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Suzuki–Miyaura Cross-Coupling Reactions of Alkylboronic Acid Derivatives or Alkyltrifluoroborates with Aryl, Alkenyl or Alkyl Halides and Triflates

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Palladium-catalysed Suzuki–Miyaura cross-couplings of organoboronic acids or organotrifluoroborates with aryl and alkenyl halides or triflates have become classic methods for generating carbon–carbon bonds. For this reaction, not only sp^2-hybridized but also sp^3-hybridized organoboron derivatives can be employed. However, alkylboronic acids or trifluoroborates are generally less reactive than arylboron derivatives. The coupling of primary alkylboronic acids or alkyltrifluoroborates with aryl or alkenyl halides is well known, and the reaction gives the coupling products with high selectivities, relatively high turnover numbers and in good yields with several catalysts. On the other hand, secondary alkylboronic acids or trifluoroborates, except for cyclopropylboron derivatives, are much less reactive, and very few catalyst are able to activate such compounds. Because of the hybridization of cyclopropanes, which confers significant aromatic character, several reactions have successfully been performed with cyclopropylboronic acids or trifluoroborates. The stereochemistries of substituted cyclopropylboron derivatives were maintained in the course of the reactions. For all these couplings with primary or secondary alkylboron derivatives, aryl iodides, bromides, chlorides or triflates and alkenyl iodides, bromides or triflates were employed. Alkenyl chlorides have attracted less attention. The reactions with alkenyl halides are stereoselective. A few examples of couplings between sp^3-hybridized organoboronic acids and alkyl halides have also been reported.

1. Introduction

There are many routes for the construction of aryl-alkyl or alkenyl-alkyl bonds. Some of the most common methods involve the use of transition metal-mediated reactions. Among these methods, Suzuki–Miyaura coupling represents one of the most important procedures.[1,2] Innumerable improvements on the original Suzuki–Miyaura protocol for couplings of aryl halides with arylboronic acids have been recorded. Important contributions include great improvements in substrate scope, catalyst/ligand systems and solvents, as well as enhanced experimental conditions. However, while the coupling of arylboronic acids with aryl or alkenyl halides has been widely explored, curiously, arylation or alkenylation using alkylboron derivatives, especially alkylboronic acids or triflates, has attracted less attention.

The alkylation of aryl or alkenyl halides and triflates with alkylboron derivatives provides a simple and easy

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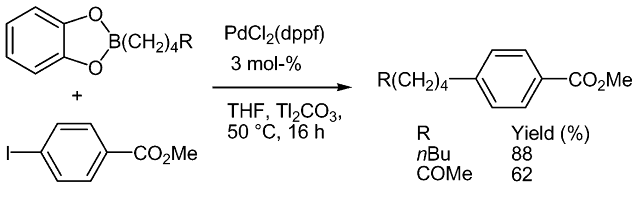
route to the corresponding aryl-alkyl or vinyl-alkyl derivatives. This reaction can be performed with B-alkyl-9-BBN compounds as reactants, but these substrates are not air-stable and so are relatively difficult to handle and therefore to isolate and purify.[1–4] Typically, cross-coupling with alkyl 9-BBN compounds is carried out in situ immediately after hydroboration of an alkenyl. There is no opportunity to purify such alkylboron derivatives if the hydroboration has not proceeded well. Furthermore, coupling in the presence of 9-BBN is not atom-economic, as the cyclooctyl unit is disposed of after the reaction. For these reasons, the use of alternative organoboron reagents such as alkylboronic acids or esters and also alkyltrifluoroborates would be extremely useful, due to their air- or water-stability. Alkylboronic acids or trifluoroborates can be easily prepared by a Grignard approach, as well as by hydroboration of alkenes. Their purification is generally relatively simple as they are crystalline compounds. Moreover, several alkylboronic acids are commercially available. Until recently, relatively little effort had been expended toward developments in the use of primary or secondary alkylboronic acids for such couplings, which is probably due to the fact that the reactions with such substrates are generally slower than those with simple arylboronic acid derivatives and initially gave moderate yields. For a few years now, however, several new catalysts such as palladium associated to electron-rich phosphane ligands or polydentate ligands have been employed and have given the coupling products in high yields. The reactivity of a wider scope of substrates including chiral compounds under modified reaction conditions has also been reported.

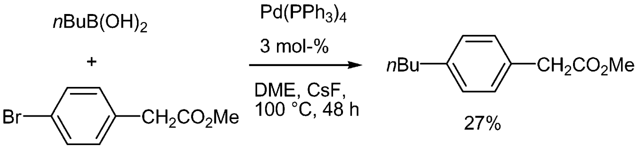
The Suzuki–Miaura cross-coupling reaction has been covered in several relevant reviews or accounts in recent years.[1–7] However, these reviews have mostly been devoted to reactions performed with arylboronates. In this short review we outline the developments and advances in palladium catalytic systems reported for the coupling of aryl, alkenyl or alkyl halides with alkylboronic acids. In the first section we report on the alkylation of aryl halides with primary alkylboronic acids, while the second part deals with the alkylation of aryl halides with secondary alkylboronic acids. We then review the alkylation of alkenyl halides with primary and secondary alkylboronic acids, and also the coupling of alkyl halides with alkylboronic acids. The two last parts involve coupling reactions with aryl or alkenyl triflates and alkyltrifluoroborates. In conclusion, the remaining challenges in the field are discussed.

2. Alkylations of Aryl Halides with Primary Alkylboronic Acid Derivatives

In 1989, Miyaura, Suzuki and co-worker reported the coupling of alkylboronic esters with aryl iodides or bromides.[8] This reaction was performed in the presence of $PdCl_2(dppf)$ as catalyst and Tl_2CO_3 as base at 50 °C in THF. This coupling also proceeds in the presence of a functionalised alkyl chain on the alkylboronate (Scheme 1). Although this protocol, employing toxic Tl_2CO_3, is not appropriate for industrial application, these preliminary results were followed by several improvements. For example, using modified reaction conditions, Wright and co-workers reported the coupling of *n*-butylboronic acid with an aryl bromide in the presence of $Pd(PPh_3)_4$, CsF and DME.[9] In this procedure, however, the coupling product was obtained in relatively low yield (Scheme 2).



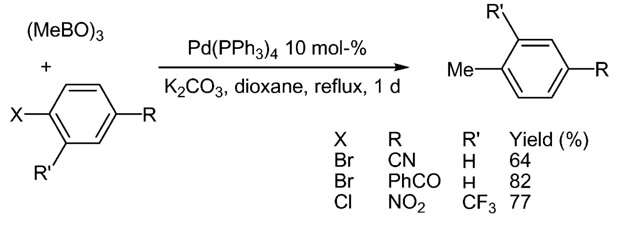
Scheme 1.



Scheme 2.

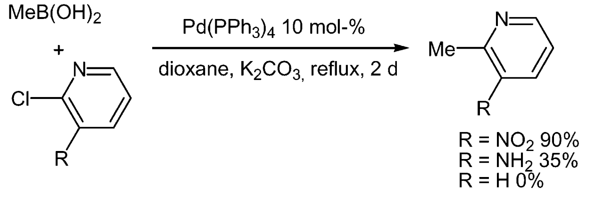
Alkyl- or arylboronic acids exist in equilibrium with their trimeric cyclic anhydrides – boroxines. This equilibrium has some influence on the coupling process. It is difficult to determine the concentration of boronic acid vs. boroxine during a catalytic reaction. Consequently, most of the protocols for cross-coupling employ excess boronic acid to ensure complete conversion of the electrophilic component of the reaction.

Trimethylboroxine has also been found to be a useful partner for the methylation of a variety of aryl halides. In the presence of $Pd(PPh_3)_4$, K_2CO_3 and dioxane, electron-deficient aryl bromides or chlorides in most cases gave the methylated products in good yields (Scheme 3).[10] The use of K_2CO_3 as base is certainly more convenient than that of Tl_2CO_3 for this type of coupling.



Scheme 3.

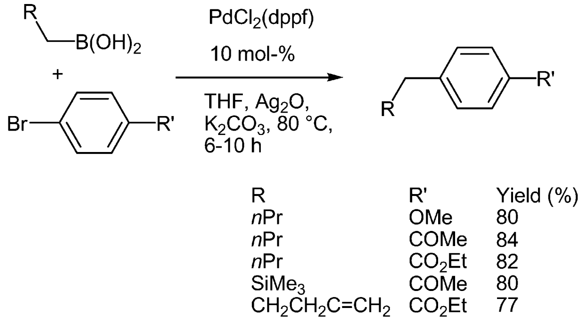
Aryl chlorides are known to be less reactive than bromides or iodides, due to their slow oxidative addition to palladium. The coupling of methylboronic acid with 2-chloropyridines gave the 2-methylpyridines in low to high yields in the presence of $Pd(PPh_3)_4$ as catalyst (Scheme 4).[11] A similar reaction using *n*-butylboronic acid was described by Hocek and co-workers and by Echavarren and co-workers.[12–14] However, the coupling products were obtained in low yields.



$R = NO_2$ 90%
$R = NH_2$ 35%
R = H 0%

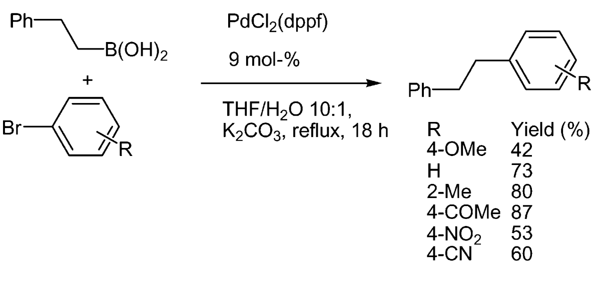
Scheme 4.

In order to enhance the yields of these reactions, Falck and co-workers examined other reaction conditions.[15] They observed that high yields of coupling products were obtained with use of $PdCl_2(dppf)$ as catalyst and Ag_2O as additive. For example, the reactions of *n*-butylboronic acid with 4-bromoanisole, 4-bromoacetophenone or ethyl 4-bromobenzoate gave the butylated products in 80, 84 and 82% yields, respectively. Interestingly, alkylboronic acids containing $SiMe_3$ or alkenyl systems on the alkyl chain were also found to be suitable reactants. It should be noted that the Hiyama or Mizoroki–Heck reactions did not proceed with these alkylboronic acids under the reaction conditions (Scheme 5). Using the same catalyst but a less expensive procedure, Molander and co-workers were able to couple 2-phenylethylboronic acid with either electron-deficient or electron-excessive aryl bromides.[16] Sterically congested 2-bromotoluene or 1-bromonaphthalene were also employed successfully. These couplings were achieved by use of $PdCl_2(dppf)$ (9 mol-%) in the presence of K_2CO_3 in a mixture of THF and H_2O (Scheme 6). With this system, coupling with electron-poor 2-chloropyridines gave the coupling products in moderate yields.



R	R'	Yield (%)
*n*Pr	OMe	80
*n*Pr	COMe	84
*n*Pr	CO_2Et	82
$SiMe_3$	COMe	80
$CH_2CH_2C{=}CH_2$	CO_2Et	77

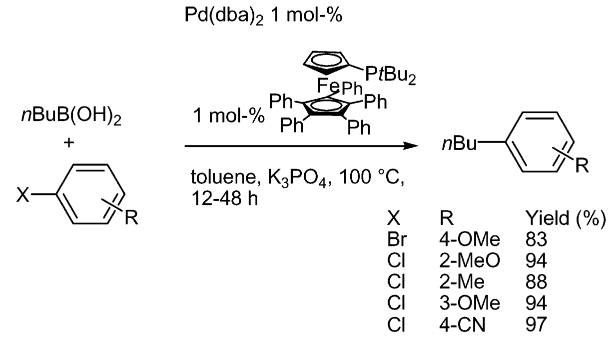
Scheme 5.



R	Yield (%)
4-OMe	42
H	73
2-Me	80
4-COMe	87
$4\text{-}NO_2$	53
4-CN	60

Scheme 6.

Several monodentate ligands associated to palladium have also been employed for these couplings. One of the most efficient catalysts is probably a ferrocenyl (di-*tert*-butylphosphane)palladium complex. With this sterically hindered electron-rich ligand associated to palladium, Hartwig and co-workers were able to couple electron-rich aryl bromides and chlorides with *n*-butylboronic acid in high yields (Scheme 7).[17] This method provides a general procedure for reactions between primary alkylboronic acids and aryl halides without toxic or expensive bases. The ligand not only generates highly active palladium catalysts, but it is air-stable in solution and in the solid state.



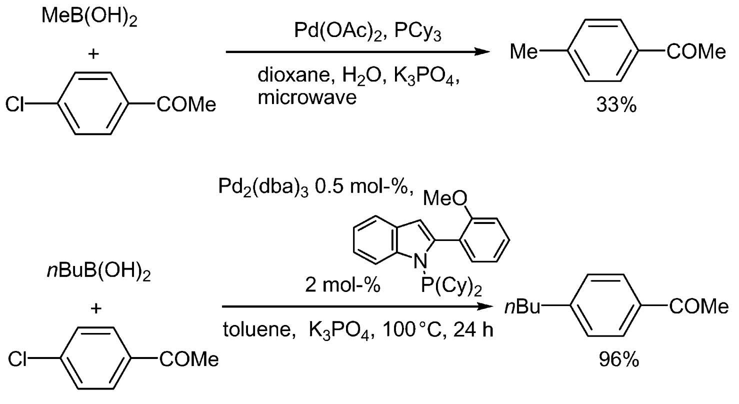
X	R	Yield (%)
Br	4-OMe	83
Cl	2-MeO	94
Cl	2-Me	88
Cl	3-OMe	94
Cl	4-CN	97

Scheme 7.

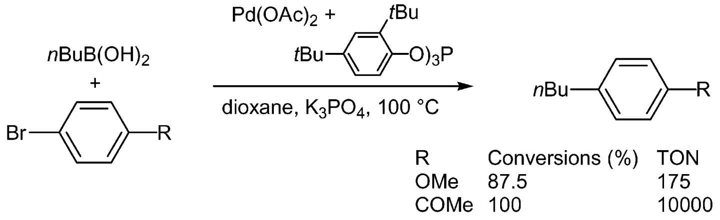
Three other electron-rich and congested phosphane ligands have also been used for such couplings. Delaude and co-workers recently reported that the reaction between a bromoaniline and $n\mathrm{BuB(OH)_2}$ in the presence of $Pd_2(dba)_3$/$PtBu_3$ (10 mol-%) as catalyst and Cs_2CO_3 as base in dioxane under reflux gave the *n*-butylaniline in 63% yield.[18] Bedford and co-workers obtained the coupling product of methylboronic acid with 4-chloroacetophenone in 33% yield by use of microwave heating in the presence of $Pd(OAc)_2$ associated to the bulky electron-rich monodentate ligand PCy_3 (Scheme 8, top).[19] An indolylphosphane ligand associated to only 0.5 mol-% $Pd_2(dba)_3$ (1 mol-% palladium) promoted the coupling of 4-chloroacetophenone with $n\mathrm{BuB(OH)_2}$ in 96% yield (Scheme 8, bottom).[20]

Orthopalladated phosphinite complexes have also been employed for this coupling.[21,22] The influence of several solvents, bases and ligands has been studied. The best results were obtained with K_3PO_4 in dioxane in the presence of $P(OC_6H_3\text{-}2,4\text{-}t\mathrm{Bu}_2)_3$ (0.5 mol-%) as ligand and $Pd(OAc)_2$ (0.5 mol-%). Under these conditions, the reaction between $n\mathrm{BuB(OH)_2}$ and 4-bromoanisole gave 4-(*n*-butyl)anisole in 85% yield (Scheme 9). In the presence of the electron-deficient aryl bromide 4-bromoacetophenone a very high turnover number (TON) of 10000 was obtained with 0.01 mol-% catalyst.

A hemilabile-type phosphane ligand associated to palladium was found to be highly effective in the cross-coupling of *n*-butyl- or *n*-hexylboronic acids with aryl chlorides with



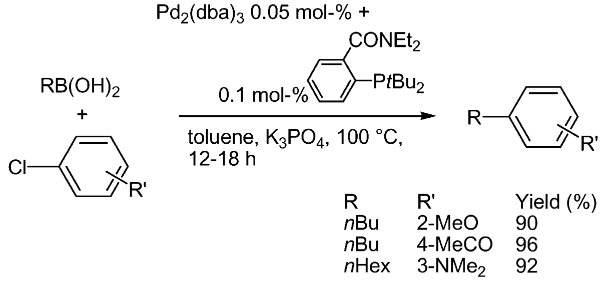
Scheme 8.



R	Conversions (%)	TON
OMe	87.5	175
COMe	100	10000

Scheme 9.

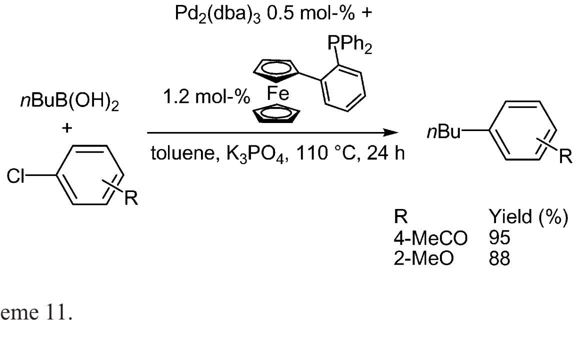
very low catalyst loadings (0.05 mol-%).[23] Even the deactivated aryl chloride 3-*N*,*N*-dimethylaminochlorobenzene gave the coupling product in good yield (Scheme 10).



R	R'	Yield (%)
nBu	2-MeO	90
nBu	4-MeCO	96
nHex	3-NMe$_2$	92

Scheme 10.

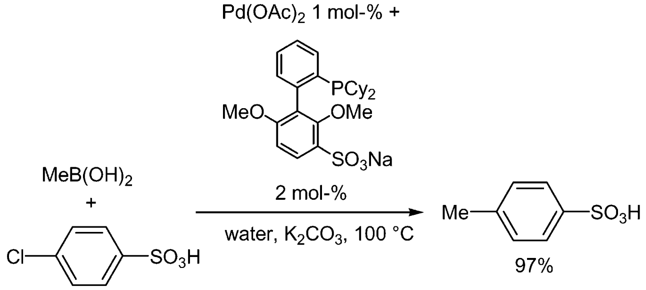
A ferrocene-based triarylphosphane ligand was also found to be effective for the cross-coupling of aryl chlorides with *n*-butylboronic acid.[24] The electron-excessive 2-chloroanisole was employed successfully. Moreover, this ligand is air-stable (Scheme 11).



R	Yield (%)
4-MeCO	95
2-MeO	88

Scheme 11.

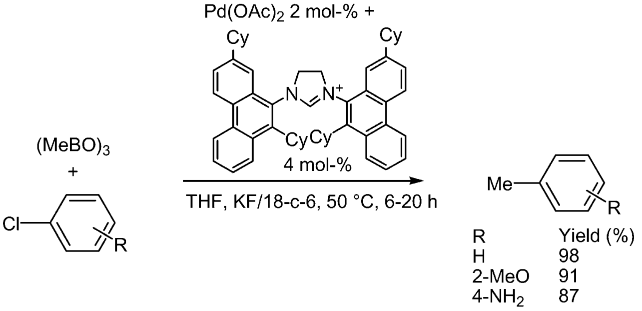
Very few examples involving palladium-catalysed cross-coupling reactions of hydrophilic aryl chlorides have been reported so far. Buchwald and Anderson performed couplings of such substrates with arylboronic acids under purely aqueous reaction conditions.[25] A water-soluble palladium catalyst with a dicyclohexylbiarylphosphane ligand was employed. They observed that 4-chlorobenzenesulfonic acid successfully coupled with methylboronic acid to give the sulfonic acid derivative in 97% yield (Scheme 12).



Scheme 12.

A carbene ligand has been employed for couplings of trimethylboroxine with a variety of aryl chlorides.[26] Use of this diphenanthryl *N*-heterocyclic carbene-based palladium acetate catalyst (2 mol-%) together with KF as base at low temperature (25 or 50 °C) gave the methylated aryl products in 78–98% yields. Even electron-rich aryl chlorides such as 2-chloroanisole gave the desired products in good yields (Scheme 13).

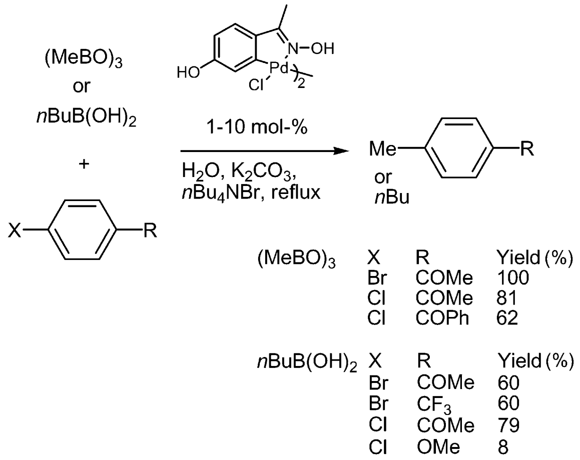
An oxime-carbapalladacycle also catalyses methylation or butylation of activated aryl chlorides and bromides with trimethylboroxine or *n*-butylboronic acid in good



R	Yield (%)
H	98
2-MeO	91
4-NH$_2$	87

Scheme 13.

yields.[27,28] This reaction was performed in water as solvent and with Bu_4NBr as additive (Scheme 14). On the other hand, the butylation of deactivated 4-chloroanisole proceeded in very low yield. This procedure was employed for the arylation of (cyclopentyl)methylboronic acid with a variety of aryl bromides in the presence of 1 mol-% catalyst.[29]



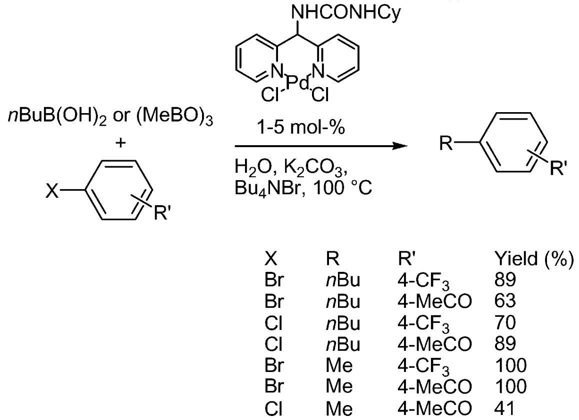
(MeBO)$_3$ X	R	Yield (%)
Br	COMe	100
Cl	COMe	81
Cl	COPh	62

nBuB(OH)$_2$ X	R	Yield (%)
Br	COMe	60
Br	CF$_3$	60
Cl	COMe	79
Cl	OMe	8

Scheme 14.

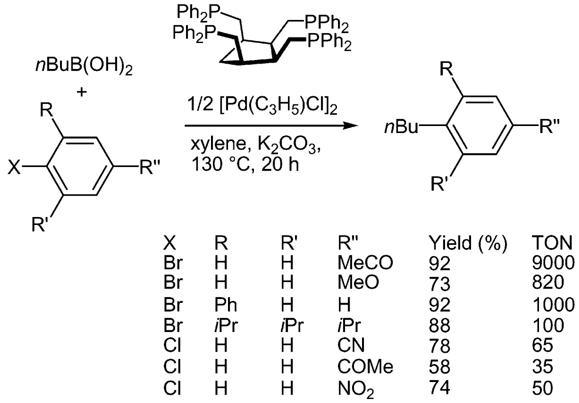
A di(2-pyridyl)methylamine-based palladium dichloride complex has also been employed for this reaction.[30] With this catalyst, trimethylboroxine or *n*-butylboronic acid were coupled with bromo- and chloroarenes in water at reflux temperature with K_2CO_3 as base and Bu_4NBr as additive to furnish methyl- and butylarenes (Scheme 15). Some of these cross-couplings have also been performed in shorter times under microwave irradiation conditions.

With $[PdCl(C_3H_5)]_2$/*cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphanylmethyl)cyclopentane as a catalyst, a wide range of aryl bromides and chlorides also undergo Suzuki cross-coupling with alkylboronic acids in good yields.[31] Several alkyl substituents on the alkylboronic acids – such as ethyl, *n*-butyl, *n*-octyl, isobutyl or 2,2-dimethylpropyl – have been successfully employed. The functional group tolerance on the aryl halide is remarkable; substituents such as fluoro, methyl, methoxy, acetyl, formyl, benzoyl, nitro or nitrile are tolerated. Furthermore, this catalyst can be used at low loading, even for reactions of sterically hindered aryl bromides. The reaction can be performed with as little as 0.01 mol-% catalyst with the most reactive aryl bromides and 1 or 2 mol-% with some aryl chlorides (Scheme 16 and Scheme 17).



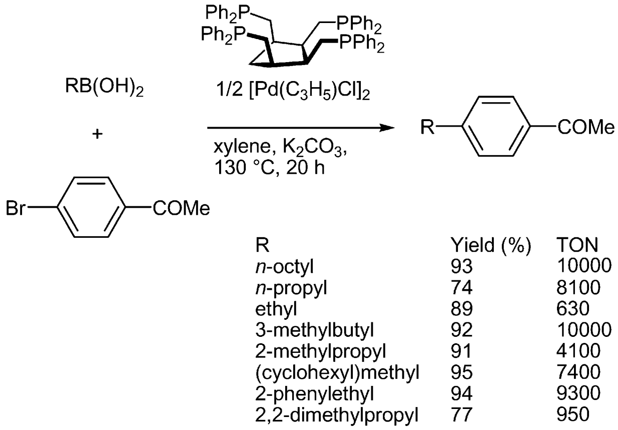
X	R	R'	Yield (%)
Br	nBu	4-CF$_3$	89
Br	nBu	4-MeCO	63
Cl	nBu	4-CF$_3$	70
Cl	nBu	4-MeCO	89
Br	Me	4-CF$_3$	100
Br	Me	4-MeCO	100
Cl	Me	4-MeCO	41

Scheme 15.



X	R	R'	R''	Yield (%)	TON
Br	H	H	MeCO	92	9000
Br	H	H	MeO	73	820
Br	Ph	H	H	92	1000
Br	iPr	iPr	iPr	88	100
Cl	H	H	CN	78	65
Cl	H	H	COMe	58	35
Cl	H	H	NO$_2$	74	50

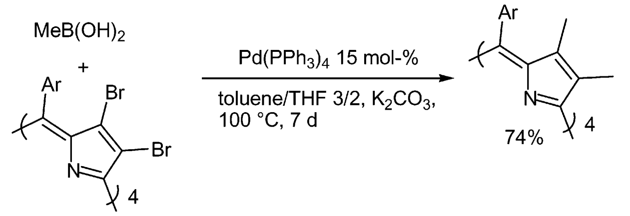
Scheme 16.



R	Yield (%)	TON
n-octyl	93	10000
n-propyl	74	8100
ethyl	89	630
3-methylbutyl	92	10000
2-methylpropyl	91	4100
(cyclohexyl)methyl	95	7400
2-phenylethyl	94	9300
2,2-dimethylpropyl	77	950

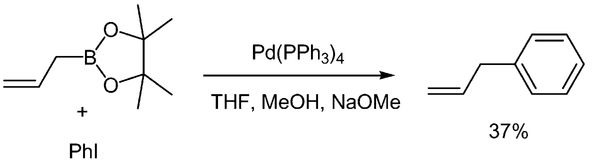
Scheme 17.

The polyalkylation of aryl polybromides has also been reported. An octamethylation of an octabromoporphyrin was performed by Chan and co-workers using $Pd(PPh_3)_4$ with K_2CO_3 as base in toluene.[32] The reaction time is relatively long (7 days), but the octamethylated porphyrin was obtained in a good 74% yield (Scheme 18).

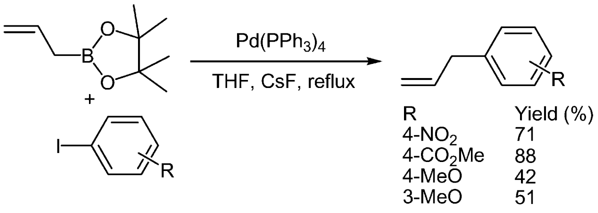


Scheme 18.

Allyl boranes were also found to be suitable reactants for these couplings. However, the selectivities of the reactions strongly depend on the coupling conditions. Palladium-catalysed arylation of 4,4,5,5-tetramethyl-2-(prop-2-enyl)-1,3,2-dioxaborolane with iodobenzene in the presence of Et_3N and $PhCH_2NMe_2$ gave a complex reaction mixture.[33] On the other hand, with Bu_4NCl and K_2CO_3 in DMF, allylbenzene was the main product, and with MeONa in THF at reflux it was the only isomer formed, albeit in moderate yield (Scheme 19). Using a slightly modified procedure, Kotha and co-workers have prepared a variety of allylbenzene derivatives in moderate to good yields (Scheme 20).[34] Allyl(dimethoxy)borane reacted with iodobenzene at 25 °C in THF in the presence of NaOH as base and $PdCl_2(PPh_3)_2$ as catalyst and produced allylbenzene in a very high 98% yield (Scheme 21).[35]

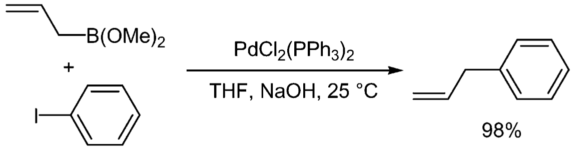


Scheme 19.



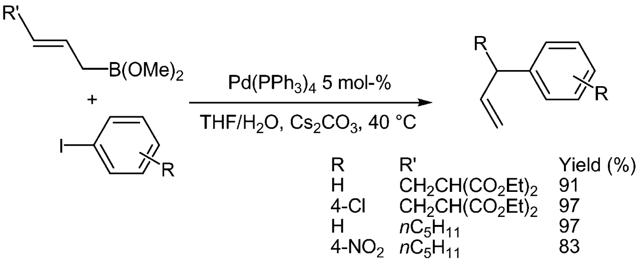
R	Yield (%)
4-NO_2	71
4-CO_2Me	88
4-MeO	42
3-MeO	51

Scheme 20.



Scheme 21.

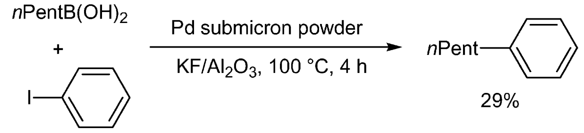
Substituted allylboronic acid derivatives and iodobenzenes were employed by Szabó and co-workers to give the coupling products in high yields and selectivities.[36] They found that the palladium-catalysed arylation of functionalised allylboronic acids with aryl iodides in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 led to the selective formation of the branched allylic isomers without employment of directing groups or specially designed ligands. As this coupling generates a new stereogenic carbon, this method allows the development of new asymmetric allylation processes (Scheme 22).



R	R'	Yield (%)
H	$CH_2CH(CO_2Et)_2$	91
4-Cl	$CH_2CH(CO_2Et)_2$	97
H	nC_5H_{11}	97
4-NO_2	nC_5H_{11}	83

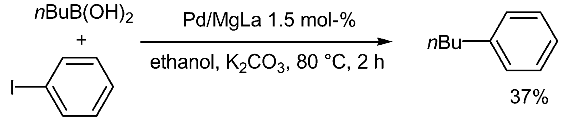
Scheme 22.

The solventless coupling of *n*-pentylboronic acid with iodobenzene on palladium-doped KF/Al_2O_3 was reported by Kabalka and co-workers (Scheme 23).[37,38] Whilst the reaction proceeded nicely with arylboronic acids, with use of *n*-pentylboronic acid the coupling product was obtained only in moderate yield.



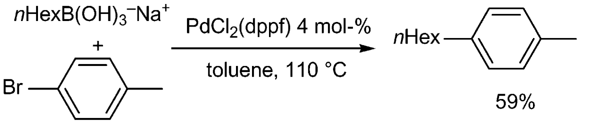
Scheme 23.

Reusable Pd/MgLa mixed-oxide catalyst has also been applied quite successfully in the Suzuki–Miyaura carbon–carbon cross-coupling reaction between iodobenzene and *n*-butylboronic acid in ethanol.[39] The catalyst is air-stable, can be stored and handled under an ambient atmosphere and can be recovered after the reaction and reused without significant loss of activity by simple filtration (Scheme 24). With this system, much better results were obtained with arylboronic acids.



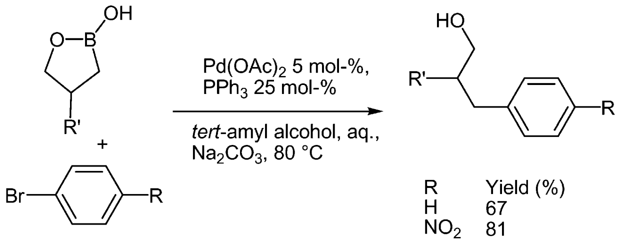
Scheme 24.

This reaction is not limited to alkylboronic acids. For example, it also proceeds with an alkyl trihydroxyborate in satisfactory yield in the presence of 4 mol-% $PdCl_2(dppf)$ as catalyst.[40] It should be noted that this reaction can be performed in the absence of additional base (Scheme 25).



Scheme 25.

A borinic acid has also been employed for couplings with aryl bromides.[41] With 5 mol-% $Pd(OAc)_2$ and 25 mol-% PPh_3, coupling products with bromobenzene, 2-bromonaphthalene, 4-bromonitrobenzene or bromopyridines were obtained in good yields (Scheme 26).



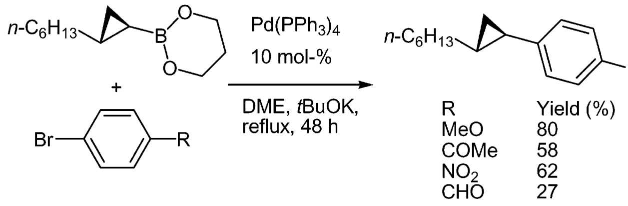
Scheme 26.

The Suzuki–Miyaura alkylation method has also been employed for the synthesis of several compounds, such as for the methylation of Binap derivatives,[42,43] the alkylation of pyrimidines,[44] the preparation of enantiopure α-amino acids,[45,46] or the synthesis of natural[47] and biologically active compounds.[48]

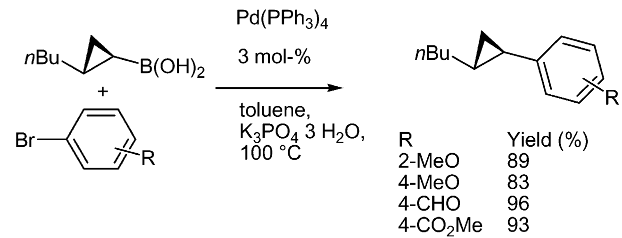
In summary, Suzuki–Miyaura cross-coupling alkylation of aryl halides with primary alkylboronic acids is now a powerful method for the synthesis of alkylarenes. However, much lower TONs have been obtained with such substrates than those for the couplings in the presence of arylboronic acids. The highest TONs so far reported with alkylboronic acids in couplings with 4-bromoacetophenone are around 10000. The reaction between phenylboronic acid and 4-bromoacetophenone proceeds with much higher TONs (up to 100000000). This is probably due to a slower transmetallation rate of the alkylboronic acids with palladium. Several catalysts bearing mono-, bi- or tetradentate ligands have been employed. These catalysts allow the coupling of aryl bromides and iodides. With the most efficient catalysts, reactions of aryl bromides can be performed with as little as 0.01 mol-% complex. Couplings with aryl chlorides are more difficult, and only catalysts bearing electron-rich and congested phosphane ligands or polydentate ligands can activate these substrates. Several sets of reaction conditions have been employed. However, in most cases, K_2CO_3, K_3PO_4 or KF have been used as bases, and toluene, xylene, dioxane, THF or even water as solvents. In general, relatively elevated reaction temperatures (80–130 °C) have been employed. In the presence of an alkyl borate the reaction can be performed in the absence of additional base.

3. Alkylations of Aryl Halides with Secondary Alkylboronic Acid Derivatives

While Suzuki–Miaura cross-coupling reactions of primary alkylboronic acids have been widely explored, examples of coupling reactions with secondary alkylboronic acids are quite rare. The transmetallation rates of these congested substrates with palladium appear to be even slower than those of primary alkylboronic acids. In fact, most results have been reported with cyclopropylboronic acid derivatives. Given that the unique hybridization of cyclopropanes confers significant aromatic character on exocyclic C–B bonds of cyclopropyl boronates, they are satisfactory partners in cross-coupling reactions with aryl halides. In 1996, for example, Marsden and Hildebrand reported stereoselective couplings of a cyclopropyl boronate with several *p*-substituted electron-deficient or excessive aryl bromides in 27–80% yields in the presence of $Pd(PPh_3)_4$ (10 mol-%) as catalyst (Scheme 27).[49] In the same year, Deng and Wang reported couplings of *trans*-2-butylcyclopropylboronic acid with aryl bromides.[50] The reactions gave stereodefined *trans*-2-butylcyclopropylarenes in high yields with both electron-rich and electron-poor aryl bromides (Scheme 28). Under similar reaction conditions, using heteroaryl halides, the corresponding cyclopropylpyridines, pyrimidines or quinolines were obtained in 51–78% yields.[51]

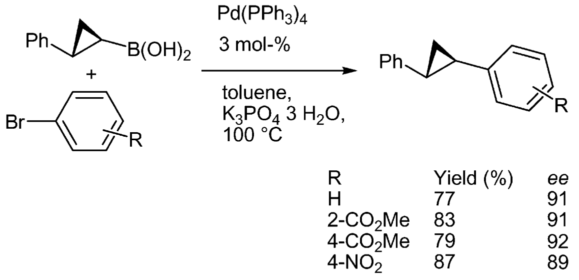


Scheme 27.



Scheme 28.

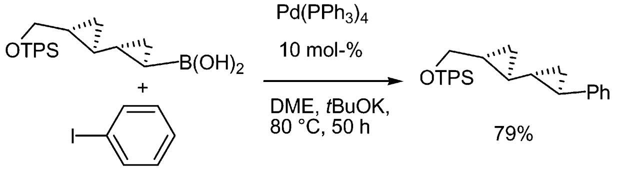
Deng and co-workers next reported an investigation into palladium-catalysed cross-coupling reactions with chiral organoboron compounds.[52] The results indicated that the absolute configurations of the chiral carbon atoms were retained in the cross-coupling process. The optical purities and yields of coupling products were satisfactory (Scheme 29).



R	Yield (%)	*ee*
H	77	91
2-CO_2Me	83	91
4-CO_2Me	79	92
4-NO_2	87	89

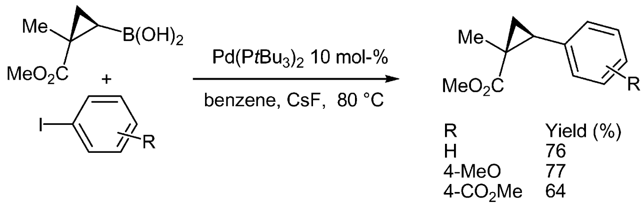
Scheme 29.

A similar reaction had been reported before by Pietruszka, but a low yield of coupling product and moderate enantiomeric excess had been obtained.[53] Then, using an enantiopure cyclopropylboronic acid in the presence of bromobenzene, iodobenzene or 1-bromonaphthalene, Pietruszka and Luithle were able to obtain enantiopure arylcyclopropanes.[54] They have also reported the coupling of a bicyclopropyl derivative with iodobenzene in good yield (Scheme 30).[55] Finally, in 2003 Pietruszka and co-workers reported the arylation of a functionalised cyclopropylboronic acid.[56]



Scheme 30.

Gevorgyan and co-workers have reported other examples of coupling reactions with chiral cyclopropylboronic acids.[57] By using 2,2′-disubstituted cyclopropyl boronates and palladium associated to the bulky electron-rich phosphane P*t*Bu$_3$, the optically active disubstituted arylcyclopropanes were obtained in good yields with retention of the cyclopropane configuration (Scheme 31).



R	Yield (%)
H	76
4-MeO	77
4-CO_2Me	64

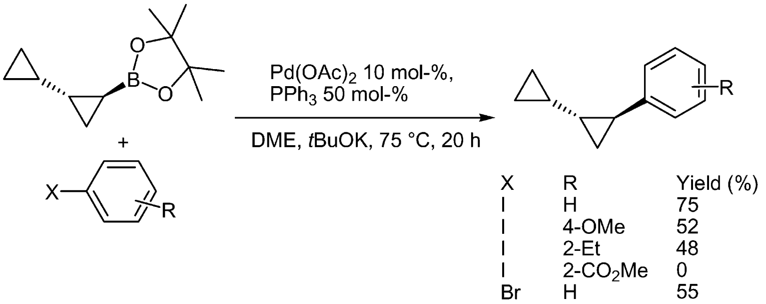
Scheme 31.

Reactions between 2-cyclopropylcyclopropylborolane and aryl halides in the presence of Pd(OAc)$_2$ (10 mol-%) and PPh$_3$ (50 mol-%) as catalyst gave the expected 2-cyclopropylphenylcyclopropanes in moderate to good yields (Scheme 32).[58] A wide variety of aryl iodides were tolerated. For example, iodobenzene, 4-bromoanisole, 2,6-dimethyliodobenzene or 4-iodopyridine have been employed successfully. On the other hand, with this boron derivative, the electron-deficient 4-bromonitrobenzene or methyl 2-iodobenzoate gave no coupling products.

Recently, Pietruszka and co-workers have reported the arylation of an enantiomerically pure cyclopropylboronic acid bearing a phthalimide substituent (Scheme 33).[59] In the presence of iodobenzene and Pd(PPh$_3$)$_4$ as catalyst, the coupling product was obtained in 40% yield.

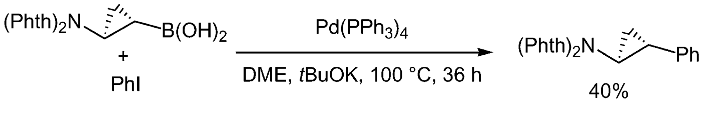
The reactions are not limited to substituted cyclopropylboronic acids. Cyclopropylboronic acid itself has also been used for couplings with aryl bromides.[60] In the presence of Pd(OAc)$_2$ (5 mol-%) associated with PCy$_3$ as catalyst, the arylcyclopropanes were obtained in 60–96% yields (Scheme 34). The reactions tolerate electron-rich aryl bromides such as 3-bromoanisole or 3-bromoaniline and also electron-poor aryl bromides such as 2-bromoacetophenone, 4-bromobenzonitrile or 4-bromobenzaldehyde. The heteroaryl bromides 2-bromopyridine, 3-bromoquinoline or a bromofuran were also used successfully.

It should be noted that coupling reactions between cyclopropylboronic acid and aryl bromides also proceed in good yields and with very high TONs in the presence of the

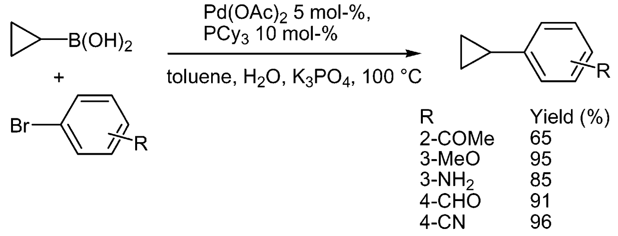


X	R	Yield (%)
I	H	75
I	4-OMe	52
I	2-Et	48
I	2-CO_2Me	0
Br	H	55

Scheme 32.



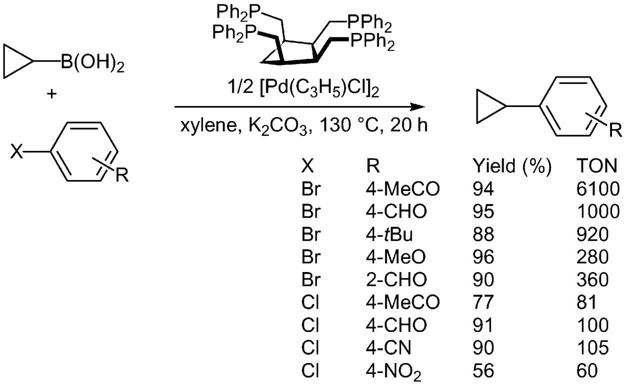
Scheme 33.



R	Yield (%)
2-COMe	65
3-MeO	95
3-NH$_2$	85
4-CHO	91
4-CN	96

Scheme 34.

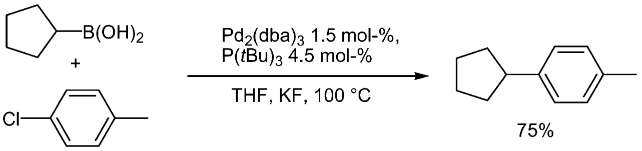
Tedicyp ligand associated to palladium.[61] The reaction with 4-bromoacetophenone, for example, led to 4-cyclopropylacetophenone with a TON of 6100. With this catalyst, even sterically highly congested aryl bromides such as 2,4,6-trimethylbromobenzene or 2,4,6-triisopropylbromobenzene were employed successfully (Scheme 35). Aryl chlorides have also been used, and the expected arylcyclopropanes were obtained in 56–91% yields. Moreover, this reaction proceeds with the cheap and nontoxic base K_2CO_3.



X	R	Yield (%)	TON
Br	4-MeCO	94	6100
Br	4-CHO	95	1000
Br	4-*t*Bu	88	920
Br	4-MeO	96	280
Br	2-CHO	90	360
Cl	4-MeCO	77	81
Cl	4-CHO	91	100
Cl	4-CN	90	105
Cl	4-NO$_2$	56	60

Scheme 35.

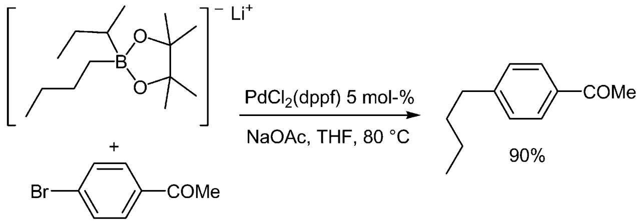
While cyclopropylboronic acids have been widely employed for Suzuki–Miyaura coupling reactions, very few other secondary alkylboronic acids have been used. This is certainly due to very slow transmetallation rates of secondary alkylboronic acids with palladium. One of the rare examples was reported by Fu and co-workers for the coupling of cyclopentylboronic acid with 4-chlorotoluene.[62] The expected tolylcyclopentane was obtained in 75% yield in the presence of $Pd_2(dba)_3$ (1.5 mol-%) associated to the bulky electron-rich ligand P*t*Bu$_3$ (4.5 mol-%) (Scheme 36).



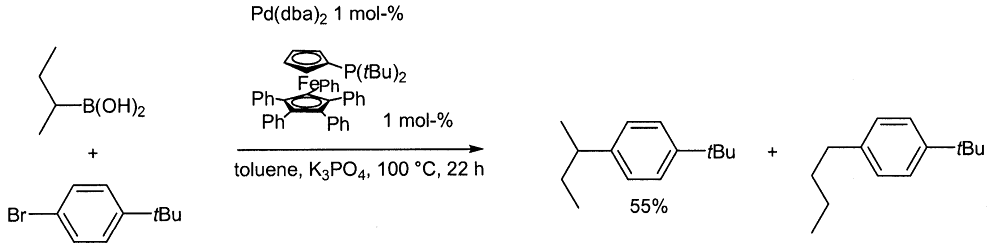
Scheme 36.

Using a sterically hindered ferrocenyl dialkylphosphane ligand, Hartwig and co-workers have successfully coupled *sec*-butylboronic acid with 4-*tert*-butylbromobenzene.[17] In this reaction, however, a mixture of *s*-butyl and *n*-butylarenes was obtained, and only a 55% yield of the desired *s*-butylarene was produced (Scheme 37). To overcome the slow transmetallation rate of this secondary alkylboronate, they also investigated reactions of *sec*-butylzinc chloride with 4-*tert*-butylbromobenzene. This substrate was found to be more reactive, and the coupling of this reagent occurred at room temperature to form the *sec*-butylarene in 76% yield. A similar observation with Tedicyp/Pd as catalyst has recently been described.[63] With this catalytic system the coupling of *sec*-butylzinc bromide with electron-excessive or -deficient aryl bromides gave the *sec*-butylarenes in good yields in most cases. Under similar reaction conditions, the coupling of *s*-butylboronic acid with aryl halides did not proceed.

It should be noted that when a boronate bearing a primary and a secondary alkyl chain was used, the selective formation of the *n*-alkylaryl product was observed (Scheme 38).[64]



Scheme 38.



Scheme 37.

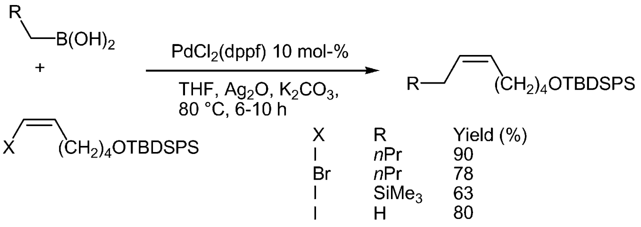
In summary, couplings of aryl halides with cyclopropylboronic acids proceed nicely. This is probably due to the unique hybridization of cyclopropanes, which confers significant aromatic character on these substrates. In the presence of chiral cyclopropylboronic acids the reactions were generally performed with retention of the configuration of the cyclopropane. With cyclopropylboronic acid, in the presence of a tetraphosphane ligand, very high TONs have been obtained for the coupling of a variety of aryl bromides. Aryl chlorides were also coupled successfully with this catalyst. On the other hand, very few results with other secondary alkylboronic acids have been described. This is probably due to slow transmetallation rates of these congested boronic acid derivatives with palladium. For such substrates the best result was probably reported by Fu, using $P(tBu)_3$ as ligand in the presence of cyclopentaneboronic acid.[62]

4. Alkylations of Alkenyl Halides with Primary Alkylboronic Acid Derivatives

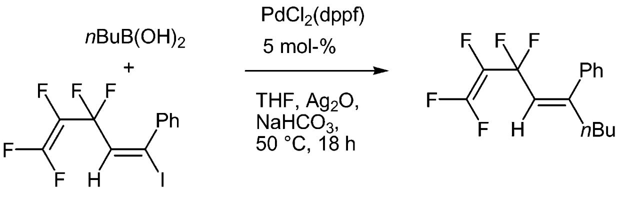
While Suzuki–Miyaura alkylations of alkenyl halides with alkylboronic acids have attracted less attention than the alkylation of aryl halides, a few examples have nevertheless been reported. For example, Suzuki, Miyaura and coworkers described the alkylations of a bromocyclohexenone and a bromoacrylate with functionalised alkylboron derivatives in the presence of $PdCl_2(dppf)$ as catalyst and Tl_2CO_3 as base (Scheme 39).[8]

Another procedure has been employed to prepare biologically active compounds. It should be noted that this procedure is stereoselective.[15,65] For example, the coupling of a *Z* alkenyl iodide in the presence of Ag_2O as additive and K_2CO_3 as base with a functionalised primary alkylboronic acid gave the corresponding *Z* alkene in good yield. When an *E* alkenyl iodide was employed the *E* alkene was also stereoselectively obtained (Scheme 40).

A iodoalkene bearing a perfluoroalkyl chain has been employed in a quite similar procedure to give a perfluoroalkyl-trisubstituted alkene.[66] Again, the stereochemistry of the double bound was retained in the reaction (Scheme 41).

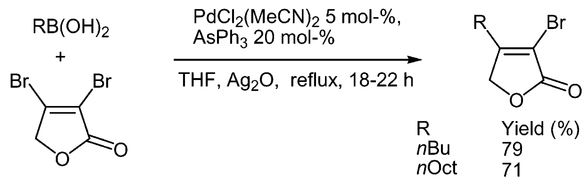


Scheme 40.



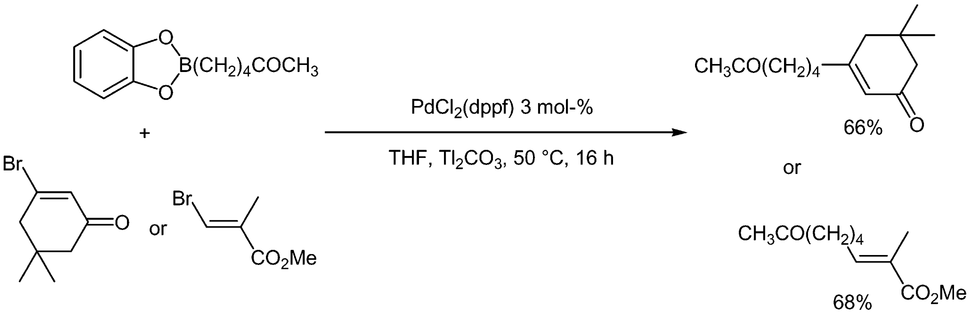
Scheme 41.

Bellina and co-workers have also described some alkylations of alkenyl bromides.[67] With a dibromofuranone and alkylboronic acids such as *n*-butyl or *n*-octylboronic acids, the monoalkylated products were obtained in 69–79% yields. This reactions were performed in the presence of $PdCl_2(MeCN)_2$ (5 mol-%) associated to $AsPh_3$ (20 mol-%) and with Ag_2O as base (Scheme 42).



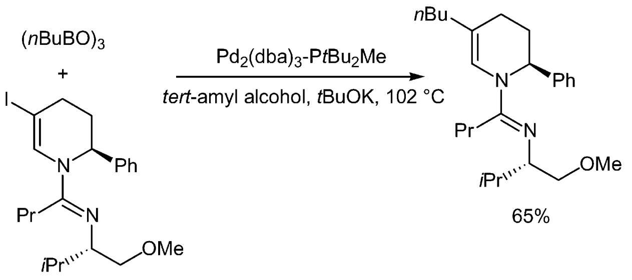
Scheme 42.

Electron-rich and bulky phosphane ligands have also been employed for such couplings. For example, the alkylation of a tetrahydroiodopyridine with tri-*n*-butylboroxine in the presence of Pd associated to $PtBu_2Me$ has been described (Scheme 43).[68] The reactions of alkenyl halides with alkylboronic acids are not limited to alkenyl iodides or bromides. Recently, the butylation of a chlorobenzyl-

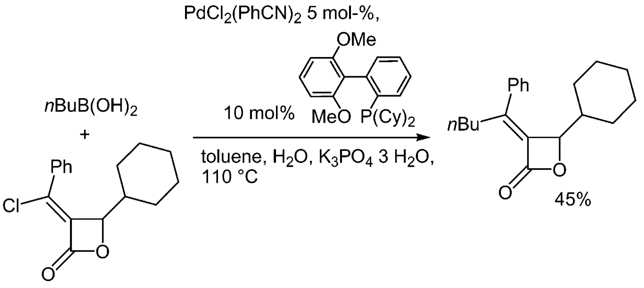


Scheme 39.

idenelactone in the presence of another bulky electron-rich ligand has been described (Scheme 44).[69] However, the yield of this coupling was quite low.

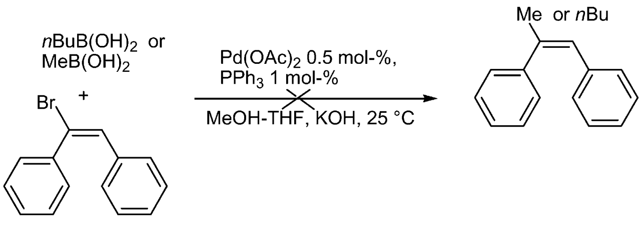


Scheme 43.



Scheme 44.

Surprisingly, with (*E*)-bromostilbene and *n*-butyl- or methylboronic acids and $Pd(OAc)_2/PPh_3$ as catalyst in the absence of additive, the expected products were not obtained (Scheme 45).[70] This might be due to the low reaction temperature. Some coupling product was obtained on raising the temperature to 100 °C, but the reduced side-product stilbene was obtained as the main product. With alkylzinc derivatives instead of alkylboronic acids, however, the reaction proceeded.

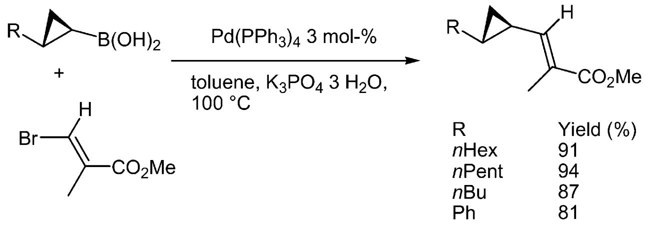


Scheme 45.

In summary, alkylations of alkenyl halides proceed stereoselectively, both from *Z* and *E* alkenes, in good yields in the presence of $PdCl_2(dppf)$, $PdCl_2(MeCN)_2/AsPh_3$ or $Pd(PtBu_3)_2$ as catalysts. In several cases Ag_2O was added, but the reactions can be performed with only *t*BuOH or K_3PO_4 as bases. Alkenyl iodides or bromides have generally been employed, but an example using an alkenyl chloride has been reported recently. So far, no such couplings using low catalyst loadings have been reported.

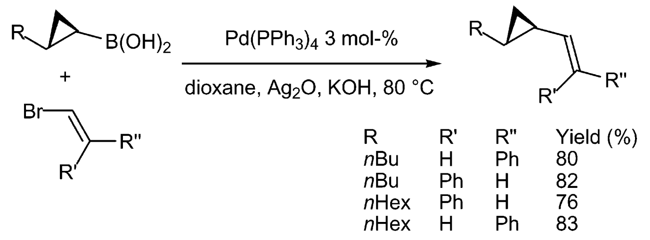
5. Alkylations of Alkenyl Halides with Secondary Alkylboronic Acid Derivatives

Again, reactions with secondary alkylboron derivatives and alkenyl halides have mostly been performed with cyclopropylboronic acid derivatives. Alkyl- or phenyl-substituted cyclopropylboronic acids led stereoselectively to the corresponding alkenylcyclopropanes in good yields in the presence of $Pd(PPh_3)_4$ as catalyst and K_3PO_4 as base in toluene.[71] The reactions tolerate ester functions on the double bond. Moreover, the stereoselectivity of the alkene was maintained during the coupling reaction (Scheme 46). Good yields were also obtained with NaOH or EtONa as bases and THF or benzene as solvents. The same group reported Tl_2CO_3- or Ag_2O-assisted Suzuki-type cross-couplings of stereodefined cyclopropylboronic acids with (*Z*)- or (*E*)-β-bromostyrene to give the corresponding stereodefined cyclopropyl-substituted alkenes in good yields (Scheme 47).[72] Coupling reactions with such *trans*-cyclopropylboronic acids were also performed in the presence of a functionalised iodoalkene bearing a CF_3 and an ester function (Scheme 48).[73] Again, the configurations of both cyclopropyl and alkenyl functions were retained in those reactions.



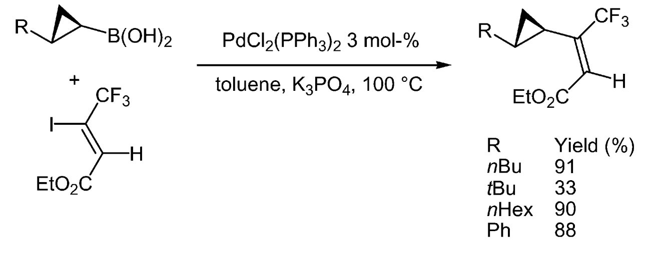
R	Yield (%)
*n*Hex	91
*n*Pent	94
*n*Bu	87
Ph	81

Scheme 46.



R	R'	R''	Yield (%)
*n*Bu	H	Ph	80
*n*Bu	Ph	H	82
*n*Hex	Ph	H	76
*n*Hex	H	Ph	83

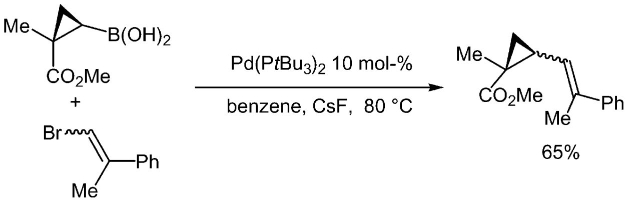
Scheme 47.



R	Yield (%)
*n*Bu	91
*t*Bu	33
*n*Hex	90
Ph	88

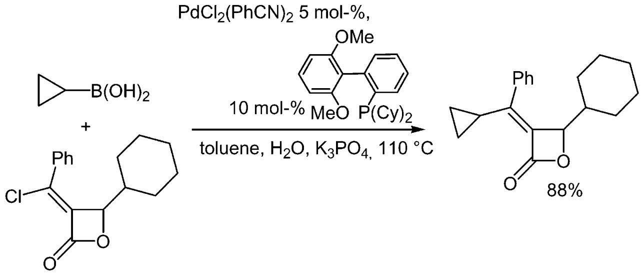
Scheme 48.

An example of Suzuki–Miyaura coupling with a chiral cyclopropylboronic acid was reported by Gevorgyan and co-workers.[57] With a 2,2′-disubstituted cyclopropylboronic acid, the optically active disubstituted alkenylcyclopropane was obtained in good yield (Scheme 49).



Scheme 49.

Alkenyl chlorides are also suitable reactants for such couplings. Recently, a bulky electron-rich ligand has been employed for the coupling of cyclopropylboronic acid and a chlorobenzylidenelactone (Scheme 50).[69]



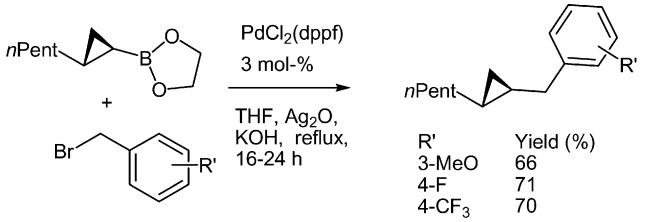
Scheme 50.

So far, couplings of secondary alkylboronic acids with alkenyl halides seem to be limited to cyclopropylboronic acids. Both alkenyl iodides and bromides have been employed, and the stereoselectivities of the alkene and cyclopropane were maintained. Only one example of coupling with a alkenyl chloride has been reported. All these reactions were performed in the presence of monodentate phosphane ligands. More work is needed in order to determine the reactivities of alkenyl chlorides and of other secondary alkylboronic acids, and also the influence of the ligands, bases and solvents on such couplings.

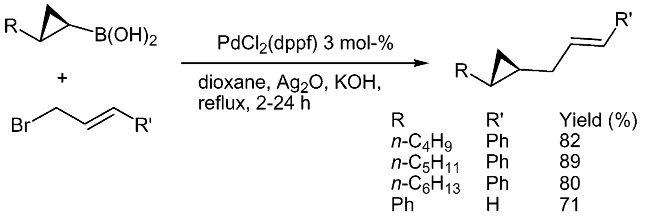
6. Couplings of Alkyl Halide Derivatives with Alkylboronic Acid Derivatives

Only a few examples of cross-couplings of alkylboronic acids with alkyl halides have been described. For example, Charette and co-workers prepared bicyclopropane derivatives by the coupling of cyclopropylboron derivatives with iodocyclopropanes.[74] These reactions proceed in the presence of $Pd(OAc)_2$ associated with PPh_3 in DME and *t*BuOK as base (Scheme 51).

Couplings of allyl or benzyl bromides with cyclopropyl boronates in the presence of $PdCl_2(dppf)$ as catalyst have been described by Deng and co-workers.[75] Suzuki–Miyaura-type coupling reactions of cyclopropylboronic acids or esters with benzyl bromides readily take place with Ag_2O with KOH as the base. The reaction rates and the cross-coupling product yields of cyclopropylboronate esters were higher and better than those of cyclopropylboronic acids (Scheme 52). Highly optically active benzyl-substituted cyclopropanes could be obtained through the coupling reactions of the corresponding optically active cyclopropylboronate esters with benzyl bromides. Under the same reaction conditions, cross-coupling reactions of cyclopropylboronic acids with allyl bromides have also been demonstrated, providing a novel, convenient and stereocontrolled synthetic approach to stereodefined allyl-substituted cyclopropanes (Scheme 53).[76]

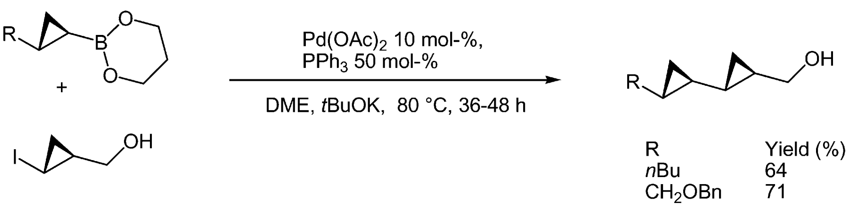


Scheme 52.



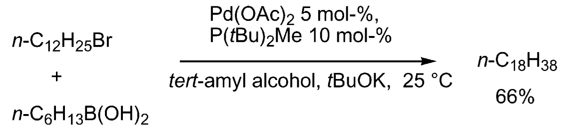
Scheme 53.

Couplings of alkylboronic acids with simple alkyl halides have only rarely been described. Fu and co-workers have reported the coupling of *n*-dodecyl bromide with *n*-hexylboronic acid in the presence of $Pd(OAc)_2$ and $P(tBu)_2Me/Pd(OAc)_2$ as catalyst and with *t*BuOK as base in *tert*-amyl alcohol. The coupling product was obtained in 66% yield (Scheme 54).[77] A very similar reaction using a phospha-

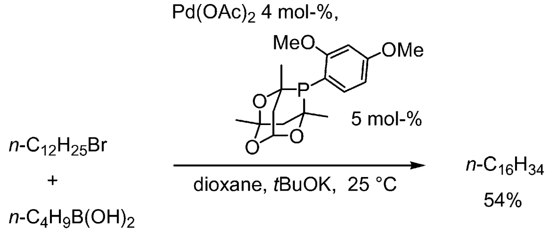


Scheme 51.

adamantane ligand and dioxane as solvent for the coupling of *n*-butylboronic acid with *n*-bromododecene was reported by Capretta.[78] Under these reaction conditions, the expected product was obtained in 54% yield (Scheme 55).



Scheme 54.

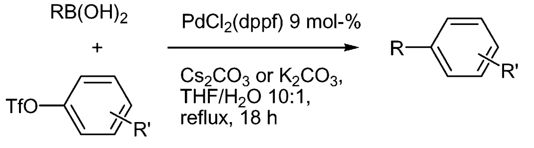


Scheme 55.

7. Alkylations of Aryl or Alkenyl Triflates with Alkylboronic Acid Derivatives

Most coupling reactions of alkylboronic acids have been performed with aryl or alkenyl halides as cross-coupling partners. However, couplings with aryl or alkenyl triflates have also been described. The major drawbacks for the use of such triflate derivatives are their relatively low stabilities at elevated temperature or under some reaction conditions and their elevated cost. Nevertheless, such coupling reactions provide an attractive procedure for the preparation of alkyl-aryl or alkyl-alkenyl derivatives, due to the very wide availability, low cost and protection capability of phenols and also to the common use of protected phenols or enols in total synthesis. Moreover, the phenolic group can be used as a means to introduce the desired functionality in the aromatic ring and then be converted into a carbon-carbon bond via the corresponding triflate.

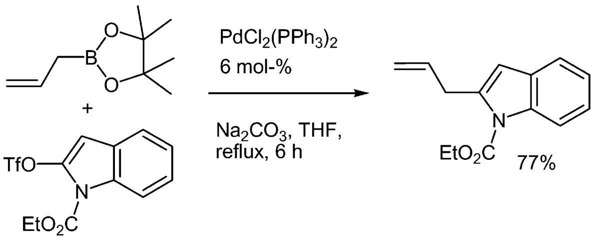
Several examples of cross-coupling reactions between primary alkylboronic acids and aryl triflates have been reported. Cockerill and co-workers and Langer and co-workers, for example, have introduced *n*-alkyl chains onto aryl triflates with $Pd(PPh_3)_4$ as catalyst (Scheme 56).[79,80] With $PdCl_2(dppf)$ as catalyst and Cs_2CO_3 or K_2CO_3 as bases, a variety of aryl triflates were coupled with methylboronic acid or 2-phenylboronic acid (Scheme 57).[16] The yields of the reactions with various aryl triflates were high regardless of the position of the functional group on the ring, and even the nitro group was tolerated. It should be noted that in general B-alkyl-9-BBN coupling reactions provide mixtures of reduced anilines with such substrates. With this catalytic system, however, the use of the electron-rich 4-methoxyphenyltriflate gave the desired product in only 15% yield. A similar procedure was recently employed for the synthesis of a precursor of a mycophenolic analogue.[81]



R	R'	Yield (%)
$PhCH_2CH_2$	4-COMe	97
$PhCH_2CH_2$	$4\text{-}NO_2$	93
$PhCH_2CH_2$	3-CN	93
$PhCH_2CH_2$	4-OMe	15
Me	4-COMe	85
Me	$4\text{-}NO_2$	80

Scheme 57.

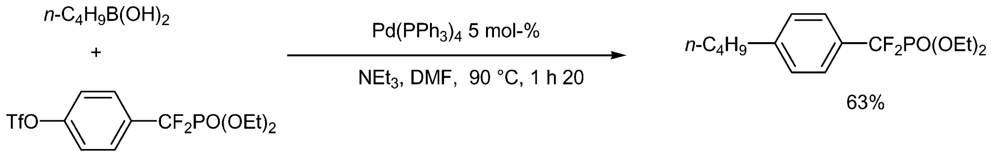
Couplings of aryl triflates with boronic esters or borates have also been described. A 2-trifluoromethanesulfonylindole has been 2-allylated by treatment with an allylboronic ester in the presence of $PdCl_2(PPh_3)_2$ as catalyst (Scheme 58).[82] With a boronate bearing a primary and a secondary alkyl chain in the presence of an aryl or a alkenyl triflate, the selective formation of the *n*-alkyl products was observed (Scheme 59).[64]



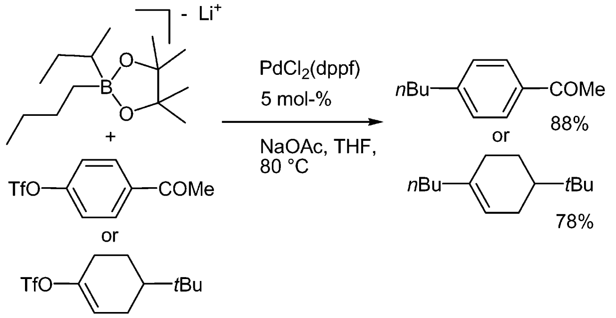
Scheme 58.

Two other examples of coupling reactions of primary alkylboronic acids with alkenyl triflates have been reported.[83,84] Again, in both cases, palladium associated to the bidentate phosphane ligand dppf was employed, but in one case Ag_2O was used as additive. The coupling products were obtained in high yields (Scheme 60 and Scheme 61).

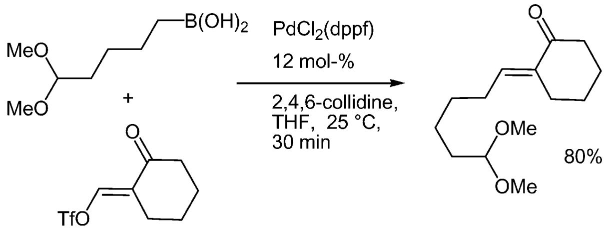
Couplings of secondary alkylboronic acids with aryl or alkenyl triflates seem to be limited to cyclopropylboronic acid derivatives. Several results with both aryl and alkenyl



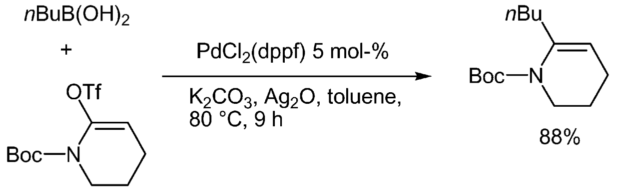
Scheme 56.



Scheme 59.

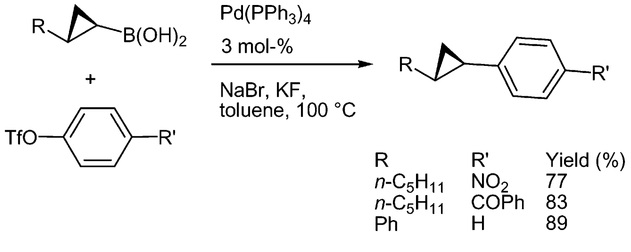


Scheme 60.



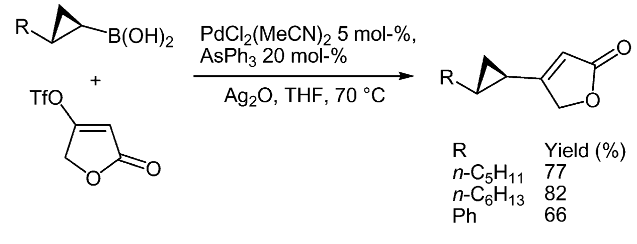
Scheme 61.

triflates have been reported by Yao and Deng.[85–88] In the presence of $Pd(PPh_3)_4$, KF or K_3PO_4 as bases and NaBr as additive, Suzuki-type reactions of aryl or heteroaryl triflates such as 4-nitro-, 4-benzoyl-, 4-acetyl- or 2-formylphenyltriflates[85] and also 2-pyridyl- or 2-quinolyltriflates[86] with *trans*-cyclopropylboronic acids proceed readily to give pure *trans*-cyclopropylarenes. In some cases phenyl-aryl exchange between the phenyl of $Pd(PPh_3)_4$ and the aryl of the triflate component occurs. Couplings of aryl triflates with optically active cyclopropylboronic acids, which were obtained in good enantiomeric excesses by asymmetric cyclopropanation of alkenylboronates with an optically pure tartaric acid derivative, have also been described. During the coupling reactions, the absolute configuration of the cyclopropyl group was retained (Scheme 62). The desired products were also obtained with alkenyl triflates. Substrates such as a β-tetronic triflate or cyclohexenyl or cyclopentenyl triflates have also been employed. Two procedures have been used. The first requires the presence of Ag_2O as additive[87] (Scheme 63). In the other procedure, on the other hand, the use of Ag_2O did not cause the alkenyl triflate to react with cyclopropenylboronic acids, and better results were obtained with $Pd(PPh_3)_4$ in the presence of Cs_2CO_3 and KF as bases in toluene (Scheme 64).[88]



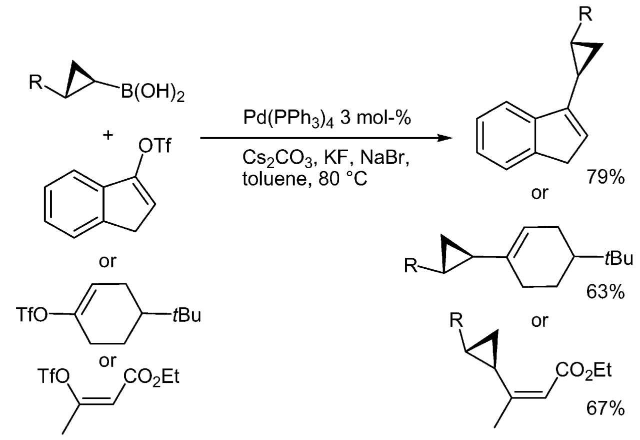
R	R'	Yield (%)
n-C_5H_{11}	NO_2	77
n-C_5H_{11}	COPh	83
Ph	H	89

Scheme 62.



R	Yield (%)
n-C_5H_{11}	77
n-C_6H_{13}	82
Ph	66

Scheme 63.



Scheme 64.

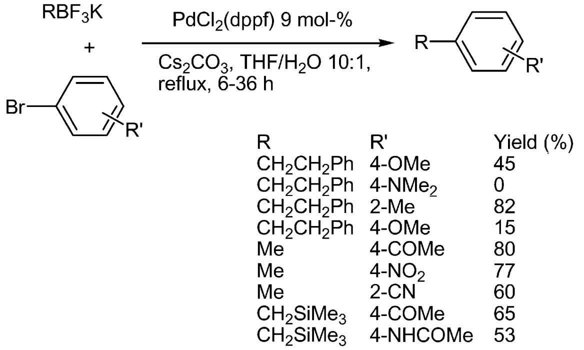
In summary, both aryl and alkenyl triflates are useful reactants for Suzuki cross-couplings with alkylboronic acids. Even if low catalyst loading procedures have not been described, the reactions allow couplings with a variety of primary alkylboronic acids and also cyclopropylboronic acids in high yields when appropriate reaction conditions are used. With cyclopropyl derivatives the retention of the chirality of the cyclopropyl group was observed. These procedures are very attractive, especially in total synthesis, due to the easy access to several phenol derivatives.

8. Alkylations of Aryl or Alkenyl Halides and Triflates with Alkyl Trifluoroborates

Organotrifluoroborates represent an alternative to boronic acids, boronates and organoboranes for Suzuki cross-couplings.[89,90] The trifluoroborate moiety is stable towards numerous functional groups that are sometimes problematic for other boron species. The tetracoordinate nature of the boron results in inhibition of undesired reactions observed in some cases with trivalent organoboron derivatives.

These compounds are monomeric, crystalline and stable in air or water. Moreover, they possess relatively low molecular weights, and the byproducts of the cross-coupling reactions are relatively benign. Functionalised alkyl trifluoroborates are readily available by a Grignard approach as well as by hydroboration of alkenes through several different hydroboration protocols.

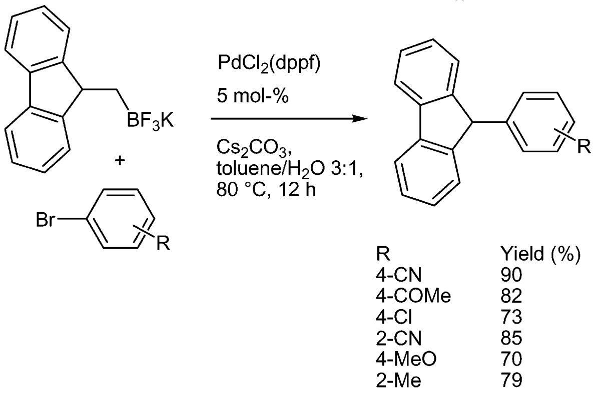
For Suzuki cross-couplings, primary alkyltrifluoroborates or cyclopropyltrifluoroborates have been employed in most cases. Both aryl and alkenyl halides and triflates have been coupled with these substrates. A large proportion of the results have been reported by Molander and coworkers.[89] For example, they have reported cross-couplings of methyl trifluoroborate, trimethylsilyl trifluoroborate or 2-phenylethyl trifluoroborate with a wide variety of aryl bromides (Scheme 65).[91] Good yields were in most cases obtained in the presence of electron-deficient aryl bromides. With electron-rich aryl bromides, on the other hand, the reactions generally led to lower yields. Molander and coworkers have also conducted cross-coupling reactions with functionalised alkyltrifluoroborates. For example, a potassium oxiranylethyltrifluoroborate was treated with 4-bromobenzonitrile as the electrophile. Under appropriate reaction conditions, the epoxide could be retained in the reaction to give an epoxyethylaryl system.[92] A potassium β-aminotrifluoroborate also gave the coupling products in good yields (Scheme 66).[93] With this reactant, both electron-rich and electron-poor aryl bromides have been employed.



R	R'	Yield (%)
CH_2CH_2Ph	4-OMe	45
CH_2CH_2Ph	4-NMe_2	0
CH_2CH_2Ph	2-Me	82
CH_2CH_2Ph	4-OMe	15
Me	4-COMe	80
Me	4-NO_2	77
Me	2-CN	60
CH_2SiMe_3	4-COMe	65
CH_2SiMe_3	4-NHCOMe	53

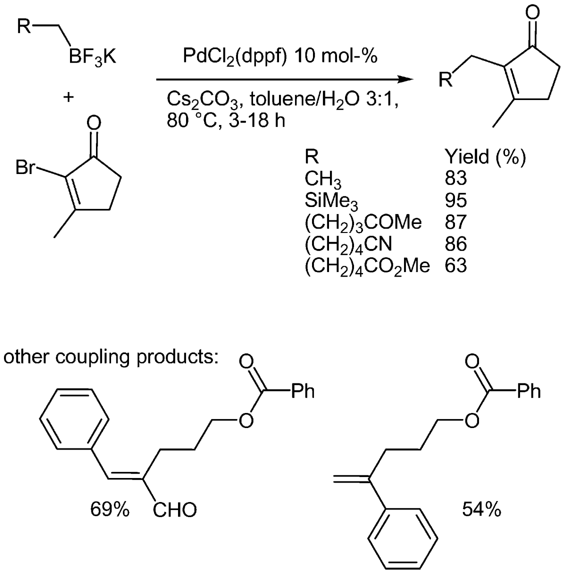
Scheme 65.

Under similar reaction conditions, the alkylation of various alkenyl bromides has been described. Relatively high catalyst loadings were employed (10 mol-%), but the coupling products were generally obtained in high yields (Scheme 67).[94,95] Several functionalised alkenyl bromides and alkyltrifluoroborates were employed. When alkyltrifluoroborates bearing ester substituents were used, the target compounds were accessed in excellent yields. Cyano- or thioether-substituted alkyltrifluoroborates could also be transformed into the desired products. In each case, only one stereoisomer was obtained. This reaction also allows the synthesis of trisubstituted 1,3-dienes from 2-bromo-1,3-diene derivatives (Scheme 68).[96]



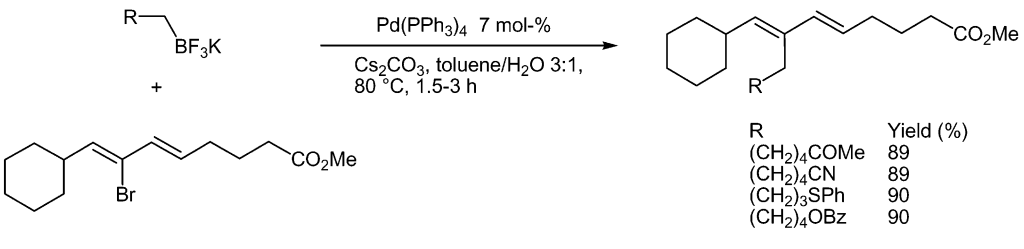
R	Yield (%)
4-CN	90
4-COMe	82
4-Cl	73
2-CN	85
4-MeO	70
2-Me	79

Scheme 66.



R	Yield (%)
CH_3	83
$SiMe_3$	95
$(CH_2)_3COMe$	87
$(CH_2)_4CN$	86
$(CH_2)_4CO_2Me$	63

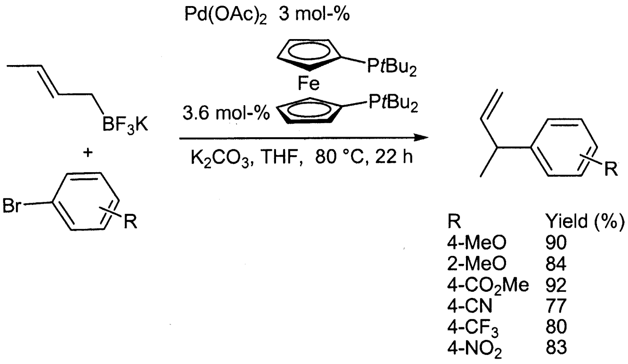
Scheme 67.



R	Yield (%)
$(CH_2)_4COMe$	89
$(CH_2)_4CN$	89
$(CH_2)_3SPh$	90
$(CH_2)_4OBz$	90

Scheme 68.

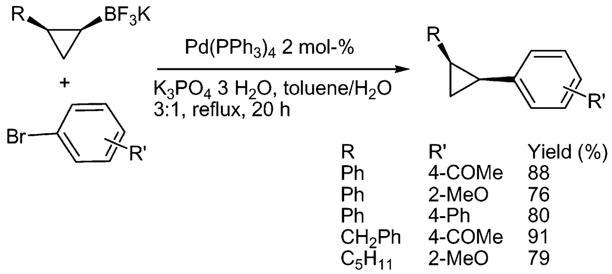
The selective cross-coupling of a substituted potassium allyltrifluoroborate with aryl bromides has recently been described.[97] The yields and coupling position selectivities were highly sensitive to the natures of the phosphane ligands. When an electron-rich bidentate ferrocenyl phosphane ligand was employed, selective arylation at the γ-carbon of the allyltrifluoroborate was observed (Scheme 69). Similar regioselectivity had been observed with substituted allylboronic acids.[36] *para*-, *meta*- or *ortho*-substituted electron-rich or electron-poor aryl bromides have been employed, and in all cases, the coupling products were obtained in high selectivities and yields.



R	Yield (%)
4-MeO	90
2-MeO	84
4-CO_2Me	92
4-CN	77
4-CF_3	80
4-NO_2	83

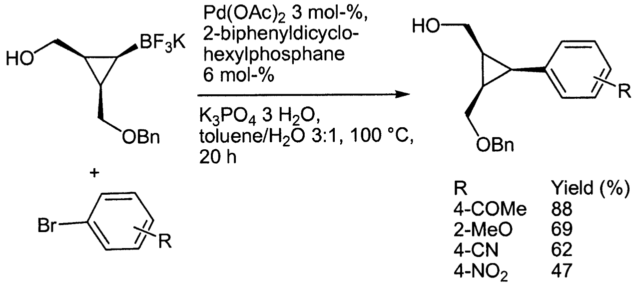
Scheme 69.

Secondary alkyltrifluoroborates have also been employed for Suzuki couplings, although the reactions seem to be limited to cyclopropyltrifluoroborates. The enhanced σ characters of the carbon-boron bonds in cyclopropyltrifluoroborates is certainly responsible for the specific reactivities of these substrates. They can be prepared in high yields by stereospecific cyclopropanation of alkenylboronic esters of pinacol followed by in situ treatment with excess KHF_2. These cyclopropyltrifluoroborates are monomeric, stable in air and easily purified. They underwent Suzuki cross-coupling reactions with electron-poor or electron-rich aryl bromides in the presence of $Pd(PPh_3)_4$ as catalyst and K_3PO_4 as base to give cyclopropyl-substituted arenes with retention of configuration (Scheme 70).[98] Couplings of bromobenzene or 2-bromonaphthalene with enantiomerically pure cyclopropyl trifluoroborate have also been reported.[59] In the presence of a 1,2,3-substituted potassium cyclopropyltrifluoroborate, stereoselective arylations with aryl bromides also gave the desired products (Scheme 71).[99]



R	R'	Yield (%)
Ph	4-COMe	88
Ph	2-MeO	76
Ph	4-Ph	80
CH_2Ph	4-COMe	91
C_5H_{11}	2-MeO	79

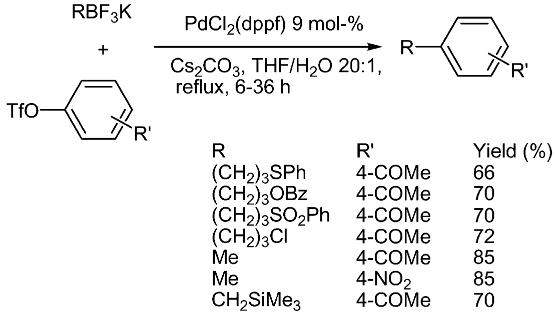
Scheme 70.



R	Yield (%)
4-COMe	88
2-MeO	69
4-CN	62
4-NO_2	47

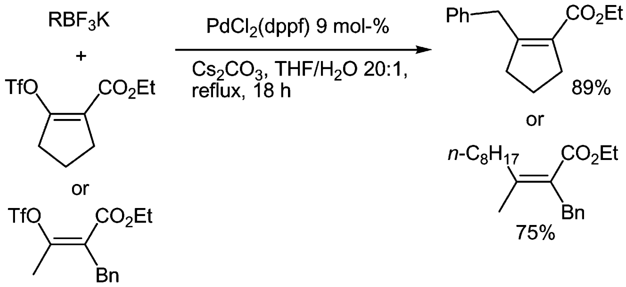
Scheme 71.

Finally, couplings of aryl or alkenyl triflates with primary alkyl trifluoroborates have been reported by Molander and co-workers (Scheme 72 and Scheme 73).[91,100,101] Yields very similar to those obtained with aryl bromides were observed. Several functionalities on the alkyl trifluoroborates and/or the aryl or alkenyl triflates are tolerated. The inclusion of water in the reaction mixtures appeared to be essential, and Cs_2CO_3 was determined to be the most effective base for such couplings.



R	R'	Yield (%)
$(CH_2)_3SPh$	4-COMe	66
$(CH_2)_3OBz$	4-COMe	70
$(CH_2)_3SO_2Ph$	4-COMe	70
$(CH_2)_3Cl$	4-COMe	72
Me	4-COMe	85
Me	4-NO_2	85
CH_2SiMe_3	4-COMe	70

Scheme 72.



Scheme 73.

In summary, alkyltrifluoroborates are effective alternatives for Suzuki cross-coupling reactions. Their air- and moisture-stability make them attractive synthetic intermediates.

9. Conclusion and Perspectives

The various recent modifications in coupling partners explored for Suzuki–Miyaura cross-couplings of alkylboronic acids or alkyltrifluoroborates demonstrate that this elegant reaction can currently be regarded as one of the most straightforward and powerful catalytic processes for the alkylation of aryl, alkenyl or alkyl halides. Several catalysts are available for the arylation of primary alkylboronic acids or alkyltrifluoroborates with aryl iodides, bromides or triflates. Even aryl chlorides have been used with the most efficient catalysts. Very high turnover numbers have been obtained by use of a polydentate phosphane ligand or an orthopalladated phosphinite complex. Couplings of cyclopropylboronic acids with aryl halides stereoselectively gave the corresponding alkyl-cyclopropyl derivatives. When chiral cyclopropylboronic acids were employed the chiralities were maintained. Alkylations of alkenyl bromides and iodides with primary alkylboronic acids or alkyltrifluoroborates were also stereoselective. Undoubtedly, these developments will help both synthetic and materials chemists a great deal, making Suzuki–Miyaura alkylation a valuable tool for diverse academic and industrial applications.

However, a number of challenges remain. Whilst a few systems for the arylation of readily available and low-cost aryl chlorides are in active use, the coupling chemistry of alkyl boron derivatives with alkenyl chlorides seems almost untouched. Moreover, the reactivity of secondary alkylboronic acids and the coupling of alkylboronic acids or alkyltrifluoroborates with alkyl bromides have to be extended. For most of these reactions, especially with alkenyl halides or secondary alkylboron derivatives, higher turnover numbers have to be obtained under industrial conditions.

With regard to catalytic cycles and elementary steps, it is also worthy of note that several studies involving catalytic systems carried out in parallel with Suzuki–Miyaura reactions on aryl- and alkylboronic acids have highlighted the fact that the systems are generally much less efficient when they are used in reactions of alkylboronic acids. A large number of questions concerning the mechanisms involved in these reactions remain unaddressed. The lower reactivities of primary and, especially, secondary alkylboronic acids probably originate from very slow transmetallation with palladium. Is it possible to accelerate this transmetallation step? Determining the origins of activity of palladium catalysts bearing mono, bi- or polydentate ligands for these cross-coupling reactions could allow further improvements in terms of the efficiency, mildness and scope of the reactions.

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[1] E. A. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, **2002**.

[2] N. Miyaura, *Cross-Coupling Reactions: A Practical Guide*, Springer, New York, **2002**.

[3] N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11.

[4] S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633–9695.

[5] P. Lloyd-Williams, E. Giralt, *Chem. Soc. Rev.* **2001**, *30*, 145–157.

[6] F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419–2440.

[7] G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275–286.

[8] M. Sato, N. Miyaura, A. Suzuki, *Chem. Lett.* **1989**, 1405–1408.

[9] S. W. Wright, D. L. Hageman, L. D. McClure, *J. Org. Chem.* **1994**, *59*, 6095–6097.

[10] M. Gray, I. P. Andrews, D. F. Hook, J. Kitteringham, M. Voyle, *Tetrahedron Lett.* **2000**, *41*, 6237–6240.

[11] C. Niu, J. Li, T. W. Doyle, S.-H. Chen, *Tetrahedron* **1998**, *54*, 6311–6318.

[12] M. Havelková, M. Hocek, M. Česnek, D. Dvořák, *Synlett* **1999**, 1145–1147.

[13] M. Havelková, D. Dvořák, M. Hocek, *Synthesis* **2001**, 1704–1710.

[14] B. Gómez-Lor, Ó. de Frutos, P. A. Ceballos, T. Granier, A. M. Echavarren, *Eur. J. Org. Chem.* **2001**, 2107–2114.

[15] G. Zou, Y. K. Reddy, J. R. Falck, *Tetrahedron Lett.* **2001**, *42*, 7213–7215.

[16] G. A. Molander, C.-S. Yun, *Tetrahedron* **2002**, *58*, 1465–1470.

[17] N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566.

[18] A. M. Maj, L. Delaude, A. Demonceau, A. F. Noels, *Tetrahedron* **2007**, *63*, 2657–2663.

[19] R. B. Bedford, C. P. Butts, T. E. Hurst, P. Lidström, *Adv. Synth. Catal.* **2004**, *346*, 1627–1630.

[20] C. M. So, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 2795–2798.

[21] R. B. Bedford, S. L. Hazelwood, P. N. Horton, M. B. Hursthouse, *Dalton Trans.* **2003**, 4164–4174.

[22] R. B. Bedford, S. L. Hazelwood, M. E. Limmert, D. A. Albisson, S. M. Draper, P. N. Scully, S. J. Coles, M. B. Hursthouse, *Chem. Eur. J.* **2003**, *9*, 3216–3227.

[23] F. Y. Kwong, W. H. Lam, C. H. Yeung, K. S. Chan, A. S. C. Chan, *Chem. Commun.* **2004**, 1922–1923.

[24] F. Y. Kwong, K. S. Chan, C. H. Yeung, A. S. C. Chan, *Chem. Commun.* **2004**, 2336–2337.

[25] K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2005**, *44*, 6173–6177.

[26] C. Song, Y. Ma, Q. Chai, C. Ma, W. Jiang, M. B. Andrus, *Tetrahedron* **2005**, *61*, 7438–7446.

[27] L. Botella, C. Nájera, *Angew. Chem. Int. Ed.* **2002**, *41*, 179–181.

[28] L. Botella, C. Nájera, *J. Organomet. Chem.* **2002**, *663*, 46–57.

[29] R. Ortiz, M. Yus, *Tetrahedron* **2005**, *61*, 1699–1707.

[30] C. Nájera, J. Gil-Moltó, S. Karlström, *Adv. Synth. Catal.* **2004**, *346*, 1798–1811.

[31] I. Kondolff, H. Doucet, M. Santelli, *Tetrahedron* **2004**, *60*, 3813–3818.

[32] X. Zhou, M. K. Tse, T. S. M. Wan, K. S. Chan, *J. Org. Chem.* **1996**, *61*, 3590–3593.

[33] K. Nilsson, A. Hallberg, *Acta Chem. Scand. Ser. B* **1987**, *41*, 569–576.

[34] S. Kotha, M. Behera, V. R. Shah, *Synlett Synlett* **2005**, 1877–1880.

[35] V. N. Kalinin, F. S. Denisov, Y. N. Bubnov, *Mendeleev Commun.* **1996**, 206–207.

[36] S. Sebelius, V. J. Olsson, O. A. Wallner, K. J. Szabó, *J. Am. Chem. Soc.* **2006**, *128*, 8150–8151.

[37] G. W. Kabalka, R. M. Pagni, C. M. Hair, *Org. Lett.* **1999**, *1*, 1423–1425.

[38] G. W. Kabalka, L. Wang, R. M. Pagni, C. M. Hair, V. Namboodiri, *Synthesis* **2003**, 217–222.

[39] A. Cwik, Z. Hell, F. Figueras, *Org. Biomol. Chem.* **2005**, *3*, 4307–4309.

[40] A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts, A. J. Whitehead, *Org. Lett.* **2006**, *8*, 4071–4074.

[41] B. D. Stevens, C. J. Bungard, S. G. Nelson, *J. Org. Chem.* **2006**, *71*, 6397–6402.

[42] A. Hu, H. L. Ngo, W. Lin, *Angew. Chem. Int. Ed.* **2004**, *43*, 2501–2504.

[43] H. L. Ngo, W. Lin, *J. Org. Chem.* **2005**, *70*, 1177–1187.

[44] F.-l. Qing, R. Wang, X. Li, B. Zheng, W.-D. Meng, *J. Fluorine Chem.* **2003**, *120*, 21–24.

[45] J. E. Harvey, M. N. Kenworthy, R. J. K. Taylor, *Tetrahedron Lett.* **2004**, *45*, 2467–2471.

[46] C. W. Barfoot, J. E. Harvey, M. N. Kenworthy, J. P. Kilburn, M. Ahmed, R. J. K. Taylor, *Tetrahedron* **2005**, *61*, 3403–3417.

[47] P. D. Johnson, J.-H. Sohn, V. H. Rawal, *J. Org. Chem.* **2006**, *71*, 7899–7902.

[48] F. Hof, A. Schütz, C. Fäh, S. Meyer, D. Bur, J. Liu, D. E. Goldberg, F. Diederich, *Angew. Chem. Int. Ed.* **2006**, *45*, 2138–2141.

[49] J. P. Hildebrand, S. P. Marsden, *Synlett* **1996**, 893–894.

[50] X.-Z. Wang, M.-Z. Deng, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2663–2664.

[51] H.-R. Ma, X.-H. Wang, M.-Z. Deng, *Synth. Commun.* **1999**, *29*, 2477–2485.

[52] S.-M. Zhou, M.-Z. Deng, L.-J. Xia, M.-H. Tang, *Angew. Chem. Int. Ed.* **1998**, *37*, 2845–2847.

[53] J. Pietruszka, M. Widenmeyer, *Synlett* **1997**, 977–979.

[54] J. E. A. Luithle, J. Pietruszka, *J. Org. Chem.* **1999**, *64*, 8287–8297.

[55] J. E. A. Luithle, J. Pietruszka, *J. Org. Chem.* **2000**, *65*, 9194–9200.

[56] J. Pietruszka, A. Witt, W. Frey, *Eur. J. Org. Chem.* **2003**, 3219–3229.

[57] M. Rubina, M. Rubin, V. Gevorgyan, *J. Am. Chem. Soc.* **2003**, *125*, 7198–7199.

[58] S. Löhr, A. de Meijere, *Synlett* **2001**, 489–492.

[59] E. Hohn, J. Pietruszka, G. Solduga, *Synlett* **2006**, 1531–1534.

[60] D. J. Wallace, C.-y. Chen, *Tetrahedron Lett.* **2002**, *43*, 6987–6990.

[61] M. Lemhadri, H. Doucet, M. Santelli, *Synth. Commun.* **2006**, *36*, 121–128.

[62] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

[63] I. Kondolff, H. Doucet, M. Santelli, *Organometallics* **2006**, *25*, 5219–5222.

[64] G. Zou, J. R. Falck, *Tetrahedron Lett.* **2001**, *42*, 5817–5819.

[65] J. R. Falck, P. S. Kumar, Y. K. Reddy, G. Zou, J. H. Capdevila, *Tetrahedron Lett.* **2001**, *42*, 7211–7212.

[66] S. Q. Liu, S. W. Wang, F.-L. Qing, *J. Fluorine Chem.* **2005**, *126*, 771–778.

[67] F. Bellina, C. Anselmi, R. Rossi, *Tetrahedron Lett.* **2001**, *42*, 3851–3854.

[68] A. Larivée, A. B. Charette, *Org. Lett.* **2006**, *8*, 3955–3957.

[69] S. Ma, X. Jiang, X. Cheng, H. Hou, *Adv. Synth. Catal.* **2006**, *348*, 2114–2124.

[70] C. M. Nunes, D. Steffens, A. L. Monteiro, *Synlett* **2007**, 103–106.

[71] S.-M. Zhou, Y.-L. Yan, M.-Z. Deng, *Synlett* **1998**, 198–200.

[72] S.-M. Zhou, M.-Z. Deng, *Tetrahedron Lett.* **2000**, *41*, 3951–3954.

[73] P.-A. Wang, M.-Z. Deng, R.-Q. Pan, S.-Y. Zhang, *J. Fluorine Chem.* **2003**, *124*, 93–97.

[74] A. B. Charette, R. Pereira De Freitas-Gil, *Tetrahedron Lett.* **1997**, *38*, 2809–2812.

[75] H. Chen, M.-Z. Deng, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1609–1613.

[76] H. Chen, M.-Z. Deng, *J. Org. Chem.* **2000**, *65*, 4444–4446.

[77] J. H. Kirchhoff, M. R. Netherton, I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.

[78] T. Brenstrum, D. A. Gerristma, G. M. Adjabeng, C. S. Frampton, J. Britten, A. J. Robertson, J. McNulty, A. Capretta, *J. Org. Chem.* **2004**, *69*, 7635–7639.

[79] G. S. Cockerill, H. J. Easterfield, J. M. Percy, S. Pintat, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2591–2599.

[80] Z. Ahmed, P. Langer, *Eur. J. Org. Chem.* **2006**, 1057–1060.

[81] M. Fardis, M. Mertzman, W. Thomas, T. Kirschberg, N. Collin, R. Polniaszek, W. J. Watkins, *J. Org. Chem.* **2006**, *71*, 4835–4839.

[82] E. Rossi, G. Abbiati, V. Canevari, G. Celentano, E. Magri, *Synthesis* **2006**, 299–304.

[83] L. E. Overman, L. D. Pennington, *Can. J. Chem.* **2000**, *78*, 732–738.

[84] E. G. Occhiato, A. Trabocci, A. Guarna, *J. Org. Chem.* **2001**, *66*, 2459–2465.

[85] M.-L. Yao, M.-Z. Deng, *Synthesis* **2000**, 1095–1100.

[86] M.-L. Yao, M.-Z. Deng, *New J. Chem.* **2000**, *24*, 425–428.

[87] M.-L. Yao, M.-Z. Deng, *J. Org. Chem.* **2000**, *65*, 5034–5036.

[88] M.-L. Yao, M.-Z. Deng, *Tetrahedron Lett.* **2000**, *41*, 9083–9087.

[89] G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275–286.

[90] S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2003**, 4313–4327.

[91] G. A. Molander, C.-S. Yun, M. Ribagorda, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 5534–5539.

[92] G. A. Molander, M. Ribagorda, *J. Am. Chem. Soc.* **2003**, *125*, 11148–11149.

[93] G. A. Molander, F. Vargas, *Org. Lett.* **2007**, *9*, 203–206.

[94] G. A. Molander, J. Ham, D. G. Seapy, *Tetrahedron* **2007**, *63*, 768–775.

[95] G. A. Molander, R. Figueroa, *Org. Lett.* **2006**, *8*, 75–78.

[96] G. A. Molander, Y. Yokoyama, *J. Org. Chem.* **2006**, *71*, 2493–2498.

[97] Y. Yamamoto, S. Takada, N. Miyaura, *Chem. Lett.* **2006**, *35*, 704–705.

[98] G.-H. Fang, Z.-J. Yan, M.-Z. Deng, *Org. Lett.* **2004**, *6*, 357–360.

[99] A. B. Charette, S. Mathieu, J.-F. Fournier, *Synlett* **2005**, 1779–1782.

[100] G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393–396.

[101] G. A. Molander, D. Pfeiffer, *Org. Lett.* **2001**, *3*, 361–363.

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