphenyl-4″-yl) acrylate (**183aaj**) in 80% yield from ethyl (*E*)-3-(4′-chloro-3-fluorobiphenyl-4-yl)acrylate (**194f**) (entry 7, Table 7).

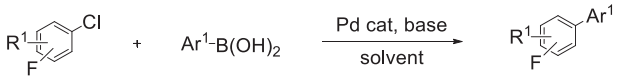
Again in 2010, it was reported that the reaction of 1-chloro-2,3,4,5,6-pentafluorobenzene (**194g**) with 2,6-dimethylphenylboronic acid in dioxane at 110 °C in the presence of Cs_2CO_3 and catalytic amounts of the amine-phosphine ligand IndNaphP (Fig. 15) and $Pd_2(dba)_3$ provided the tetra-*ortho*-substituted biphenyl **183aak** in 82% yield (entry 8, Table 7).[155a] It should be noted that some 2,3,4,5,6-pentafluorobiphenyls had previously been synthesized in high yields by direct arylation of pentafluorobenzene with aryl bromides in the presence of copper[155b] or palladium catalysts.[155c]

Very recently, synthetically interesting Pd-catalyzed highly selective monoarylation reactions of fluorinated nitrobenzenes with arylboron derivatives have also been investigated.[158a] In this respect it appears appropriate to mention that aryl fluorides have been used less frequently than aryl chlorides as electrophilic partners of C–C bond-forming reactions due to their higher C–F bond strength and the corresponding lower reactivity. Moreover, these reactions have generally been carried out by using Ni-based catalyst systems.[159,160]

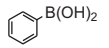
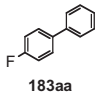
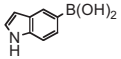
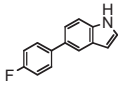
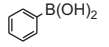
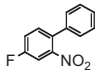
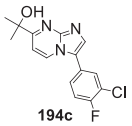
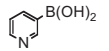
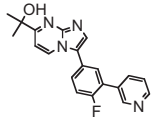
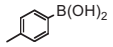
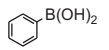
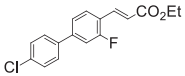
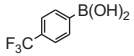
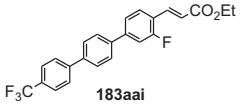
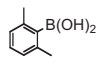
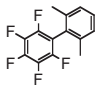
However, in 2010, Sanford et al.[158] discovered that the highly fluorinated nitrobenzene derivatives **198**, due to their significant electrophilicity, were suitable substrates for site-selective $Pd(PPh_3)_4$-catalyzed C–F bond arylation reactions with arylboronic acids or esters in the presence of KF/Al_2O_3 under both conventional heating and microwave irradiation. Remarkably, the arylations were found to occur *ortho* to the nitro group of compounds **198** providing a synthetic route to polyfluorinated 2-arylnitrobenzenes **199** (entries 1–10, Table 8).[158a]

Thus, the nitro group remained unchanged in these reactions, although it had previously been observed that the cross-coupling reaction of nitroaryl bromides and chlorides with 1.5 equiv of arylboronic acids in the presence of 3 mol% $Pd(OAc)_2$, 6 mol% DABCO and 3 equiv of K_2CO_3 in a mixture of DMF and water at

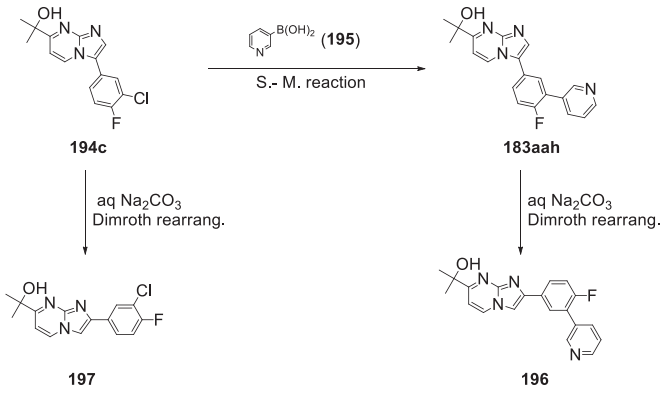
Table 7
Chemoselective S.–M. monocoupling reactions of chlorofluoroarenes **194** with arylboronic acids



194 **183**

Entry	Reagents		Ar^1–$B(OH)_2$/**194** molar ratio	Pd catalyst (mol %)	Base	Solvent	Reaction conditions (°C/h)	Product		Ref.
	194	Ar^1–$B(OH)_2$						**183**	Yield (%)	
1	 **194a**		1.5	POPd2[a]	Cs_2CO_3	DMA/H_2O+TBAI (12 mol %)	150/0.25 μW	 **183aa**	76	149
2	 **194a**		1.5	POPd2[a]	Cs_2CO_3	DMA/H_2O+TBAI (12 mol %)	150/0.25 μW	 **183aaf**	78	149
3	 **194b**		1.1	$Pd(PPh_3)_4$ (10)	Na_2CO_3	PhMe/H_2O	Reflux/42	 **183aag**	55	150
4	 **194c**		1.05	$Pd_2(dba)_3$ (5) $P(t\text{-}Bu)_3$ (5)	K_3PO_4	Dioxane/H_2O	70/16	 **183aah**	96	151
5	 **194d**		1.5	Na_2PdCl_4 (0.05) EtFluPCy2[b] (0.1)	Cs_2CO_3	Dioxane	100/24	 **183y**	99	152
6	 **194e**		1.5	$(\eta^3\text{-}C^3H^5)PdCl(dcpmp)$[c] (1)	K_3PO_4	MeCN	140/0.17 μW	 **183aac**	50	153
7	 **194f**		1.5	$Pd(OAc)_2$ (2) IPr·HCl (4)[d]	Cs_2CO_3	DMF	80/3	 **183aai**	80	154
8	 **194g**		2.0	$Pd_2(dba)_3$ (1) IndNaphP (4)	Cs_2CO_3	Dioxane	110/24	 **183aaj**	82	155a

[a] POPd2=Dihydrogen-di-μ-chlorodichloro bis(di-*tert*-butylphosphinito-k-P) dipalladate.
[b] EtFluCy2: see Fig. 15.
[c] Dcpmp: see Fig. 15.
[d] IPr: 1,3-Bis(2,6-diisopropylphenyl)imidazolylidene.



Scheme 73.

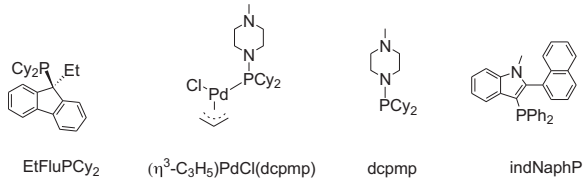
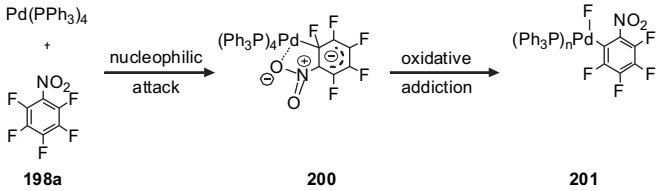


Fig. 15. Structures of ligands EtFluPCy$_2$ and indNaphP, and of the precatalyst (η_3-C_3H_5)PdCl(dcpmp).

150 °C occurred with simultaneous reduction of the nitro to amino group.[158b] The additive DABCO was found to have a beneficial effect on the rate and yield of the reaction.[158b]

It was also noted that tetrafluoronitrobenzenes **198b** and **198c** (entries 6 and 7, Table 8) and trifluoronitrobenzenes **198d–f** (entries 8–10, Table 8) were less reactive than pentafluorobenzene (**199a**), as expected, due to the corresponding reduction in electrophilicity of their benzene ring. Sanford et al.[158] postulated a catalytic cycle for the Pd-catalyzed C–F activation of **198a** in which the nitro group directs the nucleophilic Pd center towards the adjacent C–F bond to give the intermediate **200**, which leads directly to the oxidative addition complex **201** (Scheme 74).

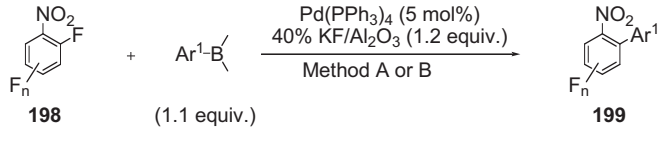


Scheme 74.

In the same year, Clark et al.[153] found that the air-stable precatalyst (η^3-C_3H_5)PdCl(dcpmp) (Fig. 15), which was readily prepared from the amine-phosphine ligand, dcpmp, promoted the chemoselective reaction of 3-chlorofluorobenzene (**194e**) with phenylboronic acid to give compound **183aac** in 50% yield (entry 6, Table 7)

5.1.4. Monocoupling reactions of haloaryl triflates, mesylates and tosylates. In 1990, Suzuki et al. reported, in a letter, the first example of highly chemoselective Pd-catalyzed cross-coupling reactions of bromoaryl triflates with organoboron compounds.[161] They found that the Pd(PPh$_3$)$_4$-catalyzed reaction of 4-

Table 8
Pd-catalyzed S.–M. reaction of fluorinated nitrobenzenes **198** with arylboronic acids or esters



Method A : DMF, 150°C, μW
Method B : DMSO, 150°C, μW

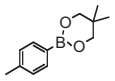
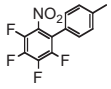
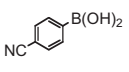
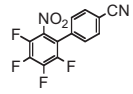
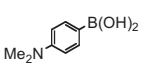
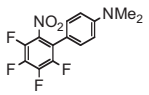
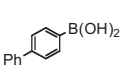
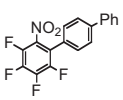
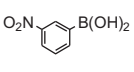
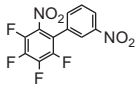
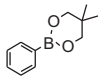
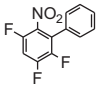
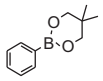
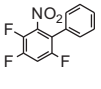
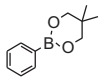
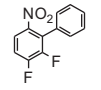
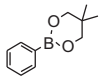
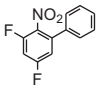
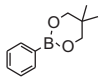
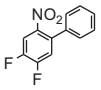
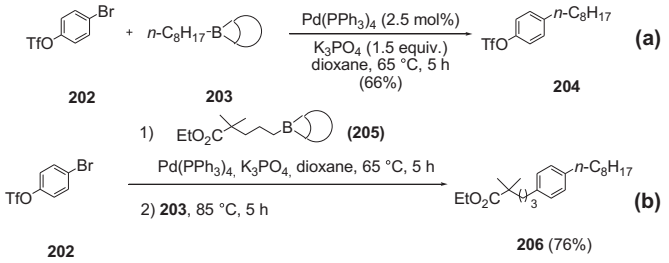
Entry	Reagents		Method	Reaction time (min)	Product	
	198	Ar^1-B			**199**	Yield (%)
1	 **198a**		A	15	 **199a**	56
2	 **198a**		A	15	 **199b**	56
3	 **198a**		A	15	 **199c**	64
4	 **198a**		A	15	 **199d**	73
5	 **198a**		A	15	 **199e**	70

Table 8 (*continued*)

Entry	Reagents		Method	Reaction time (min)	Product	
	198	Ar^1-B			**199**	Yield (%)
6	 **198b**		B A	30 30	 **199f**	81 54[a]
7	 **198c**		B A	120 120	 **199g**	54 48[b]
8	 **198d**		B	120	 **199h**	50
9	 **198e**		B	120	 **199i**	54
10	 **198f**		B	120	 **199l**	34

[a] A major by-product, 4-dimethylamino-2,3,6-trifluoronitrobenzene, was obtained in 18% yield.
[b] A major by-product, 2-dimethylamino-3,5,6-trifluoronitrobenzene, was obtained in 6% yield.

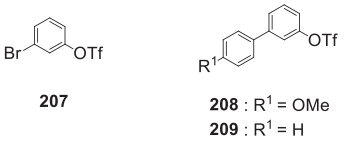
bromophenyl triflate (**202**) with 9-*n*-octyl-9-BBN (**203**) in dioxane at 65 °C in the presence of K_3PO_4 occurred at the C–Br bond of **202** to give 4-*n*-octylphenyl triflate (**204**) in 66% yield (Scheme 75, Eq. a) together with a very small amount (<1%) of 1,4-di-*n*-octylbenzene. They also described that the sequential $Pd(PPh_3)_4$-catalyzed cross coupling of **202** with 9-alkyl-9-BBN derivatives **205** and **203** furnished the unsymmetrical 1,4-disubstituted benzene derivative **206** in 76% yield (Scheme 75, Eq. b).[161]



Scheme 75.

In 1993, the same research group described the experimental details of these reactions and a variety of Pd-catalyzed cross couplings of organoboron compounds with organic triflates.[162]

Several years later, bromide/triflate selectivity analogous to that disclosed by Suzuki et al.[161,162] was observed by Brown et al.[163] who prepared compounds **208** and **209** (Fig. 16) in 76 and 52% yield, respectively, by the Pd-catalyzed reaction of 3-bromophenyl triflate (**207**) with the required arylboronic acids.



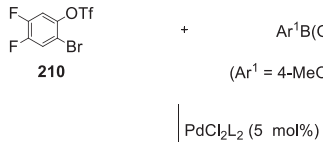
207

208 : R^1 = OMe
209 : R^1 = H

Fig. 16. Structures of compounds **207**, **208** and **209**.

These authors found that the arylation reaction occurs selectively at the C–Br bond of **207** irrespective whether the catalyst system is composed of a mixture of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$, as in the case of the synthesis of **208**, or is $PdCl_2$(dppp), as for the synthesis of **209**.[163]

Brown et al. also investigated the Pd-catalyzed reaction of 2-bromo-4,5-difluorophenyl triflate (**210**) with arylboronic acids under a variety of conditions (Scheme 76).[163] They found that the couplings by using PPh_3 or dppp as the ligand resulted in the prevalent formation of the products of Br-displacement, i.e., compounds **211a**,**b**, while the products deriving from the OTf-displacement, i.e., compounds **212a**,**b**, and the bis-arylated derivatives **213a**,**b** were observed in low amounts. Remarkably, the



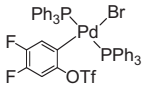
211a Ar^1 = 4-$MeOC_6H_4$
211b Ar^1 = Ph

212a Ar^1 = 4-$MeOC_6H_4$
212b Ar^1 = Ph

213a Ar^1 = 4-$MeOC_6H_4$
213b Ar^1 = Ph

Entry	L_2	Reaction conditions (°C/h)	Solvent	Base	211/212/213	Conversion (%)
1	dppp	23/4	THF	KF	**211a/212a/213a** = 65: 35: --	28
2	dppp	reflux/22	PhMe	K_3PO_4	**211a/212a/213a** = 90: --: 10	54
3	2 PPh_3	reflux/22	PhMe	K_3PO_4	**211a/212a/213a** = >95: --: <5	88
4	dppp	reflux/22	PhMe	K_3PO_4	**211b/212b/213b** = 60: 25: 15	57
5	dppp	reflux/22	PhMe	K_3PO_4+ LiBr	**211b/212b/213b** = >90: --: <10	78
6	2 PPh_3	reflux/22	PhMe	K_3PO_4	**211b/212b/213b** = 100: --: --	66
7	2 PPh_3	reflux	PhMe	K_3PO_4+ LiBr	**211b/212b/213b** = >95: --: <5	89

Scheme 76.



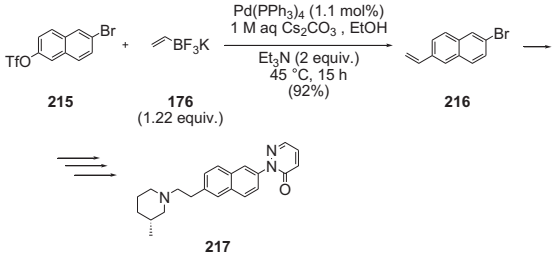
214

Fig. 17. Structure of compound **214**.

cross-coupling reactions carried out at higher temperatures proved to be more selective than those performed al lower temperatures.

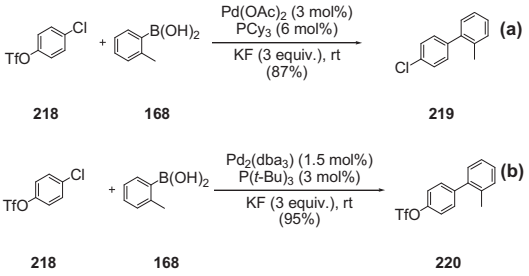
In keeping with these results, the reaction of **210** with a stoichiometric amount of $Pd(PPh_3)_4$ in hot toluene gave in high yield complex **214** (Fig. 17) involving oxidative addition of Pd(0) into the C–Br bond of **210**.[163]

In 2009, Ku et al.[164] described a protocol for the Pd-catalyzed site-selective vinylation of 6-bromo-2-(trifluoromethylsulfonyloxy) naphthalene (**215**) with potassium vinyltrifluoroborate (**176**). The reaction (Scheme 77) was carried out in EtOH in the presence of Cs_2CO_3, Et_3N and a catalytic amount of $Pd(PPh_3)_4$ and gave 2-bromo-6-vinylnaphthalene (**216**) in 92% yield with good selectivity (90/2).[164] Interestingly, the chemoselectivity of this reaction was opposite to that of the Pd-catalyzed reaction of compound **202** with 9-alkyl-9-BBN derivatives[161,162] as well as of the cross couplings of bromophenyl triflates **207** and **210** with arylboronic acids.[163] As illustrated in Scheme 77, compound **216** was used as a precursor to compound **217**, a naphthalenoid histamine-3 antagonist.[164]



Scheme 77.

In 2000, Fu et al. investigated the ligand-controlled selectivity of Pd-catalyzed reactions of 4-chlorophenyl triflate (**218**) with *o*-tolylboronic acid (**168**)[99] and obtained 4-chloro-2′-methylbiphenyl (**219**) in 87% yield by using a $Pd(OAc)_2/PCy_3$ catalyst system (Scheme 78, Eq. a). On the contrary, the use of a $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system allowed the synthesis of biphenyl triflate **220** from **218** in 95% yield (Scheme 78, Eq. b).[99,165]

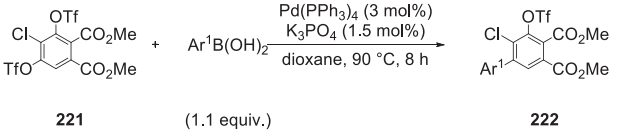


Scheme 78.

Later, it was concluded that a monoligated Pd complex, $PdP(t\text{-}Bu)_3$, is involved in $Pd/P(t\text{-}Bu)_3$-catalyzed reactions of aryl chlorides[166] and, more recently, it has been established that: (i) the principal reason for the preferential attack on the C–Cl bond of compound **218** by monoligated Pd is the low distortion energy of the C–Cl bond, and (ii) the selectivity is controlled by distortion energy differences.[167]

In 2007, Sajiki et al. reported that the ligand-free, heterogeneous Pd/C-catalyzed S.–M. reaction of **218** with 1.5 equiv of phenylboronic acid in 50% EtOH at room temperature in the presence of Na_2CO_3 as base gave 4-chlorobiphenyl (**171b**) in 93% yield.[168] Compound **171b** had previously been synthesized by Molander and Biolatto[123] in 50% yield by the reaction of neat **218** with potassium phenyltrifluoroborate at room temperature, in the presence of 3 equiv of K_2CO_3 and 0.5 mol % $Pd(OAc)_2$ under ligandless conditions.

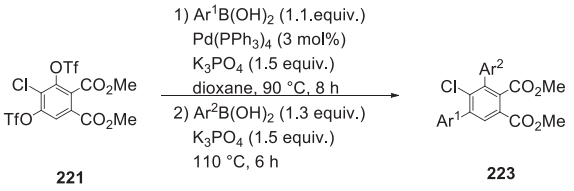
In 2010, Langer et al. synthesized 5-aryl-4-chloro-3-(trifluoromethylsulfonyloxy)phthalates **222a–f** in satisfactory yields by the chemo- and site-selective $Pd(PPh_3)_4$-catalyzed arylation reaction of chlorobis(triflate) **221** with arylboronic acids in dioxane at 90 °C in the presence of K_3PO_4 as base (Scheme 79).[169]



222	Ar^1	Yield (%)
a	2-$MeOC_6H_4$	47
b	Ph	65
c	3, 4-$(MeO)_2C_6H_3$	47
d	4-CF3C6H4	63
e	3, 5-$Me_2C_6H_3$	61
f	2, 6-$(MeO)_2C_6H_3$	48

Scheme 79.

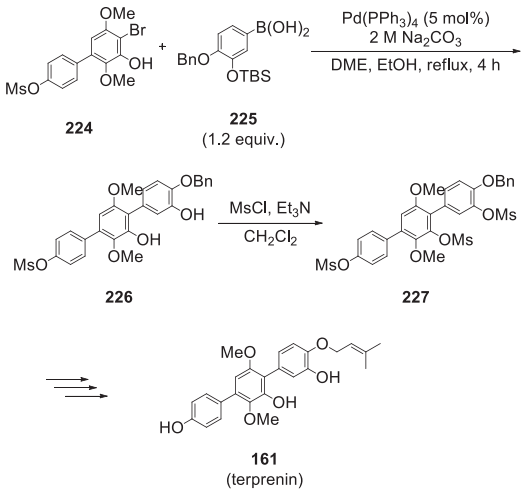
The authors also prepared directly dimethyl 3,4-diaryl-4-chlorophthalates **223a** and **223b** from **221** by the application of a one-pot procedure involving the treatment of **221** with 1.1 equiv of an arylboronic acid $Ar^1B(OH)_2$ in dioxane at 90 °C in the presence of 1.5 equiv of K_3PO_4 and 3 mol % $Pd(PPh_3)_4$, followed by the addition of 1.3 equiv of an arylboronic acid $Ar^2B(OH)_2$ and 1.5 equiv of K_3PO_4 to the in situ-formed monocoupling products (Scheme 80).[169]



223	Ar^1	Ar^2	Yield (%)
a	4-EtC_6H_4	4-$CF_3C_6H_4$	57
b	4-EtC_6H_4	3-F-C_6H_4	53

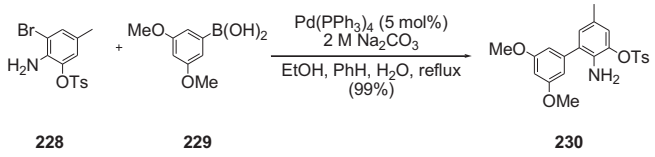
Scheme 80.

An interesting example of a chemoselective S.–M. reaction of a bromoaryl mesylate with an arylboronic acids, in which it was shown that the cross coupling occurred selectively at the C–Br bond of the substrate containing two different electrophilic sites, was reported in 1998 by Kawada, Ohtani et al. in 1998.[170] They found that the reaction of 4-bromo-4′-(methylsulfonyloxy)-2,5-dimethoxy-[1,1′]-biphenyl-3-ol (**224**) with 1.2 equiv of arylboronic acid **225** in a mixture of DME and EtOH under reflux, in the presence of Na_2CO_3 as base and 5 mol % $Pd(PPh_3)_4$ gave terphenyl **226** in high yield. Trismesylate **227**, obtained by mesylation of this compound, was then used as a precursor to terprenin (**161**), an immunosuppressive substance (Scheme 81).[170]



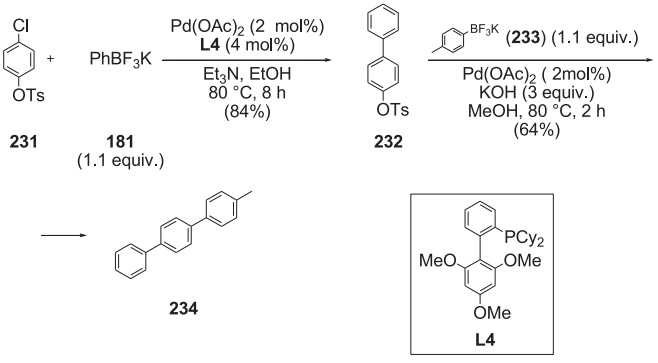
Scheme 81.

Two examples of chemoselective Pd-catalyzed S.–M. reactions of haloaryl tosylates with organoboron derivatives, in which the cross coupling occurred at the carbon–halogen bond of these electrophiles, have also been reported in the literature.[171,172] In 2000, Lin[171] described that the S.–M. reaction of 2-amino-5-methyl-4-(*p*-toluenesulfonyloxy)benzene (**228**) with 3,5-dimethoxyphenylboronic acid (**229**) under conventional conditions gave biphenyl tosylate **230** in quantitative yield (Scheme 82).



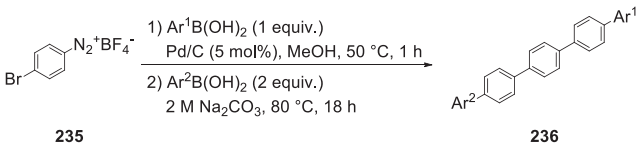
Scheme 82.

In 2007, Wu et al.[172] found that, in the $Pd(OAc)_2$/2-dicyclohexylphosphino-2′,4′,6′-trimethoxybiphenyl-catalyzed reaction of 1-chloro-4-(*p*-toluenesulfonyloxy)benzene (**231**) with potassium phenyltrifluoroborate (**181**) in a mixture of Et_3N and EtOH at 80 °C the tosyloxy group in **231** is retained and compound **232** was obtained in 84% yield (Scheme 83). This biphenyl derivative was further elaborated by a Pd-catalyzed reaction with potassium aryltrifluoroborate **233** under ligandless conditions to give terphenyl **234** in 64% yield (Scheme 83).[172]



Scheme 83.

In the same year, Taylor and Felpin[173] developed a new application of the Pd/C-catalyzed S.–M. reaction that involved the use of 4-bromophenyldiazonium tetrafluoroborate (**235**) in a chemoselective one-pot sequential arylation process with two different arylboronic acids in the absence of base under ligandless conditions. Compounds **236a**–**f** were prepared in yields ranging from 65 to 78% (Scheme 84).



236	Ar^1	Ar^2	Yield (%)
a	3,4-$(MeO)_2C_6H_3$	Ph	75
b	Ph	3,4-$(MeO)_2C_6H_3$	78
c	4-$MeOC_6H_4$	3,4-$(MeO)_2C_6H_3$	72
d	4-ClC_6H_4		67
e		3,4-$(MeO)_2C_6H_3$	65
f	4-ClC_6H_4	Ph	74

Scheme 84.

Interestingly, the first arylation of this orthogonal functionalization of **235** through chemoselective double cross-coupling reactions occurred at the C–N_2BF_4 bond of **236** to give a bromobiphenyl derivative.[173]

5.2. Monocoupling reactions of polyhalogenated benzenes bearing identical carbon–halogen bonds

Selective Pd-catalyzed monocoupling reactions of organoboron compounds with benzene derivatives **237** bearing two (or more) identical carbon–halogen bonds have been found to be much more difficult to perform than chemoselective Pd-catalyzed monocouplings of dihalo- and polyhalobenzenes bearing different carbon halogen bonds. This fact can be justified taking into account that the reactions of compounds **237** bearing isoelectronic sites can produce halobiaryls **238** together with terphenyls **239** (Fig. 18), the relative amounts of compounds **238** versus **239** being mainly dependent on the **237**/organoboron molar ratio and the nature of the catalyst system used in the cross-coupling reactions.

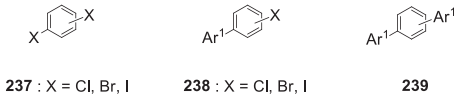
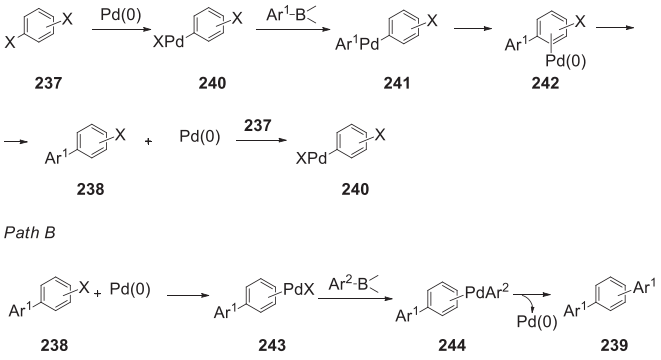


Fig. 18. Structures of compounds **237**, **238** and **239**.

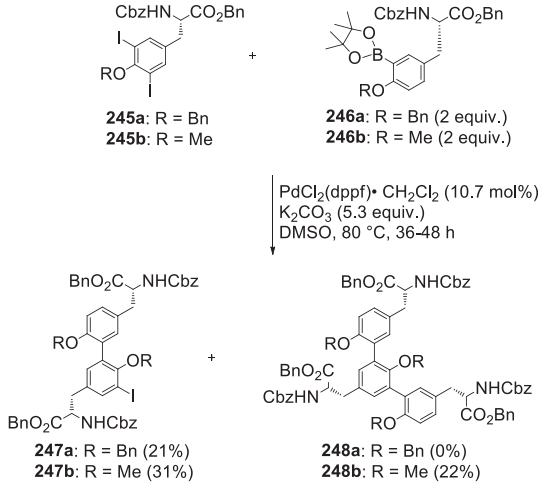
Path A of the reported catalyst cycle summarized in Scheme 85 might explain the formation of compounds **238**. This involves: (i) formation of complex **240** by oxidative addition of **237** to a Pd(0) catalyst; (ii) a transmetalation reaction between **240** and the organoboron compound**,** followed by reductive elimination of the resulting arylPd(II) complex **241**, which provides complex **242**; (iii) diffusion of Pd(0) from **242** and generation of **238**; and (iv) oxidative addition of Pd(0) to **237**, because the amount of this compound is in excess relative to that of **238** and because **237** would be more reactive than **238**, due to steric and/or electronic effects.[174]

Alternatively, Pd(0) diffused from **242** would undergo oxidative addition to **238** to generate complex **243**. A transmetalation reaction between this Pd(II) complex and the organoboron compound, followed by reductive elimination from the resulting diarylPd(II) species **244**, would then give rise to terphenyls **239** (Scheme 85, path B).[174]



Scheme 85.

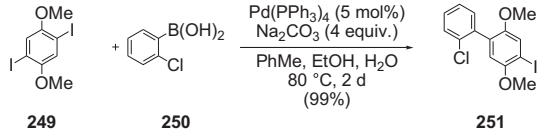
Over the past years, scattered reports on the highly selective synthesis of iodobiaryls from diiodoarenes and arylboron derivatives have been published.[107,175,176] In 2005, Hutton et al.[175] investigated the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed reaction between 3,5-diiodo-L-tyrosine derivative **245a** and a large molar excess of the boronate derivative **246a** and found that the reaction in DMSO at 80 °C in the presence of K_2CO_3 gave only compound **247a** in 21% yield, while the doubly coupled product **248a** was not observed (Scheme 86).



Scheme 86.

On the other hand, the cross coupling between methyl ether **245b** and boronate **246b** under similar experimental conditions gave the iodotyrosine derivative **247b** and the trityrosine derivative **248b** in 31 and 22% yield, respectively (Scheme 86).[175]

In 2007, Nakano and Nozaki[107] reported that reacting 1,4-diiodo-2,5-dimethoxybenzene (**249**) with 2 equiv of 2-chlorophenylboronic acid (**250**) in a mixture of toluene, EtOH and water at 80 °C for a long reaction time, in the presence of 4 equiv of Na_2CO_3 and 5 mol % $Pd(PPh_3)_4$, produced 2′-chloro-2,5-dimethoxy-4-iodobiphenyl (**251**) in 99% yield (Scheme 87).



Scheme 87.

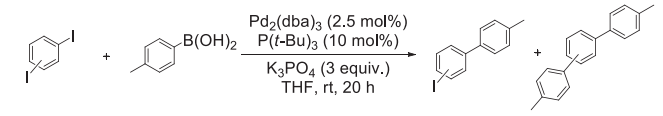
This monocoupling compound was then used as a precursor to two unsymmetrical terphenyls, which were prepared in high yields by the $Pd(PPh_3)_4$-catalyzed reaction of **251** with 2 equiv of arylboronic acid pinacolates in a mixture of toluene, EtOH and water at 90 °C for 2 days in the presence of Na_2CO_3 as base.[107]

On the contrary, significant selectivity for double coupling over single coupling was observed by Sherburn[176] in $Pd(PPh_3)_4$-catalyzed reactions of 1,3- and 1,4-diiodobenzene, **252a** and **252b** (Fig. 19), with arylboronic acids or esters in THF or a mixture of toluene and methanol under reflux in the presence of Ag_2CO_3 or Cs_2CO_3 as base. Significant selectivity for double coupling was observed, even when a diiodobenzene/boronic acid molar ratio of 10/1 was used.[176]

252a : 3-I
252b : 4-I
252c : 2-I

Fig. 19. Structures of compounds **252a**–**c**.

Selective double couplings were also found to occur when Hu[174] reacted 1,2-, 1,3- and 1,4-diiodobenzene **252a**, **252b** and **252c**, respectively (Fig. 19), with 1 equiv of *p*-tolylboronic acid (**253**) in THF at room temperature in the presence of 3 equiv of K_3PO_4, 2.5 mol % $Pd_2(dba)_3$ and 10 mol % $P(t\text{-}Bu)_3$. As shown in Scheme 88, excellent molar ratios between bis- and mono-coupling products **255** and **254**, respectively, were obtained in the reaction of **253** with **252a** and **252b**, but a lower **255**/**254** molar ratio was obtained in the reaction involving **252c**.



252c : *ortho*
252b : *meta*
252a : *para*

253

254c : *ortho*
254b : *meta*
254a : *para*

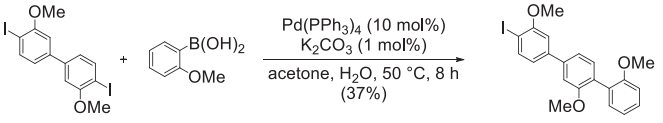
255c : *ortho*
255b : *meta*
255a : *para*

Entry	Electrophile	Product		
		254/**255** molar ratio	**255**	Yield of **255** (%)
1	**252c**	21: 79	**c**	72
2	**252a**	0.3: 99.7	**a**	96
3	**252b**	3: 97	**b**	43

Scheme 88.

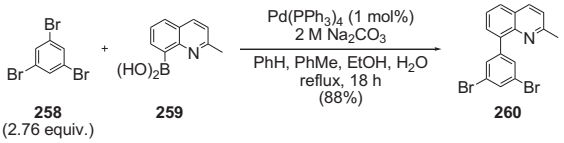
These results indicated that the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-catalyzed reactions of diiodides **252a**–**c** with **253** proceeded preferentially via path B of Scheme 85, involving in this case the Pd(0) catalyst regenerated in the cross couplings of **252a**–**c** with **253** that provided monocoupling products **254a**–**c**. This regenerated Pd(0) catalyst then undergoes oxidative addition preferentially to **254a**–**c**, rather than to **252a**–**c**.

In 2004, a protocol significantly different from that used by Nakano and Nozaki[107] for the synthesis of compound **251** was employed by Matile et al.[177] for the Pd-catalyzed monoarylation of 4,4′-diiodo-3,3′-dimethoxybiphenyl (**256**). In fact, 3 equiv of **256** were reacted with 1 equiv of 2-methoxyphenylboronic acid (**71**) in a mixture of acetone and water at 50 °C in the presence of 1 equiv of K_2CO_3 and 10 mol % $Pd(PPh_3)_4$ (Scheme 89).[177] Compound **257** was obtained in 37% yield.



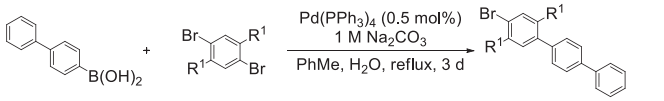
Scheme 89.

The Pd-catalyzed monoarylation reactions of dibromo- and polybromobenzenes with arylboron derivatives[75,127a,178–188] have attracted much more attention than the corresponding reactions of diiodoarenes. In the first examples reported in the literature, these monoarylations were achieved by using a high di-(poly)brominated arene/arylboron derivative molar ratio. In fact, in 1993, Koga et al.[178] synthesized 8-(3,5-dibromophenyl)-2-methylquinoline (**260**) in 88% yield by the $Pd(PPh_3)_4$-catalyzed reaction between boronic acid (**259**) and 2.7 equiv of 1,3,5-tribromobenzene (**258**) in a refluxing mixture of benzene, toluene and EtOH containing 2 M aqueous Na_2CO_3 (Scheme 90).



Scheme 90.

Moreover, in 1996, Galda and Rehahn[179] prepared bromoterphenyls **263a** and **263b** in 96 and 99% yield, respectively, by treatment of 4-biphenylboronic acid (**261**) with 10 equiv of dibromobenzenes **262a** and **262b** in toluene under reflux for 3 days in the presence of 1 M aqueous Na_2CO_3 and 0.5 mol % $Pd(PPh_3)_4$ (Scheme 91).



Scheme 91.

Repetitive S.–M. reactions were then used to convert compounds **263a,b** into 2″,5″-dialkyl-4-bromo-*p*-quinquephenyls **264a,b**, 2″,5″,2‴,5‴-tetraalkyl-*p*-decaphenyls **265a,b**, and 2″,5″,2‴,5‴,2⁗,5⁗-hexa-*x*-alkyl-*p*-quindeciphenyls **266a**,**b** (Fig. 20).[179]

Interestingly, the reactions involving electron-deficient arylboronic acids were found to require longer reaction times and in these cases, the yields of the required monocoupling products were reduced, due to boronic acid decomposition.

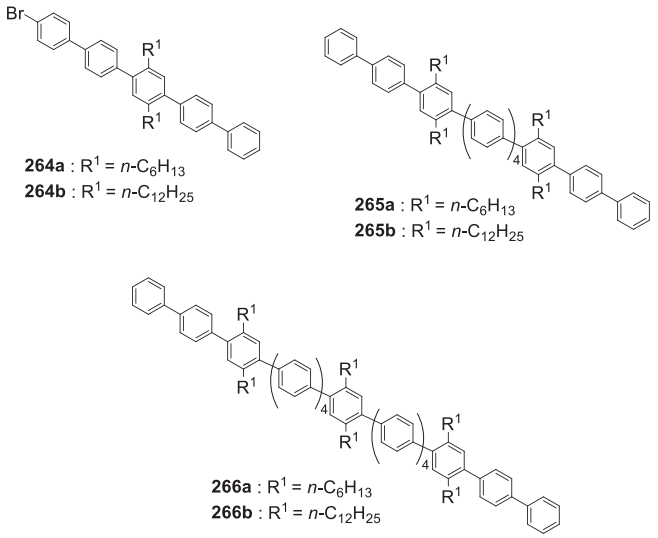
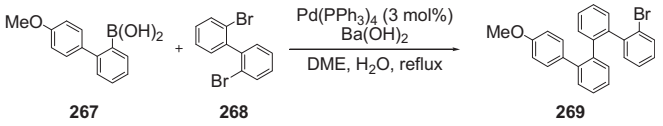


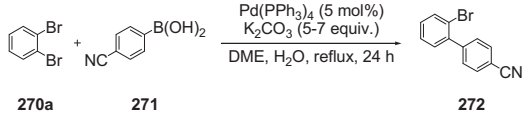
Fig. 20. Structures of compounds **264a,b**, **265a,b** and **266a,b**.

In 1998, Simpkins et al.[75] synthesized *o*-tetraphenylenes bromide **269** in 75% yield by the $Pd(PPh_3)_4$-catalyzed reaction of boronic acid **267** with 2,2′-dibromobiphenyl (**268**) in a mixture of DME and water under reflux in the presence of $Ba(OH)_2$ as the base (Scheme 92). Unfortunately, the **267**/**268** molar ratio, the number of equiv of $Ba(OH)_2$ and the reaction time were not reported.[75]



Scheme 92.

On the other hand, in 2002, Miyaura and his group found that 2-bromo-4′-cyanobiphenyl (**272**) could be conveniently and selectively synthesized in 53% yield via $Pd(PPh_3)_4$-catalyzed S.–M. Reaction of 4-cyanophenylboronic acid (**271**) in DME and water under reflux in the presence of Na_2CO_3 as the base (Scheme 93).[180]



Scheme 93.

In 2004, a similar $Pd(PPh_3)_4$-catalyzed reaction, in which Cs_2CO_3 was used instead of Na_2CO_3 as the base, allowed Tanaka et al.[181] to prepare 8-methoxy-1-(2′-bromophenyl)naphthalene (**274**) in 82% yield from **270a** and 1.1 equiv of **273**, a sterically hindered arylboronic acid (Fig. 21).

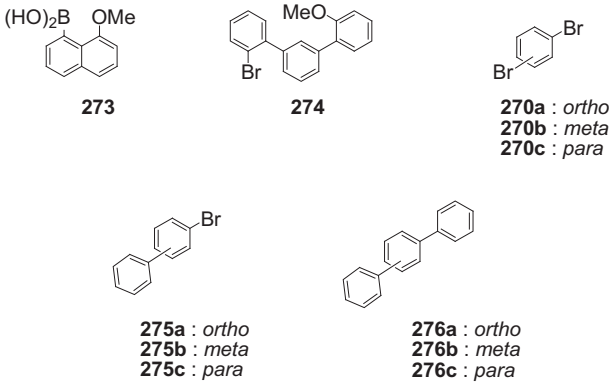
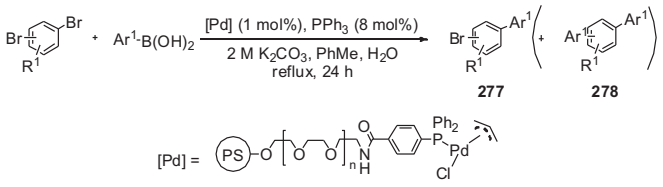


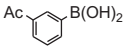
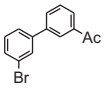
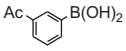
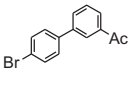
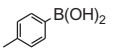
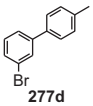
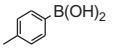
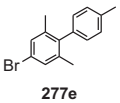
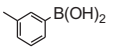
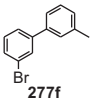
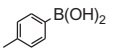
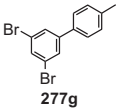
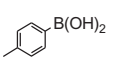
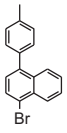
Fig. 21. Structures of compounds **270a**–**c**, **273**, **274**, **275a**–**c** and **276a**–**c**.

One year later, Rasoanaivo et al.[182] found that the $Pd(OAc)_2$/PPh_3-catalyzed coupling of dibromobenzenes **270a**–**c** with 1.2 equiv of phenylboronic acid in a mixture of 1-propanol and water under reflux in the presence of 2 equiv of Na_2CO_3 gave rise to a small amount (7–12%) of terphenyls **276a**–**c** along with the target biphenyl bromides **275a**–**c** (Fig. 21) in 58–67% yield.

In 2005, several substituted bromobiaryls **277** were regioselectively synthesized in high yields by Uozumi and Kikuchi[183] through highly selective monoarylation reactions of dibromoarenes **270a**–**c**, **279** and **281** and tribromobenzene **280** with equimolar amounts of arylboronic acids in a mixture of toluene and water in the presence of K_2CO_3 as base, by using an amphiphilic polystyrene-poly(ethylene glycol)(PS-PEG) resin-supported phosphine Pd complex as heterogeneous catalyst. The synthesis of compounds **277a**–**i** in yields ranging from 77 to 92% according to this protocol is illustrated in Table 9.

Table 9
Pd-catalyzed S.–M. monoarylation of dibromo- and tribromoarenes in water with a polymeric Pd-catalyst



Entry	Reagents		Product		**277**/**278** molar ratio
	Electrophile	Ar^1–$B(OH)_2$	**277**	GLC Yield (%)	
1	 **270b**		 **277a**	90	96/4
2	 **270b**		 **277b**	84	>99/<1
3	 **270b**		 **277c**	90	>99/<1
4	 **270b**		 **277d**	90	98/2
5	 **279**		 **277e**	88	>99/<1
6	 **270b**		 **277f**	92	98/2
7	 **270c**		 **277g**	81	81/19
8	 **270d**		 **277h**	81	99/1
9	 **270a**		 **277i**	77	>99/<1

Interestingly, excellent selectivities were achieved in the cross couplings of 3-acetylboronic acid with dibromobenzenes **270b** and **270c** (entries 2 and 3, respectively, Table 9), in the reactions of *p*-tolylboronic acid with dibromides **279** and **281** (entries 5 and 8, respectively, Table 9), and by treatment of *o*-tolylboronic acid with **270a** (entry 9, Table 9). However, the S.–M. reaction of **280** with *p*-tolylboronic acid gave the required dibromobiphenyl **277g** in 81% yield along with 19% of 5′-bromo-4,4″-dimethyl-*m*-terphenyl **278g** (Fig. 22) (entry 7, Table 9).[183]

Remarkably, the polymeric Pd catalyst used in these reactions could be readily recovered and recycled and was suitable for the one-pot synthesis of terphenyl **280** in 83% yield by addition of 1.3 equiv of 3-methoxyphenylboronic acid (**279**) to the reaction mixture obtained from the monoarylation reaction of **270b** with 1 equiv of *p*-tolylboronic acid (**253**) in the presence of aqueous K_2CO_3, 2 mol % polymeric Pd catalyst, and 16 mol % PPh_3 at 105 °C (Scheme 94).

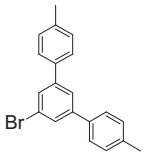
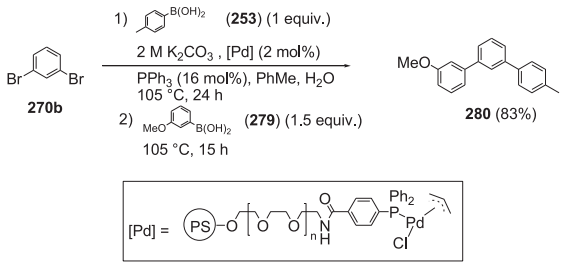
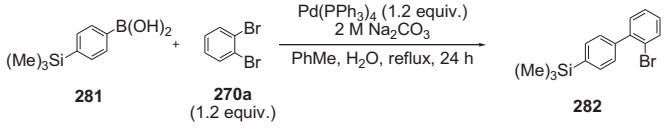

278g

Fig. 22. Structure of compound **278g**.



Scheme 94.

Again in 2005, Chen et al.[184] synthesized (2′-bromobiphenyl-4-yl)trimethylsilane (**282**) in 76.3% yield by the $Pd(PPh_3)_4$-catalyzed reaction of commercially available 4-(trimethylsilyl)phenylboronic acid (**281**) with 1.2 equiv of 1,2-dibromobenzene (**270a**) in toluene under reflux in the presence of 2 M Na_2CO_3 (Scheme 95).



Scheme 95.

One year later, Zhou et al.[185] reported that the $Pd(PPh_3)_4$-catalyzed reaction of 2-methoxyphenylboronic acid (**71**) with 1.5 equiv of **270a** and 3.1 equiv of K_2CO_3 in dioxane at 50 °C gave 2′-bromo-2-methoxybiphenyl (**283**) (Fig. 23) in 71% yield.

Cram et al.[186] had previously synthesized bromobiphenyl **285** (Fig. 23) in 50% yield by the reaction of 1,4-dibromobenzene (**270c**) with 2,6-dimethoxyphenylboronic acid (**284**) (Fig. 23), Cs_2CO_3 as base and a catalytic quantity of $Pd(PPh_3)_4$ in a refluxing mixture of toluene and methanol. Unfortunately, the experimental details of this reaction were not reported.

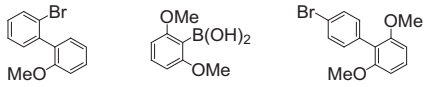
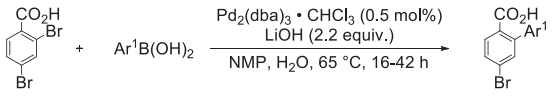


Fig. 23. Structures of compounds **283**, **284** and **285**.

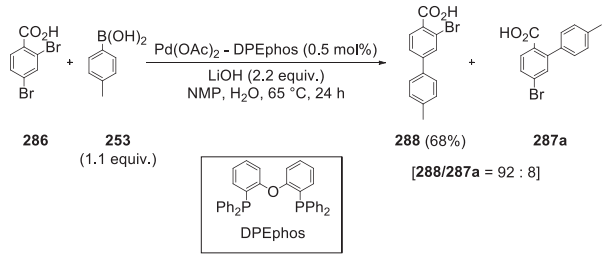
Recently, Houpis et al.[187] investigated the Pd-catalyzed cross-coupling reaction of the lithium salt of 2,4-dibromobenzoic acid (**286**) with arylboronic acids and found that *o*-aryl-substituted carboxylic acids **287a**–**e** were obtained with excellent site selectivity (>99/<1) and good yields when the reactions were performed in a 1/1 mixture of NMP and water at 65 °C in the presence of 0.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ under ligandless conditions (Scheme 96).



287	Ar^1	Yield (%)
a	4-MeC_6H_4	80
b	Ph	75
c	3-$MeOC_6H_4$	72
d	4-FC_6H_4	64
e	4-$CF_3C_6H_4$	55

Scheme 96.

Interestingly, the reactions involving electron-deficient arylboronic acids were found to require longer reaction times and, in these cases, the yields of the required monocoupling products were reduced, due to boronic acid decomposition. The authors supposed that the Pd-catalyzed site-selective arylation of **286** was controlled by an irreversible oxidative addition reaction at the C-2 position of the lithium salt of **286**, which was directed by the carboxylate anion.[187] They also found that, when the reaction of the lithium salt of **286** with 1.1 equiv of *p*-tolylboronic acid (**253**) was performed by using a Pd catalyst incorporating the diphosphine, DPEphos, significant selectivity for C-4 over C-2 arylation was obtained (92/8) and compound **288** was isolated in 68% yield (Scheme 97).[187]



Scheme 97.

In 2009, two convenient and efficient protocols to access a variety of bromobiphenyls **277** through Pd/C/PPh_3- or $Pd(PPh_3)_4$/PPh_3-catalyzed highly selective monoarylation of dibromobenzenes **270a**–**c**, **289** and **290** with 1.1 equiv of arylboronic acids were developed by Hu et al.[188] The synthesis of compounds **277i**–**o**, **277f** and **277p** according to these protocols is illustrated in entries 1–9 of Table 10. Interestingly, the reactions involving 1,2-dibromobenzenes **270a**, **289** and **290** (entries 1–7, Table 10) proved to be more selective than that concerning 1,3-dibromobenzene (**270b**) (entry 8, Table 10).[188]

High selectivity was also observed in the S.–M. reactions of *O*-protected 1,6-dibromo-2-naphthols **291** with 1.1–1.2 equiv of heteroarylboronic acids (Scheme 98).[189]

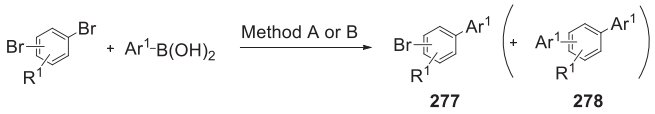
Consistent with both electronic and steric factors, the couplings occurred at position 6 of compound **291** to give 6-heteroaryl-substituted derivatives **292a**–**e** in modest-to-excellent yields. However, both attempts to couple 2-benzofurylboronic acid with the methyl carboxylate acid and methyl tetrazole derivatives of 1,6-dibromo-2-naphthol failed to give the corresponding cross-coupling products.[189]

In 2009, Takahashi et al.[190] performed the first total synthesis of vialinin B (**293**) (Fig. 24), a dibenzofuran derivative isolated from the dry fruiting bodies of an edible Chinese mushroom, *Thelephora vialis*,[191] via a reaction sequence in which two key intermediates, *p*-terphenyls **299** and **300**, were synthesized by a site-selective cross coupling of 4,7-dibromo-6-(methoxymethoxy)-benzo[*d*][1,3]dioxole-5-carbaldehyde (**299**) with two different boronic acids **295** and **297** (Scheme 99).

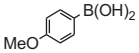
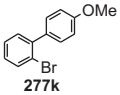
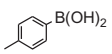
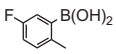
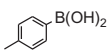
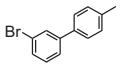
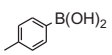
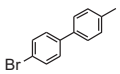
In particular, the $Pd(PPh_3)_4$-catalyzed reaction of **294** with 1.2 equiv of boronic acid **295** afforded bromobiphenyl **296** in 84% yield. This substance was then converted into *p*-terphenyl **299** in 84% yield by $Pd(OAc)_2$/X-Phos-catalyzed reaction with 1.5 equiv of boronic acid **297**. On the other hand, the $Pd(PPh_3)_4$-catalyzed reaction of **294** with **297** gave bromobiphenyl **298** in 54% yield, whereas, by the use of a $Pd(OAc)_2/PPh_3$ catalyst system, compound **298** was obtained in 78% yield.

The coupling of **298** with boronic acid **295** did not proceed by using a $Pd(OAc)_2/PPh_3$ catalyst system, but an exchange of PPh_3 with X-Phos dramatically improved the reaction, providing *p*-terphenyl **300** in 91% yield (Scheme 99).

Table 10
Pd/C/PPh_3- and $Pd(PPh_3)_4$/PPh_3-catalyzed monoarylation reactions of dibromobenzenes with arylboronic acids



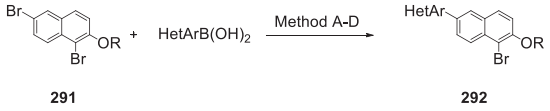
Method A: $Pd(PPh_3)_4$ (3 mol%); PPh_3 (6 mol%), 2 M K_2CO_3; THF, H_2O; 80°C.
Method B: Pd/C (3 mol%), PPh_3 (12 mol%); 2 M K_2CO_3; PhMe, H_2O; 100°C.

Entry	Reagents		Method	Product		277/278
	Dibromo-benzene	Ar^1–$B(OH)_2$		277	Yield (%)	
1	 **270a**		A B	 **277i**	82 75	99/1 99/1
2	 **270a**		A	 **277j**	56	94/6
3	 **270a**		A	 **277k**	71	94/6
4	 **270a**		B	 **277l**	62	96/4
5	 **270a**		A	 **277m**	95	99/1
6	 **289**		A	 **277n**	86	97/3
7	 **290**		A	 **277o**	82	96/4
8	 **270b**		A B	 **277f**	60 67	81/19 86/14
9	 **270c**		A B	 **277p**	51 61	85/15 93/7

Although it has long been known that several dichloro- and polychlorobenzene derivatives are toxic and probably carcinogenic to humans,[192] in recent years, some studies have also been carried out on the Pd-catalyzed monoarylation reactions of these electrophiles with arylboronic acids.[193–196]

In 2006, Zlotin et al.[193] reported that the reaction of 2,4-dichloroacetophenone (**301**) with 1.1 equiv of phenylboronic acid, 4 equiv of K_3PO_4, 8 mol % $Pd(OAc)_2$, 8 mol % 1,3-bis(tetrazol-1-yl)benzene (BTB) and 12 mol % 18-crown-6 in DMF at 95 °C produced a mixture of 2-arylated, 4-arylated and 2,4-diarylated derivatives, **302**, **303** and **304**, respectively, in a 75/10/15 M ratio (Scheme 100). One year later, the same research group described that 1,2-dichlorobenzene (**305**) and 1,4-dichlorobenzene (**306**) were converted in high yield into chlorobiphenyls **171y** and **171b**, respectively, by treatment with 1.5 equiv of phenylboronic acid in the presence of K_3PO_4 as base and a catalyst system consisting of a mixture of $Pd(OAc)_2$ and 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (BTPIm) in dioxane at 85–90 °C (Scheme 101).[194] However, these reaction conditions were unsuitable for arylation of 1,2,4,5-tetrachlorobenzene with phenylboronic acid. On the other hand, the use of NaO*t*-Bu instead of K_3PO_4 as base produced a complex mixture of cross-coupling products.[194]

Wang et al.[195] had previously found that the $PdCl_2$-catalyzed reaction of **306** with 1 equiv of phenylboronic acid in the presence of 2.5 equiv of K_2CO_3 in PEG(300) as solvent at room temperature gave 4-chlorobiphenyl (**171b**) in 86% yield. However, these reaction conditions were ineffective for arylation of **305**.[195]

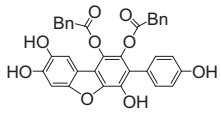


291 **292**

Method A: $Pd(PPh_3)_4$ (10 mol%); boronic acid (1.1 equiv.); Na_2CO_3 (4 equiv.); 80 °C; 8 h; DME.
Method B: $PdCl_2(dppf)$ (10 mol%); boronic acid (1.2 equiv.); Na_2CO_3 (4 equiv.); 80 °C; 5 h; DME.
Method C: $Pd(OAc)_2$ (1.5 mol%); boronic acid (1.0 equiv.); Bu_4NBr (1 equiv.); K_2CO_3 (2 equiv.); rt; 15 h; THF/H_2O.
Method D: $Pd(OAc)_2$ (1.2- 2.7 mol%); boronic acid (1.0 equiv.); Bu_4NBr (1-3 equiv.); K_2CO_3 (2 equiv.); 70 °C; 3.5- 7 h; THF/H_2O.

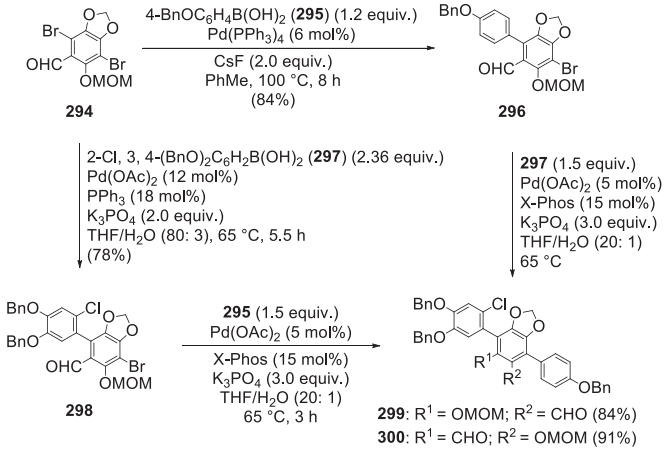
292	Method	HetAr	R	Yield (%)
a	A		CH_2CN	40
a	B		CH_2CN	52
a	C		CH_2CN	90
b	D		CH_2CN	86
c	D		CH_2CO_2Et	42
d	C		Et	80
e	C		H	21

Scheme 98.



293 (vialinin B)

Fig. 24. Structure of compound **293** (vialin B).

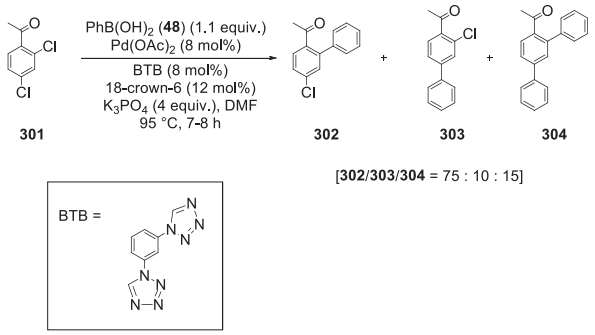


Scheme 99.

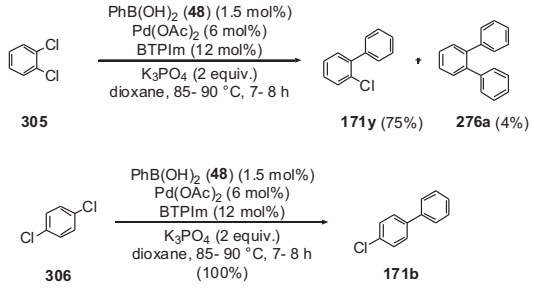
Finally, Diaconescu et al.[196] described that the reaction of **305** with 1 equiv of phenylboronic acid in the presence of 4 equiv of aqueous NaOH and 0.05 mol % Pd nanoparticles supported on polyaniline nanofibers [Pd/PANI], followed by treatment of the resulting cross-coupling product with 5 equiv of KOH in a 1/1 mixture of dioxane and water for 6 h afforded 2-hydroxybiphenyl (**307**) in 70% yield (Scheme 102).

5.3. Monocoupling reactions of bis(triflates) of dihydroxyarenes

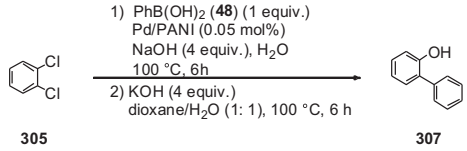
Several examples have been reported in the literature showing that aryl triflates, readily prepared from the corresponding commercially available and inexpensive phenols,[197] are electrophiles



Scheme 100.



Scheme 101.

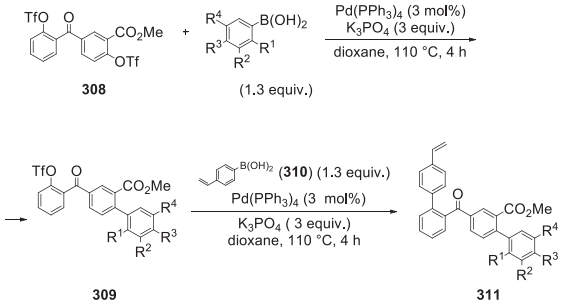


Scheme 102.

suitable for efficient Pd-catalyzed S.–M. cross-coupling reactions.[198] In this context, very recently, Langer's research group has carried out several investigations showing that bis(triflates) of dihydroxyarenes are able to undergo selective Pd-catalyzed S.–M. monoarylation reactions with arylboronic acids.[199–206]

Thus, 4-aryl-2-(trifluoromethylsulfonyloxy)benzophenones **309a**–**g** were prepared with good site-selectivity in yields ranging from 43 to 89% by the $Pd(PPh_3)_4$-catalyzed reaction of bis(triflate) **308** of 2′,4-dihydroxybenzophenone with 1.3 equiv of the required arylboronic acids (Scheme 103).[205] Noteworthy, the remaining triflate group of compounds **309** could be further reacted with 4-vinylphenylboronic acid (**310**) in the presence of 3 equiv of K_3PO_4 and a catalytic amount of $Pd(PPh_3)_4$ to give 2′,4-diarylbenzophenones **311a**–**e** in satisfactory yields (Scheme 103).[205]

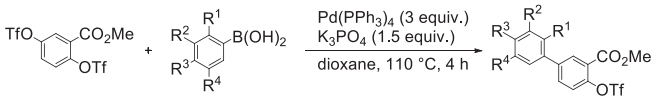
The $Pd(PPh_3)_4$-catalyzed reactions of bis(triflate) **312** of methyl 2,5-dihydroxybenzotae with 1.3 equiv of arylboronic acids in dioxane at 110 °C in the presence of K_3PO_4 as base were found to occur site selectively at the less sterically hindered C-5 position to give biaryls **313a**–**g** in satisfactory yields (Scheme 104).[199] However, in some cases, compounds **313** were obtained together with small amounts of bis-coupling products and the C-2 arylated



308 309 311

Reaction product	R^1	R^2	R^3	R^4	Yield (%)
309a	H	Me	H	Me	78
309b	H	H	Cl	H	45
309c	EtO	H	H	H	89
309d	Br	H	H	H	78
309e	H	MeO	MeO	H	44
309f	H	H	OH	H	63
309g	H	MeO	MeO	MeO	43
311a	H	Me	H	Me	60
311b	H	H	OH	H	55
311c	H	H	H	H	65
311d	H	MeO	MeO	MeO	62
311e	H	MeO	MeO	MeO	44

Scheme 103.



312 (1.3 equiv.) 313

313	R^1	R^2	R^3	R^4	Yield (%)
a	H	Me	H	Me	83
b	MeO	H	H	MeO	72
c	H	H	Me	H	64
d	H	MeO	MeO	H	67
e	H	H	Br	H	63
f	MeO	H	MeO	H	73
g	H	H	Cl	H	59

Scheme 104.

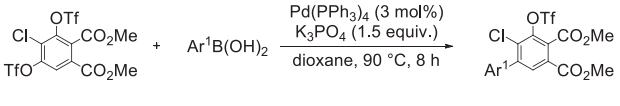
regioisomers, and a chromatographic purification was necessary to obtain the required pure C-5 monocoupling compounds. Interestingly, the $Pd(PPh_3)_4$-catalyzed reaction of compounds **313** with arylboronic acids allowed Langer et al. to prepare methyl 2,5-diarylbenzoates containing two different aryl groups.[199]

Chemo- and site-selective cross-coupling reactions were also found to occur when bis(triflate) **314** of dimethyl 4-chloro-3,5-dihydroxyphthalate was reacted with 1.1 equiv of arylboronic acids under experimental conditions similar to those employed for the synthesis of compounds **313** from **312**.[200]

Dimethyl 5-aryl-4-chloro-3-(trifluoromethylsulfonyloxy)-phthalates **315a**–**f** were obtained in satisfactory yields (Scheme 105). As for the synthesis of compounds **313**, the site selectivity of these cross-coupling reactions was explained on the basis of steric reasons.[200]

Interestingly, the protocol used for the synthesis of compounds **313** also enabled Langer et al. to prepare dimethyl 5-aryl-4-fluorophthalates **317a**–**f** in satisfactory yields and with excellent site selectivity from bis(triflate) **316** of dimethyl 4-fluoro-3,5-dihydroxyphthalate and arylboronic acids (Scheme 106).[191]

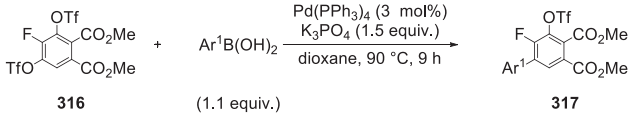
Moreover, a similar protocol was employed for the reaction of bis(triflate) **318** of 2,4′-bis(hydroxy)diphenylsulfone with 1.1 equiv of arylboronic acids that resulted in the site-selective cross-



314 (1.1 equiv.) 315

315	Ar^1	Yield (%)
a	2-$MeOC_6H_4$	47
b	Ph	65
c	3,4-$(MeO)_2C_6H_3$	47
d	4-$CF_3C_6H_4$	63
e	3,5-$Me_2C_6H_3$	61
f	2,6-$(MeO)_2C_6H_3$	48

Scheme 105.

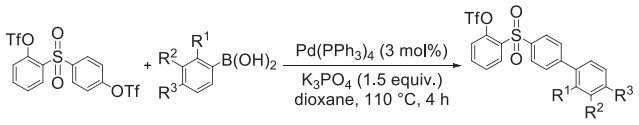


316 (1.1 equiv.) 317

317	Ar^1	Yield (%)
a	2-$CF_3C_6H_4$	59
b	3-FC_6H_4	71
c	3,4-$(MeO)_2C_6H_3$	56
d	4-$CF_3C_6H_4$	68
e	3,5-$Me_2C_6H_3$	75
f	2-EtC_6H_4	60

Scheme 106.

coupling reaction onto the 4′-position of this substrate.[202] 2-Trifluoromethylsulfonyloxy-4′-aryldiphenylsulfones **319a**–**e** were prepared in yields ranging from 55 to 76% with very good site selectivity (Scheme 107).[202]



318 (1.1 equiv.) 319

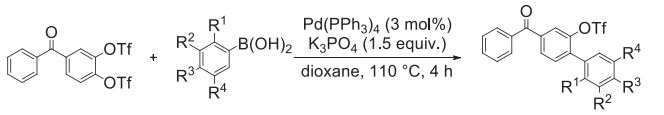
319	R^1	R^2	R^3	Yield (%)
a	H	H	Et	75
b	H	H	MeO	76
c	H	H	*t*-Bu	70
d	MeO	MeO	H	55
e	H	H	Me	62

Scheme 107.

On the other hand, electronic instead of steric reasons were proposed to explain the site selectivity of the $Pd(PPh_3)_4$-catalyzed cross-coupling reactions of 3,4-bis(trifluoromethylsulfonyloxy) benzophenone (**320**) with 1.3 equiv of arylboronic acids.[203] The formation of compounds **321a**–**e** (Scheme 108) was in fact explained taking into account that the oxidative addition of Pd(0) occurs at the C-4 position of **320**, which is more electron deficient than the C-3 position.[203]

Langer et al. also found that compound **320** underwent sequential S.–M. reactions with two different arylboronic acids to give unsymmetrical 3,4-disubstituted benzophenones in good yields.[203]

The site selectivity of the $Pd(PPh_3)_4$-catalyzed reaction used to prepare 1-aryl-2-(trifluoromethylsulfonyloxy)-anthraquinones **323** from bis(triflate) **322** of alizarin and 1 equiv of arylboronic acids

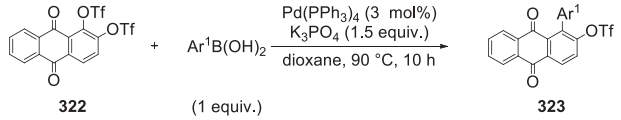


320 (1.3 equiv.) 321

321	R^1	R^2	R^3	R^4	Yield (%)
a	H	MeO	H	H	68
b	MeO	H	H	MeO	72
c	H	H	Me	H	64
d	H	MeO	MeO	MeO	76
e	H	H	*t*-Bu	H	70

Scheme 108.

was also explained on the basis of electronic reasons.[203] The reaction was found to proceed with excellent site selectivity to give compounds **323a**–**h** in yields ranging from 50 to 85% (Scheme 109).[203] It should be noted that position 1 of compound **322**, where the arylation reaction was proved to occur, is more hindered, but more electron-deficient, than position 2.

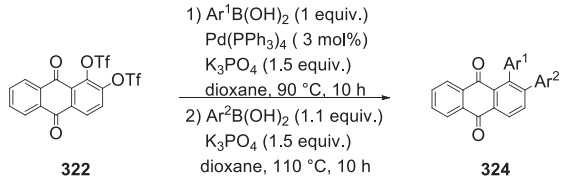


322 (1 equiv.) 323

323	Ar^1	Yield (%)
a	4-$CF_3C_6H_4$	74
b	4-$MeOC_6H_4$	67
c	4-*t*-BuC_6H_4	61
d	4-ClC_6H_4	85
e	3-$CF_3C_6H_4$	84
f	3-$MeOC_6H_4$	79
g	4-FC_6H_4	50
h	4-$CF_3OC_6H_4$	52

Scheme 109.

As previously found for compound **320**, bis(triflate) **322** proved to be able to undergo a one-pot $Pd(PPh_3)_4$-catalyzed reaction with two different arylboronic acids, which were sequentially added.[204] The first step of the optimized one-pot process (Scheme 110) was carried out at 90 °C and the second was performed at 110 °C. Unsymmetrical 1,2-diarylanthraquinones **324a**–**f** were prepared in 50–68% yields.[202]

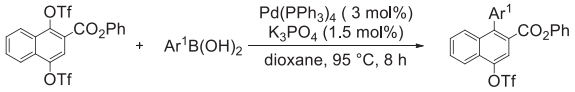


322 324

324	Ar^1	Ar^2	Yield (%)
a	4-$CF_3C_6H_4$	4-*t*Bu-C_6H_4	65
b	4-$MeOC_6H_4$	4-*t*-Bu-C_6H_4	50
c	4-*t*-Bu-C_6H_4	4-$CF_3C_6H_4$	60
d	3-$CF_3C_6H_4$	4-*t*-Bu-C_6H_4	61
e	3-$CF_3C_6H_4$	4-$CF_3C_6H_4$	68
f	4-ClC_6H_4	4-*t*-Bu-C_6H_4	61

Scheme 110.

Finally, Langer et al. recently described the synthesis of phenyl 1-aryl-4-(trifluoromethylsulfonyloxy)-2-naphthoates **326a**–**e** in good yields and with high site selectivity via a $Pd(PPh_3)_4$-catalyzed reaction of bis(triflate) **325** of phenyl 1,4-dihydroxynaphthoate with 1.1 equiv of the required arylboronic acids in dioxane at 95 °C in the presence of 1.5 equiv of K_3PO_4 (Scheme 111).[206]

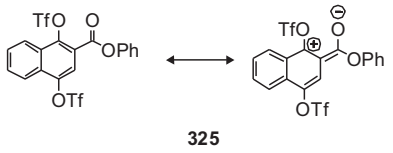


325 (1.1 equiv.) 326

326	Ar^1	Yield (%)
a	2-$EtOC_6H_4$	59
b	2,4-$(MeO)_2C_6H_3$	66
c	2,6-$(MeO)_2C_6H_3$	33
d	4-ClC_6H_4	73
e	4-*t*-BuC_6H_4	71

Scheme 111.

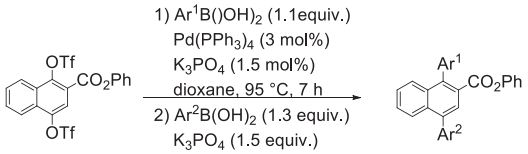
Thus, the arylation reaction occurred at the C-1 position of **325**, which is more sterically hindered, but more electron deficient, than C-4 due to the diene character of this substrate (Fig. 25).[206]



325

Fig. 25. Resonance structures of compound **325**.

It was also found that the one-pot $Pd(PPh_3)_4$-catalyzed reaction of **325** with two different, sequentially added arylboronic acids gave unsymmetrical phenyl 1,4-diaryl-2-naphthoates **327a**–**d** in 51–67% yields (Scheme 112).[206]



325 327

327	Ar^1	Ar^2	Yield (%)
a	4-FC_6H_4	3,4-$(MeO)_2C_6H_3$	54
b	2,4-$(MeO)_2C_6H_3$	3-MeC_6H_4	63
c	4-FC_6H_4	3,4-$(MeO)_2C_6H_3$	51
d	4-$(CH_2{=}CH)C_6H_4$	4-$MeOC_6H_4$	67

Scheme 112.

6. Conclusions

Finding effective methods for the site-, chemo- and stereoselective synthesis of densely functionalized organic compounds is a long-lasting goal in organic synthesis. Since the report by Roush et al.[31] in 1988, which concerned the first examples of chemo- and stereoselective Pd-catalyzed monocoupling reactions of a highly functionalized 1,1-dibromo-1-alkene with a 1,3-dienylboronic acid, and the letter published in 1990 by Suzuki et al.,[161] in which highly chemoselective Pd-catalyzed monocoupling reactions of a bromophenyl triflate with 9-alkyl-9-BBN derivatives were described, the development and use of highly selective Pd-catalyzed

monocoupling reactions of alkene and arene derivatives with two or more electrophilic sites and non-functionalized and functionalized organoboron derivatives have become a vibrant area of research and these reactions have found application as central strategic steps in the synthesis of a wide variety of biologically active compounds, drugs, naturally occurring substances, liquid crystals and luminophores. The main factors that have contributed to the extensive use of these reactions include: (i) their high functional tolerance that in recent years has been implemented in several orthogonal functionalization protocols; (ii) the stability and general availability of the organoboron derivatives; (iii) the use of catalyst systems that frequently do not contain sophisticated, or are devoid of, ligands and can be easily recycled without significant loss of activity; and (iv) their application in one-pot polycoupling procedures of multiple halogenated alkenes and arenes.

This mature area of research, however, needs the development of more rapid and environmentally friendly protocols involving the use of very low catalyst loadings, 'green' solvents, short reaction times and very mild reaction conditions. For example, room temperature S.–M. monoarylation reactions of substrates with two or more electrophilic sites are infrequent.[31,48,69,71,99,108,121,122,138,174] Moreover, as far as we know, Pd-catalyzed highly selective monoarylation reactions of these substrates in water as the only solvent under exceedingly mild conditions have not been reported so far.[207] We can therefore expect that, in the near future, studies on Pd-catalyzed S.–M. monoarylation reactions continue actively[208] and that particular attention is paid to the use of efficient one-pot site-selective polycoupling reactions of polyhalogenated substrates in the synthesis, even on a large scale, of highly functionalized bioactive organic substances including pharmaceuticals.

References and notes

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Biographical sketch

Renzo Rossi was born in Pisa (Italy) and graduated in Organic Chemistry with first-class honours at the University of Pisa defending a thesis performed under the guidance of Professor Piero Pino. In 1969 he became Assistant Professor and in 1971 he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he again joined the University of Pisa where he held the Chair of Chemistry of Naturally Occurring Compounds until October 31, 2010. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. His current research interests include: (i) the preparation of substances, which exhibit significant cytotoxicity against human tumour cell lines and antivascular properties; (ii) the study of new methodologies for carbon–carbon bond formation that involve the use of organometallic reagents, transition metal-catalyzed direct arylation reactions of substrates with activated sp^3-hybridized C–H bonds with aryl halides and pseudohalides; (iii) methods, different from the Mizoroki–Heck reaction, to introduce C–C double bonds in a stereocontrolled manner onto heteroarene moieties by using transition metal-catalyzed reactions that do not involve the use of stoichiometric amounts of organometallic reagents; (iv) the design and development of new, highly chemo- and regioselective methods for the transition metal-catalyzed direct C- and N-arylation of electron-rich heteroaromatic systems, including free (NH)-azoles, with aryl halides and pseudohalides; and (v) the application of these methods to the synthesis of direct precursors to compounds with relevant biological properties. In recent years, several successful studies have also been performed by his research group in the field of synthesis and evaluation of the biological properties of naturally occurring compounds of marine origin and their structural analogues, which are characterized by the 2(5*H*)-furanone ring. Professor Rossi, who has coauthored over 230 research publications and a number of highly cited review articles and patents, is a fellow of the Royal Society of Chemistry, the American Chemical Society, and the Società Chimica Italiana.

Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in 1990. In 1992, he joined the University of Pisa as an Organic Chemistry Researcher in the Department of Chemistry and Industrial Chemistry. In October 2003, he was appointed by the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry. His research interests were initially mainly devoted to the total synthesis of naturally-occurring compounds of biological and/or pharmacological interest and to the synthesis of structural analogues of naturally occurring fungicidal derivatives of agrochemical interest. More recently, Professor Bellina focused his attention on new and efficient protocols for regioselective transition metal-mediated carbon–carbon and carbon–heteroatom bond forming reactions, with a particular interest in the selective functionalization of oxygen-containing unsaturated heterocycles such as 2(5*H*)-furanones and 2(2*H*)-pyranones. Currently, he is working on the development of novel and efficient protocols for the transition metal-catalyzed direct C–H and N–H bond arylation of heteroarenes, the direct functionalization of active C(sp^3)–H bonds, and the application of these new procedures to the selective preparation of bioactive natural and synthetic compounds.

Marco Lessi was born in Livorno (Italy) in 1979. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in June 2004 defending a thesis performed under the guidance of Professor Dario Pini. In January 2005, he began his Ph.D. fellowship in the laboratory of Professor Pini and received his Ph.D. degree in 2008, submitting a thesis on the preparation and applications of new insoluble polymer-bound (IPB) enantioselective catalytic systems. The studies were focused on the synthesis of transition metal complexes obtained from bisoxazoline and BINOL ligands. In the period January 2008–March 2009, Dr. Lessi worked for Solvay Solexis S.p.A. on the development of new routes for the preparation of high-fluorinated low-molecular-weight molecules and oligomers. In March 2009, he re-joined the University of Pisa where he currently cooperates with Professor Bellina. The current research interests of Dr. Lessi involve the development of novel and efficient protocols for highly selective transition metal-catalyzed direct C(sp^3)–H arylation reactions in aqueous media, and the discovery of new synthetic routes and applications of functionalized ionic liquids obtained from naturally-occurring building blocks.