1.1.4 Alkylboron Cross-Coupling Reactions

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General Introduction

The ability to append alkyl moieties onto preexisting molecular scaffolds is of significant interest owing to the breadth of the diversified compounds that can be accessed in late stage synthesis. There are a number of procedures that are capable of incorporating alkyl subunits into organic molecules; however, many of these strategies are limited in scope. In particular, the highly reactive nature of organomagnesium compounds used in the Kumada–Corriu reaction limits their use to molecules that are virtually void of any reactive functional group. Less electropositive metals are also used in this context to overcome the limitations associated with highly reactive species; however, many of these organometallic reagents require careful in situ preparation and use, owing to their highly air- and moisture-sensitive nature. In response to the growing need for a class of bench-stable alkylmetal reagents, organotin and organoboron compounds have come to the fore. However, the perceived toxicity associated with organotin compounds has led to the *B*-alkyl Suzuki–Miyaura cross-coupling reaction becoming the platform of choice to accomplish this desired bond formation.

1.1.4.1 The *B*-Alkyl Suzuki–Miyaura Reaction

Owing to the importance of the *B*-alkyl Suzuki–Miyaura reaction in the industrial, medicinal, and academic communities, new advances in the assembly of complex molecules are frequently reported. The use of sp^3-organometallics is plagued by competitive protodeboronation and β-hydride elimination, and by a relatively slow transmetalation step, which results in low product yields and long reaction times. Since the first report detailing the cross coupling of an alkylboron reagent was described in 1986,[1] the reaction platform has matured dramatically, and the highlights are described in this review.

1.1.4.1.1 Classes of Alkylboron Reagents

Since the original disclosure of the Suzuki–Miyaura reaction in 1979,[2] tremendous efforts have been devoted to diversifying the nucleophilic partner employed. With respect to the alkyl derivative, the nucleophilic partner can be broken down into three main classes: trialkylboranes (Section 1.1.4.1.1.1), alkylboronic acids and alkylboronate esters (Section 1.1.4.1.1.2), and alkyltrifluoroborates and *N*-methyliminodiacetic acid (MIDA) boronates (Section 1.1.4.1.1.3).

1.1.4.1.1.1 Trialkylboranes

Trialkylboranes are often employed as the nucleophilic partner in the Suzuki–Miyaura reaction owing to the ease with which the trialkylborane unit can be incorporated into molecules. They are easily accessed via hydroboration of the corresponding alkenes or alkynes with a host of dialkylborane derivatives. The cross coupling with these derivatives has been optimized extensively in the literature; however, their use is often limited owing to the incompatibility of the corresponding hydroborating agent with preexisting func-

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tional groups in the molecule. Additionally, the air sensitivity associated with the resulting trialkylborane requires their use immediately upon reagent preparation. Thus, many of the examples utilizing this reaction platform prepare and use the trialkylborane species in situ.

1.1.4.1.1.2 Alkylboronic Acids and Alkylboronate Esters

Alkylboronic acids and alkylboronate esters are also used as the organoboron derivative in the *B*-alkyl Suzuki–Miyaura reaction. These compounds are readily prepared from organomagnesium and -lithium complexes and through hydroboration/borylation approaches with catecholborane-, pinacolborane-, and tetrahydroxydiboron-based boron sources. Reactions employing alkylboronic acids as the nucleophilic partner tend to suffer from varying degrees of protodeboronation and β-hydride elimination; therefore, superstoichiometric quantities of the reagents are often used. Although the alkylboronate ester analogues have a decreased propensity for these side reactions, coupling reactions employing this class of reagent proceed very sluggishly and lead to low yields unless highly toxic thallium bases (TlOH or Tl_2CO_3) are added to promote transmetalation.

1.1.4.1.1.3 Alkyltrifluoroborates and *N*-Methyliminodiacetic Acid (MIDA) Boronates

Some of the most significant advances, with respect to the development of the nucleophilic partner, have come from the use of alkyltrifluoroborates and *N*-methyliminodiacetic acid (MIDA) boronates (particularly the cyclopropyl derivatives). These compounds are prepared via a host of methods and, once prepared, most of them are indefinitely stable to air and moisture. Many functionalized alkyltrifluoroborates have been prepared and utilized in cross-coupling reactions, revealing the active cross-coupling species in situ from a partial or complete hydrolysis under basic aqueous/protic conditions.

N-Methyliminodiacetic acid boronates are stable, protected forms of the boronic acid that also undergo a deprotection step to reveal the active boronic acid in situ by a slow release method or in a step prior to the cross-coupling reaction. The highly bench-stable nature of these compounds and the alkyltrifluoroborates described above validate their use as suitable reagents for the *B*-alkyl Suzuki–Miyaura cross-coupling reaction.

1.1.4.1.2 General Mechanistic Considerations

The general mechanism for the *B*-alkyl Suzuki–Miyaura reaction entails the oxidative addition of the electrophilic organic halide or pseudohalide to the active palladium(0) species, followed by transmetalation of the alkylboron component and, finally, reductive elimination to generate the cross-coupled product and regenerate the palladium(0) catalyst.

1.1.4.1.2.1 Oxidative Addition

The oxidative addition is described as the catalytic step that limits the turnover of the reaction; thus, the electronic nature of the electrophile utilized has a great impact on the catalyst turnover and reaction rate. Recent advances detail the use of sterically demanding, electron-rich phosphine ligands to facilitate the oxidative addition step.[3,4]

1.1.4.1.2.2 Transmetalation

The relatively slow transmetalation step in the *B*-alkyl Suzuki–Miyaura reaction is a result of the low nucleophilicity associated with the transferring alkyl group of an organoboron derivative. Since the discovery of the reaction, it has been observed that base is required

to promote product formation, and the choice of the base used greatly influences product formation.

Much debate has surrounded the role of the base in the catalytic cycle. It has been suggested that the main role of the base is to react with the organoboron species to generate a more nucleophilic "ate" complex that can coordinate with the palladium intermediate to provide a substrate that is favorably poised for alkyl transfer.[5] This is particularly important for alkyl derivatives, which are known to undergo transmetalation more slowly. More recent investigations detail studies related to aryl cross-coupling reactions, which, while significant, will not be discussed here.[6,7]

The nature of the organoboron species plays an important role in the transmetalation step. Electron-rich, primary alkylborane species are known to react most readily as the nucleophilic partner, and the corresponding secondary alkyl species react much more slowly. The rate of transmetalation has also been found to be dependent on the Lewis acidity of the organoboron species used.[8]

The stereochemistry of the transmetalation step has been studied independently by two groups,[8,9] who both observed that this step proceeds with retention of configuration. Soderquist proposed the formation of a four-centered transition state, and Woerpel deduced the stereochemical retention from a deuterium-labeling experiment using diastereomers prepared from hydroboration of a dideuterioalkene with 9-borabicyclo-[3.3.1]nonane.

More recently, examples have been disclosed of stereodefined alkylorganoboron derivatives that undergo transmetalation with inversion of configuration.[10,11] In each of these cases, the opposite stereochemical outcome is favored as a result of intramolecular coordination that occurs within the transmetalated species.

1.1.4.1.2.3 Reductive Elimination

Owing to the propensity of alkyl substituents on intermediate diorganopalladium species to undergo β-hydride elimination, care must be taken in choosing the proper ligands to facilitate reductive elimination over other side-reactions. In the past, bidentate ligands have been favored to enforce a *cis* arrangement of the organic species on the diorganopalladium complex and thus limit side reactions. More recent advances have detailed the use of electron-rich, sterically-encumbered, monocoordinated ligand complexes to induce a more rapid reductive elimination step. The steric hindrance associated with these ligands decreases the propensity for the β-hydride elimination pathway.

1.1.4.2 Cross Coupling of Primary Alkylboron Derivatives

In the early 1970s, Kochi,[12] Kumada,[13] and Corriu[14] independently reported the use of alkyl Grignard reagents with alkenyl and aryl electrophiles, and Negishi[15] extended these works to include the use of alkylzinc reagents. Since these early reports, the cross coupling of primary alkylboron derivatives has been extensively explored. The reaction scope has been expanded to include the cross coupling of standard alkylboron derivatives with aryl, hetaryl, alkenyl, and alkyl electrophiles. Additionally, a number of specialized primary alkylboron derivatives can participate in this reaction.

1.1.4.2.1 Cross Coupling of Trialkylboranes

Unhindered, electron-rich organoboranes are generally the most reactive nucleophilic partner in the Suzuki–Miyaura reaction, and these substrates have been shown to be suitable reaction partners for a variety of electrophilic species.

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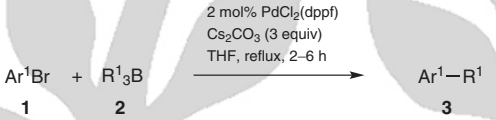
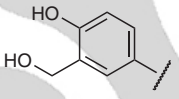
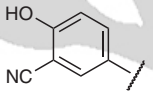
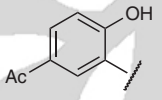
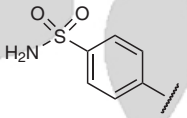
1.1.4.2.1.1 With Aryl Electrophiles

Primary alkylboranes can be cross coupled with a variety of aryl electrophiles. In particular, the cross coupling of trialkylboranes **2** with aryl and hetaryl bromides **1** to give alkylarenes **3** can be accomplished using [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) in combination with cesium carbonate and tetrahydrofuran (Scheme 1).[16] These conditions are amenable to the presence of a number of functional groups, including aldehydes, ketones, nitriles, and various protecting groups.

Scheme 1 Cross Coupling of Trialkylboranes with Aryl and Hetaryl Bromides[16]



Ar^1	R^1	Yield (%)	Ref
	Et	73	[16]
	Bu	95	[16]
indol-5-yl	Et	85	[16]
	Et	70	[16]
	Et	88	[16]
3-pyridyl	Bu	88	[16]
3-quinolyl	Et	90	[16]

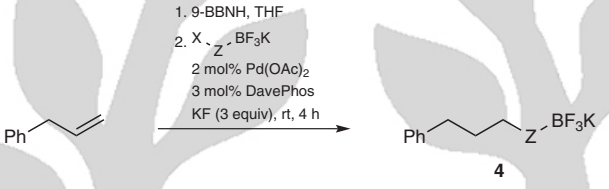
Alkylarenes 3; General Procedure:[16]

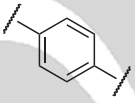
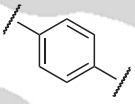
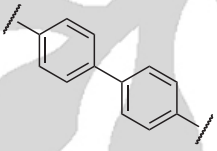
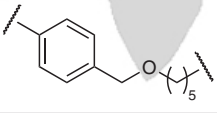
To an argon-purged Schlenk tube, containing a mixture of the bromoarene **1** (1.0 mmol), Cs_2CO_3 (977 mg, 3.0 mmol), and $PdCl_2$(dppf) (15 mg, 0.02 mmol), was added freshly distilled THF (2 mL). To the mixture was added a 1 M soln of the trialkylborane **2** in THF (3.0 mL, 3.0 mmol), and the mixture was refluxed for 2–6 h, cooled to 0 °C, and quenched with NaOH and 30% aq H_2O_2. After warming to rt, the mixture was stirred for 30 min at 25 °C, acidified with dil aq HCl, and extracted with Et_2O (3 ×). The combined organic layers were washed with aq $FeSO_4$ and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was purified by flash chromatography.

1.1.4.2.1.2 With (Haloaryl)trifluoroborates

The cross coupling of trialkylboranes with halo-substituted aryltrifluoroborates to give [(3-phenylpropyl)aryl]trifluoroborates **4** has been demonstrated with complete selectivity. Utilizing palladium(II) acetate and 2-(dicyclohexylphosphino)-2′-(dimethylamino)biphenyl (DavePhos), this cross-coupling strategy is amenable to the use of both aryl bromides and chlorides (Scheme 2).[17]

Scheme 2 Cross Coupling of a Trialkylborane with (Haloaryl)trifluoroborates[17]



Z	X	Yield (%)	Ref
	Br	91	[17]
	Cl	85	[17]
	Br	81	[17]
	Br	71	[17]

[(3-Phenylpropyl)aryl]trifluoroborates 4; General Procedure:[17]

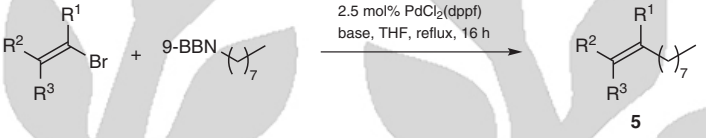
In a glovebox, into a 10-mL Biotage microwave vial was added 9-BBNH dimer (67.1 mg, 0.55 mmol). The reaction vessel was sealed with a PTFE-lined septum and removed from the glovebox. Under N_2, anhyd THF (4 mL) was added, and the mixture was allowed to stir for 5 min. Allylbenzene (65.0 mg, 0.55 mmol) was added dropwise to the vial and the resulting mixture was allowed to stir for 2 h at rt. Into a separate 10-mL Biotage microwave vial were added $Pd(OAc)_2$ (2.20 mg, 0.01 mmol), DavePhos (5.90 mg, 0.015 mmol), KF (87.2 mg, 1.50 mmol), and the (haloaryl)trifluoroborate (0.50 mmol). The vial was purged with N_2, and the THF mixture containing the trialkylborane species was added dropwise to it via a double-ended needle. The mixture was stirred at rt and, after 4 h, the mixture was concentrated, the residue was dissolved in acetone (50 mL), and the soln was filtered through Celite. The filtrate was concentrated, the crude trifluoroborate was dissolved in a minimal amount of hot acetone (2 mL), and Et_2O was added to precipitate the product.

for references see p 357

1.1.4.2.1.3 With Alkenyl Electrophiles

One of the most widely used *B*-alkyl Suzuki–Miyaura reactions is the cross coupling of alkylboranes with alkenyl electrophiles to give alkylalkenes such as **5**. A variety of reports have outlined the cross coupling of 9-alkyl-9-borabicyclo[3.3.1]nonanes with alkenyl electrophiles using [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Scheme 3).[18]

Scheme 3 Cross Coupling of a Trialkylborane with Alkenyl Bromides[18]



5

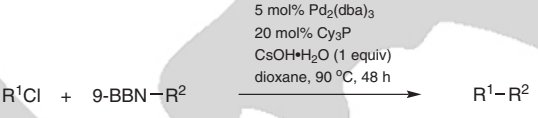
R^1	R^2	R^3	Base (Equiv)	Yield (%)	Ref
H	Ph	H	3 M aq NaOH (3)	85	[18]
H	H	Ph	3 M aq NaOH (3)	90	[18]
H	Me	Me	3 M aq NaOH (3)	94	[18]
Me	H	Me	3 M aq NaOH (3)	98	[18]
H	$(CH_2)_5Me$	H	NaOMe (1.5)	75	[18]

Alkylalkenes, e.g. 5; General Procedure:[18]
To prepare the trialkylborane, a soln of the corresponding alkene (oct-1-ene in the case illustrated in Scheme 3; 0.56 mmol) was prepared in THF (4 mL) and to it was added a soln of 9-BBNH (0.59 mmol) in THF at 0 °C, and the mixture was stirred at rt. After 6 h, $PdCl_2$(dppf) (0.015 mmol), 3 M aq NaOH (0.6 mL, 1.8 mmol), and the alkenyl halide (0.62 mmol) were added, and the mixture was heated to reflux. After 16 h, the reaction was quenched, and the crude product was purified by column chromatography (silica gel).

1.1.4.2.1.4 With Alkyl Electrophiles

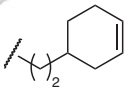
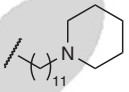
Alkyl iodides undergo cross coupling with alkylboranes in the presence of tetrakis(triphenylphosphine)palladium(0). More recently, the scope of the sp^3—sp^3 Suzuki–Miyaura cross coupling has been extended to include the union of alkylboranes and alkyl chlorides to give coupled alkanes **6** (Scheme 4).[19] This reaction, which is promoted by tris(dibenzylideneacetone)dipalladium(0), is tolerant of a variety of functional groups, including nitriles and amines.

Scheme 4 Cross Coupling of Trialkylboranes with Alkyl Chlorides[19]



6

R^1	R^2	Yield (%)	Ref
$(CH_2)_{11}Me$	$(CH_2)_7Me$	83	[19]
$(CH_2)_4Me$	$4\text{-}MeOC_6H_4(CH_2)_3$	82	[19]
$(CH_2)_2iPr$	$(CH_2)_5OBn$	74	[19]

R^1	R^2	Yield (%)	Ref
$(CH_2)_3CH(OEt)_2$	$(CH_2)_5OBn$	70	[19]
$(CH_2)_6OTBDMS$		72	[19]
$(CH_2)_6OTBDMS$		73	[19]
$(CH_2)_6CN$	$(CH_2)_7Me$	73	[19]

Alkanes 6; General Procedure:[19]
To an argon-purged vial equipped with a septum screw cap was added a terminal alkene (1.20 mmol) followed by a 0.50 M soln of 9-BBNH in THF (2.4 mL, 1.20 mmol), and the resulting soln was stirred for 6 h at rt. After the hydroboration was complete, the THF was removed under reduced pressure and dioxane (0.9 mL) was added. Into a second vial were added $Pd_2(dba)_3$ (45.8 mg, 0.05 mmol), Cy_3P (56.0 mg, 0.20 mmol), and $CsOH•H_2O$ (185 mg, 1.10 mmol). The vial was capped with a septum screw cap and purged with argon, and then dioxane (0.3 mL) was added. Then, the borane soln was transferred via cannula to the reaction vial and the vial which had contained the borane was rinsed with dioxane (2 × 0.3 mL). The alkyl chloride (1.00 mmol) was then added to the mixture, which was stirred vigorously for 48 h at 90 °C under an argon atmosphere. The mixture was allowed to cool to rt, diluted with Et_2O (5 mL), and filtered through a plug of silica gel, eluting with Et_2O (30 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography.

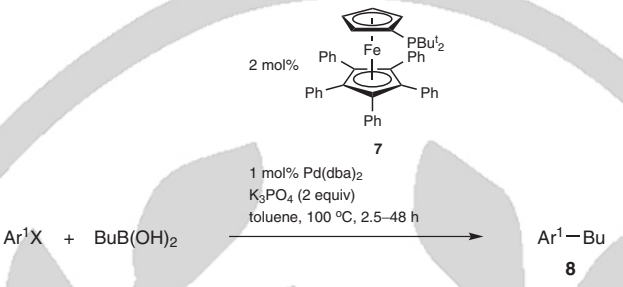
1.1.4.2.2 Cross Coupling of Alkylboronic Acids or Alkylboronate Esters

Although the strategies described in Section 1.1.4.2.1 are carried out extensively and quite successfully, their main limitation is the limited opportunity for purification of the intermediate trialkylborane. Alternatively, alkylboronic acids and derived esters are advantageous in this regard because their air and water stability permit purification before use in cross-coupling reactions. Until recently, alkylboronic acids and esters have seen limited use in cross-coupling strategies owing to their sluggish reactivity; however, recent developments in catalysts and electron-rich or polydentate ligand systems have expanded their use.

1.1.4.2.2.1 Of Alkylboronic Acids with Aryl Electrophiles

One of the most robust strategies described for the cross coupling of alkylboronic acids with aryl bromides and chlorides, to give alkylated arenes **8**, involves the use of a palladium complex of sterically hindered electron-rich (di-*tert*-butylphosphino)ferrocene ligand **7** as the catalyst (Scheme 5).[20]

Scheme 5 Cross Coupling of an Alkylboronic Acid with Aryl Halides[20]



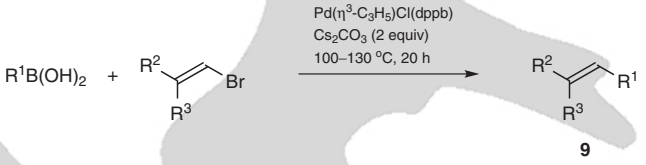
Ar^1	X	Yield (%)	Ref
4-*t*-BuC$_6$H$_4$	Br	82	[20]
4-MeOC$_6$H$_4$	Br	83	[20]
2-MeOC$_6$H$_4$	Cl	94	[20]
4-NCC$_6$H$_4$	Cl	97	[20]
3-MeOC$_6$H$_4$	Cl	94	[20]
2-Tol	Cl	88	[20]

Butylbenzenes 8; General Procedure:[20]
In a drybox, the aryl halide (1.00 mmol), Pd(dba)$_2$ (5.8 mg, 0.01 mmol), ligand **7** (14.2 mg, 0.02 mmol), powdered K$_3$PO$_4$ (430 mg, 2.02 mmol), the alkylboronic acid (1.21 mmol), and toluene (2 mL) were added to a vial, which was then capped with a PTFE-lined septum. The vial was removed from the drybox and the contents were stirred at 100 °C for 2.5–48 h. The reaction was monitored by GC and, upon complete consumption of the electrophile, the mixture was allowed to cool to rt and purified by column chromatography (silica gel).

1.1.4.2.2.2 Of Alkylboronic Acids with Alkenyl Electrophiles

The cross coupling of alkylboronic acids and alkenyl halides has only been described to a limited extent in the literature; however, a reliable procedure to effect this transformation, giving coupled alkenes **9** in modest yields, is available using allylchloro[1,4-bis(diphenylphosphino)butane]palladium(II) (Scheme 6).[21] Lastly, although still an immature area in alkylboron chemistry, a single example exists that partners an alkylboronic acid with an alkyl bromide electrophile.[22]

Scheme 6 Cross Coupling of Alkylboronic Acids with Alkenyl Bromides[21]



R^1	R^2	R^3	Catalyst (mol%)	Solvent	Temp (°C)	Yield (%)	Ref
(CH$_2$)$_7$Me	Ph	H	1	xylene	130	51	[21]
(CH$_2$)$_3$Ph	Ph	H	2	xylene	130	47	[21]
(CH$_2$)$_2$Ph	Me	Me	2	toluene	100	64	[21]
(CH$_2$)$_3$Ph	Me	Me	2	toluene	100	63	[21]

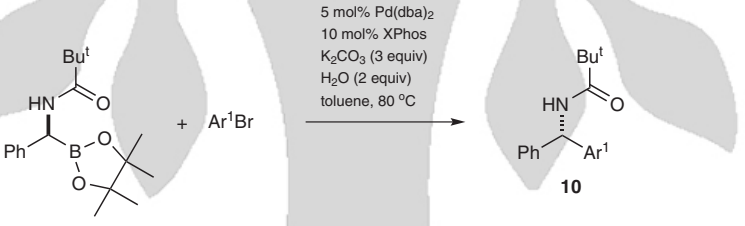
R^1	R^2	R^3	Catalyst (mol%)	Solvent	Temp (°C)	Yield (%)	Ref
$(CH_2)_7Me$	Me	Me	1	toluene	100	60	[21]
$(CH_2)_{11}Me$	Me	Me	2	xylene	110	63	[21]
$(CH_2)_2Ph$	H	Me	2	toluene	100	67	[21]
$(CH_2)_3Ph$	H	Me	2	toluene	100	65	[21]

Alkylalkenes 9; General Procedure:[21]
Into a flask under an argon atmosphere was added the alkenyl halide (1 mmol), the alkylboronic acid (2 mmol), Cs_2CO_3 (652 mg, 2 mmol), and Pd(η³-C_3H_5)Cl(dppb). The mixture was heated to 100–130 °C with stirring for 20 h. The mixture was then diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the product was purified by column chromatography (silica gel).

1.1.4.2.2.3 Of Alkylboronate Esters with Aryl Electrophiles

Although alkylboronate esters do not readily participate in the Suzuki–Miyaura cross-coupling reaction unless highly toxic thallium bases or lithium reagents are added,[23] the cross coupling of stereodefined α-(acylamino)benzylboronate esters with aryl bromides has been demonstrated. The enantiospecificity (es) of the reaction is defined as follows: $es = ee_{product}/ee_{starting\ material} \times 100$, and it represents the conservation of enantiomeric purity over the course of the reaction.[10] Using bis(dibenzylideneacetone)palladium(0) and 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl (XPhos), the reaction gives propanamides **10** in good yields with inversion of configuration (Scheme 7).

Scheme 7 Cross Coupling of an α-(Acylamino)benzylboronate Ester with Aryl Bromides with Inversion of Configuration[10]



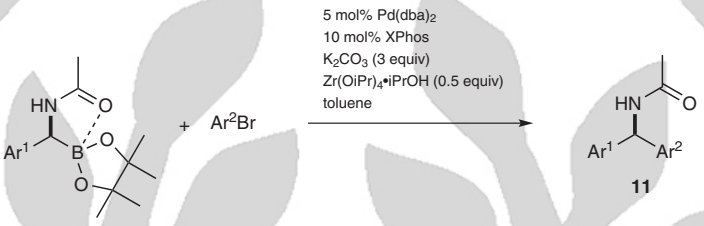
Ar^1	ee (%)	es (%)	Yield (%)	Ref
4-$MeOC_6H_4$	93	97	76	[10]
4-$EtO_2CC_6H_4$	93	97	87	[10]
4-$F_3CC_6H_4$	92	96	85	[10]
4-AcC_6H_4	92	96	71	[10]
4-$OHCC_6H_4$	94	98	84	[10]
3-pyridyl	88	92	72	[10]

A subsequent publication details the effect that additives have on the stereochemical outcome of the cross coupling of α-(acetylamino)benzylboronic acids. Specifically, the cross-coupling reaction in the presence of phenol leads to products with inversion of configu-

for references see p 357

ration. Conversely, when the cross coupling is performed in the presence of an acidic additive [Zr(OiPr)$_4$•iPrOH], the desired cross-coupled acetamides **11** are obtained with retention of configuration (Scheme 8).[24]

Scheme 8 Cross Coupling of α-(Acetylamino)benzylboronate Esters with Aryl Bromides with Retention of Configuration[24]



Ar^1	Ar^2	Temp (°C)	Time (h)	es (%)	Yield (%)	Ref
Ph	4-MeOC$_6$H$_4$	80	18	78	67	[24]
Ph	4-F$_3$CC$_6$H$_4$	80	18	83	96	[24]
Ph	4-F$_3$CC$_6$H$_4$	60	96	87	54	[24]
Ph	2-Tol	80	18	86	73	[24]
Ph	2-Tol	60	96	93	56	[24]
4-MeOC$_6$H$_4$	4-Tol	80	18	85	71	[24]

***N*-(Diarylmethyl)-2,2-dimethylpropanamides** 10**; General Procedure with Inversion of Configuration:**[10]
Into a glass tube with a PTFE stopcock were added Pd(dba)$_2$ (5.8 mg, 10.0 μmol), XPhos (10 mg, 20 μmol), K$_2$CO$_3$ (83 mg, 0.60 mmol), H$_2$O (8.0 μL, 0.40 mmol), toluene (0.40 mL), the organoboronate ester (0.20 mmol), and the aryl bromide (0.24 mmol). After 12–72 h at 80 °C, the product was purified by preparative TLC.

***N*-(Diarylmethyl)acetamides** 11**; General Procedure with Retention of Configuration:**[24]
Into a glass tube equipped with a PTFE stopcock, were added Pd(dba)$_2$ (2.9 mg, 5.0 μmol), XPhos (4.8 mg, 10 μmol), K$_2$CO$_3$ (41 mg, 0.30 mmol), Zr(OiPr)$_4$•iPrOH (19 mg, 50 μmol), toluene (0.20 mL), the boronate ester (0.10 mmol), and the aryl bromide (0.12 mmol). The tube was sealed with the stopcock, and the mixture was heated to 60 or 80 °C with stirring. After 96 h (at 60 °C) or 18 h (at 80 °C), H$_2$O was added to the mixture, which was then extracted with EtOAc. The combined organic layers were dried (MgSO$_4$), filtered, and concentrated. The crude material was purified by preparative TLC. The enantiomeric excesses of the products were determined by HPLC analysis.

1.1.4.2.3 Cross Coupling of Alkyltrifluoroborates

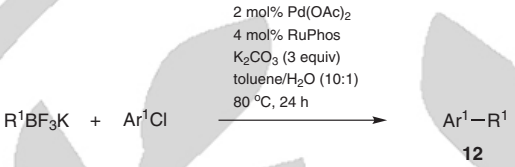
Primary potassium alkyltrifluoroborates are used frequently in the Suzuki–Miyaura cross-coupling reaction owing to their enhanced stability and reactivity compared with other alkylboron derivatives.

1.1.4.2.3.1 Of Primary Alkyltrifluoroborates with Aryl Electrophiles

A general protocol has been established using palladium(II) acetate and 2-(dicyclohexylphosphino)-2′,6′-diisopropoxybiphenyl (RuPhos) that permits the cross coupling of a variety of primary alkyltrifluoroborates with aryl and hetaryl chlorides to give alkylarenes **12**.

These conditions also facilitate the cross coupling with aryl bromides, iodides, and trifluoromethanesulfonates (Scheme 9).[25]

Scheme 9 Cross Coupling of Primary Alkyltrifluoroborates with Aryl and Hetaryl Chlorides[25]



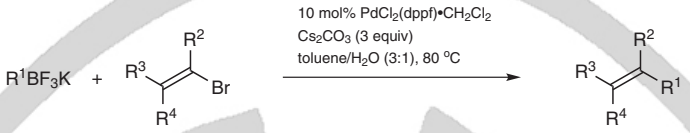
R^1	Ar^1	Yield (%)	Ref
$(CH_2)_4OBz$	2-$MeOC_6H_4$	87	[25]
$(CH_2)_4OBz$	4-$O_2NC_6H_4$	96	[25]
$(CH_2)_4OBz$	3-pyridyl	93	[25]
$(CH_2)_4CN$	4-$MeOC_6H_4$	80	[25]
CH_2TMS	4-$MeOC_6H_4$	71	[25]
$(CH_2)_4OCOt\text{-}Bu$	4-$MeOC_6H_4$	82	[25]

Alkylarenes 12; General Procedure:[25]
Into a Biotage microwave vial were added $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), RuPhos (9.3 mg, 0.02 mmol), the aryl electrophile (0.50 mmol), the alkyltrifluoroborate (0.50 mmol), and K_2CO_3 (207 mg, 1.5 mmol). The vial was sealed with a Teflon-lined septum and purged with N_2, and toluene (2.5 mL) and H_2O (0.25 mL) were added. The mixture was heated to 80 °C for 24 h and then allowed to cool to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (silica gel).

1.1.4.2.3.2 Of Primary Alkyltrifluoroborates with Alkenyl Electrophiles

A number of procedures for the cross coupling of primary alkyltrifluoroborates with alkenyl halides have been described and performed successfully. In particular, the use of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)–dichloromethane complex with cesium carbonate and a toluene/water solvent system provides the cross-coupled alkenes **13** from a number of alkenyl bromides in good yields (Scheme 10).[26]

Scheme 10 Cross Coupling of Primary Alkyltrifluoroborates with Alkenyl Bromides[26]



13

R^1	R^2	R^3	R^4	Yield (%)	Ref
$(CH_2)_3OBz$	Me	Me	Me	93	[26]
$(CH_2)_3OBz$	H	$(CH_2)_5$		96	[26]
$(CH_2)_4Ac$	$CO(CH_2)_2$		Me	87	[26]
$(CH_2)_5Br$	$CO(CH_2)_2$		Me	69	[26]
CH_2TMS	$CO(CH_2)_2$		Me	71	[26]
$(CH_2)_2CH(OH)CH_2OH$	$CO(CH_2)_2$		Me	94	[26]

Alkenes 13**; General Procedure:**[26]
Into a test tube were added the potassium alkyltrifluoroborate (0.11 mmol), Cs_2CO_3 (97.8 mg, 0.3 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (8.2 mg, 0.01 mmol), and the alkenyl bromide (0.1 mmol). The vial was sealed and purged with N_2, degassed toluene (0.6 mL) and H_2O (0.2 mL) were added, and the mixture was heated at 80 °C. After complete consumption of the electrophile, the mixture was allowed to cool to rt, and then diluted with EtOAc (2 mL). The organic extract was filtered through a small plug of silica gel and concentrated under reduced pressure to provide the crude product, which was then purified by preparative TLC.

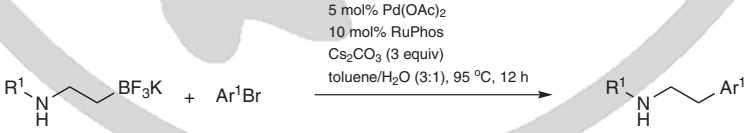
1.1.4.2.3.3 Of Functionalized Primary Alkyltrifluoroborates

In addition to the cross couplings of the alkylboron derivatives described above, a number of specialized primary alkylboron derivatives have been prepared and strategies have been developed for their cross coupling.

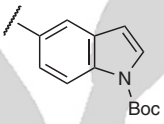
1.1.4.2.3.3.1 (2-Aminoethyl)trifluoroborates

The preparation and cross coupling of (2-aminoethyl)trifluoroborates has been described.[27,28] The combination of palladium(II) acetate and RuPhos or [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)–dichloromethane complex facilitates the cross coupling of (2-aminoethyl)trifluoroborates **14** with aryl and hetaryl electrophiles to give (2-aminoethyl)arenes **15** (Scheme 11).

Scheme 11 Cross Coupling of (2-Aminoethyl)trifluoroborates with Aryl and Hetaryl Bromides[27,28]



14 15

R^1	Ar^1	Yield (%)	Ref
Cbz	Mes	85	[28]
Cbz	3-$MeOC_6H_4$	86	[28]
Boc	4-$OHCC_6H_4$	79[a]	[28]
Boc	pyrimidin-5-yl	83	[28]
Cbz	4-isoquinolyl	84	[28]
Cbz		89	[28]

[a] Reaction performed using 5 mol% $PdCl_2(dppf)•CH_2Cl_2$ at 80 °C.

(2-Aminoethyl)arenes 15; General Procedure:[28]

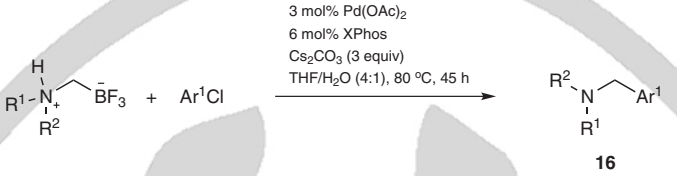
Into a Biotage microwave vial were added the potassium (2-aminoethyl)trifluoroborate **14** (0.242 mmol), the electrophile (0.24 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), and RuPhos (11.2 mg, 0.024 mmol). The vial was purged with N_2 and toluene and H_2O (3:1; 1.5 mL) were added. The mixture was heated at 95 °C for 12 h, and then allowed to cool to rt. To the mixture was added sat. aq NH_4Cl (4 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (silica gel).

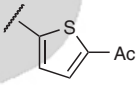
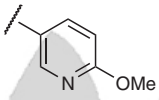
1.1.4.2.3.3.2 (Ammoniomethyl)- and (Aminomethyl)trifluoroborates

(Ammoniomethyl)trifluoroborates have been prepared and shown to be suitable nucleophilic partners for the Suzuki–Miyaura cross-coupling reaction. Using palladium(II) acetate and XPhos, a variety of (ammoniomethyl)trifluoroborate substrates react with aryl and hetaryl chlorides to give benzylic amines **16** (Scheme 12).[29]

for references see p 357

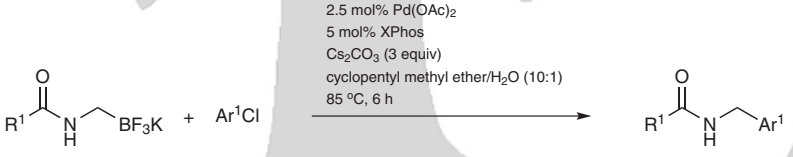
Scheme 12 Cross Coupling of (Ammoniomethyl)trifluoroborates with Aryl and Hetaryl Chlorides[29]

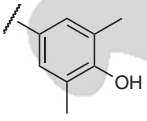


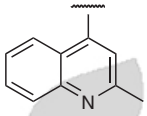
R^1	R^2	Ar^1	Yield (%)	Ref
$(CH_2)_5$		4-NCC_6H_4	81	[29]
$(CH_2)_5$			83	[29]
$(CH_2)_5$			96	[29]
Et	Et	4-$MeOC_6H_4$	90	[29]
$(CH_2)_2NBoc(CH_2)_2$		4-$MeOC_6H_4$	98	[29]
$(CH_2)_2S(CH_2)_2$		4-$MeOC_6H_4$	60	[29]

N-(Arylmethyl)carboxamides are common structural motifs found in a number of biologically active compounds, and this structural subunit can be accessed through the use of (carboxamidomethyl)trifluoroborates. The synthesis of (carboxamidomethyl)trifluoroborates from 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane can be carried out with a number of acyl chlorides.[30] The resulting (carboxamidomethyl)trifluoroborates **17** are suitable cross-coupling partners for aryl and hetaryl chlorides, providing the desired *N*-(arylmethyl)carboxamides **18** in good to excellent yields (Scheme 13).

Scheme 13 Cross Coupling of (Carboxamidomethyl)trifluoroborates with Aryl and Hetaryl Chlorides[30]

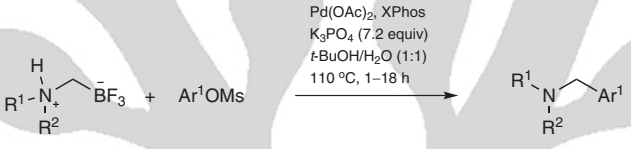


R^1	Ar^1	Yield (%)	Ref
Ph		87	[30]
Ph	4-$OHCC_6H_4$	88	[30]
cyclopentyl	4-$MeOC_6H_4$	90	[30]

R^1	Ar^1	Yield (%)	Ref
t-Bu	4-$MeOC_6H_4$	81	[30]
Ph	3-pyridyl	79	[30]
Ph		86	[30]

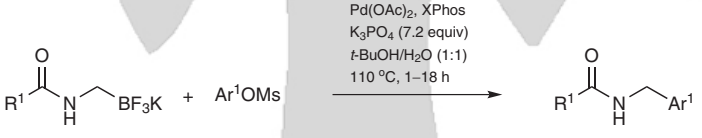
The cross coupling of (ammoniomethyl)- and (carboxamidomethyl)trifluoroborates has also been extended to methanesulfonate electrophiles. Since they are less toxic and easier to handle than other sulfonate-containing nucleofuges, methanesulfonates are an attractive and atom-economical alternative to 4-toluenesulfonates. Using palladium(II) acetate and XPhos, this modestly reactive functional group is activated for cross coupling to generate (aminomethyl)arenes **19** and (carboxamidomethyl)arenes **20** (Scheme 14).[31]

Scheme 14 Cross Coupling of (Aminomethyl)- and (Carboxamidomethyl)trifluoroborates with Aryl and Hetaryl Methanesulfonates[31]



19

R^1	R^2	Ar^1	$Pd(OAc)_2$ (mol%)	XPhos (mol%)	Yield (%)	Ref
$(CH_2)_5$		1-naphthyl	1	2	84	[31]
$(CH_2)_2O(CH_2)_2$		1-naphthyl	1	2	97	[31]
$(CH_2)_5$		2-$MeOC_6H_4$	5	10	83	[31]
$(CH_2)_5$		3-pyridyl	2	4	96	[31]



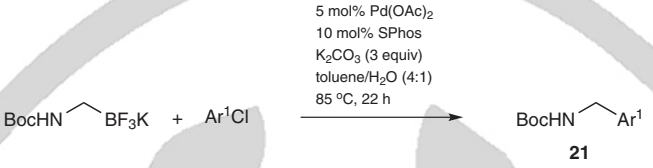
20

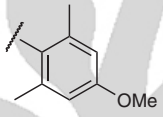
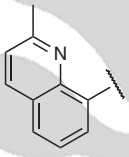
R^1	Ar^2	$Pd(OAc)_2$ (mol%)	XPhos (mol%)	Yield (%)	Ref
Ph	1-naphthyl	1	2	88	[31]
t-Bu	5-isoquinolyl	2	4	64	[31]

tert-Butoxycarbonyl-protected potassium (aminomethyl)trifluoroborate can be prepared utilizing di-*tert*-butyl dicarbonate to access the desired starting material. This particular reagent is the synthetic equivalent of a primary aminomethyl unit, and it readily undergoes cross coupling with aryl and hetaryl chlorides, using palladium(II) acetate and XPhos or SPhos [2-(dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl], to provide access to the *tert*-butoxycarbonyl-protected arylmethylamines **21** (Scheme 15).[32]

for references see p 357

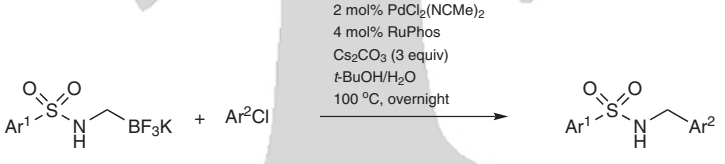
Scheme 15 Cross Coupling of *tert*-Butoxycarbonyl-Protected Potassium (Aminomethyl)trifluoroborate with Aryl and Hetaryl Chlorides[32]

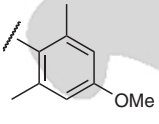


Ar^1	Yield (%)	Ref
2,6-$Me_2C_6H_3$	90	[32]
	78	[32]
4-$O_2NC_6H_4$	90	[32]
2-thienyl	78	[32]
	76	[32]
indol-6-yl	65	[32]

N-(Arylmethyl)sulfonamides are an important class of compounds, showing potent biological activity in a variety of therapeutic areas. One procedure to access these compounds is the cross coupling of (sulfonamidomethyl)trifluoroborates with aryl and hetaryl chlorides.[33] Using bis(acetonitrile)dichloropalladium(II) and RuPhos, the corresponding cross-coupled arenesulfonamides **22** are obtained in good to excellent yields (Scheme 16).

Scheme 16 Cross Coupling of (Sulfonamidomethyl)trifluoroborates with Aryl and Hetaryl Chlorides[33]

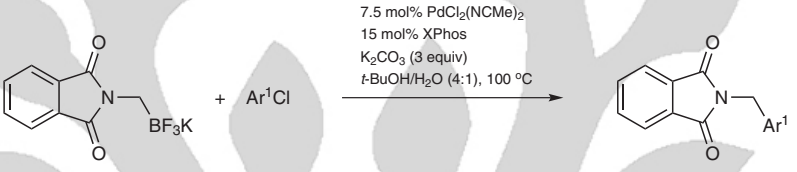


Ar^1	Ar^2	Yield (%)	Ref
Mes		78	[33]
Mes	2-$MeOC_6H_4$	91	[33]
Mes	3-pyridyl	89	[33]

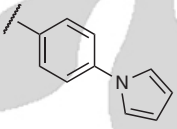
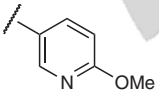
Ar^1	Ar^2	Yield (%)	Ref
4-$MeOC_6H_4$	4-$MeOC_6H_4$	70	[33]
1-naphthyl	4-$MeOC_6H_4$	70	[33]
4-FC_6H_4	4-$MeOC_6H_4$	64	[33]

The aminomethylation platform also extends itself to use with imide species. The synthesis of potassium (phthalimidomethyl)trifluoroborate (**23**) can be accomplished via a boronate intermediate, and the cross coupling of this salt with aryl and hetaryl chlorides, to give (phthalimidomethyl)arenes **24**, proceeds in the presence of bis(acetonitrile)dichloropalladium(II) and XPhos (Scheme 17).[34]

Scheme 17 Cross Coupling of an (Imidomethyl)trifluoroborate with Aryl and Hetaryl Chlorides[34]



23 **24**

Ar^1	Yield (%)	Ref
Ph	58	[34]
2-Tol	71	[34]
4-$MeO_2CC_6H_4$	51	[34]
3,5-$(MeO)_2C_6H_3$	74	[34]
	61	[34]
	35	[34]

1-Arylmethanamines 16**; General Procedure:**[29]
To a microwave vial were added the (ammoniomethyl)trifluoroborate (1.2 mmol), Cs_2CO_3 (977 mg, 3.0 mmol), the aryl chloride (1.0 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), and XPhos (29 mg, 0.06 mmol). The vial was sealed with a PTFE-lined septum and was purged with N_2. To the vial were then added THF (3.2 mL) and H_2O (0.80 mL), and the mixture was stirred and heated to 80 °C. After 45 h, the mixture was cooled to rt and diluted with H_2O (1 mL). The mixture was extracted with EtOAc (3 × 3 mL), and the combined organic phases were dried ($MgSO_4$), filtered through Celite, concentrated under reduced pressure, and purified by flash column chromatography.

***N*-(Arylmethyl)carboxamides** 18**; General Procedure:**[30]
To a sealed tube were added the potassium (carboxamidomethyl)trifluoroborate **17** (0.3 mmol), Cs_2CO_3 (293 mg, 0.9 mmol), $Pd(OAc)_2$ (1.5 mg, 0.0075 mmol), XPhos (7.2 mg,

0.015 mmol), and the aryl chloride (0.3 mmol). The vial was purged with argon, and then a mixture of cyclopentyl methyl ether and H_2O (10:1; 3.3 mL) was added. The resulting mixture was heated with stirring to 85 °C for 6 h, and then allowed to cool to rt before being diluted with H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (13 × 10 mL), and the combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the desired product was obtained after purification by column chromatography (silica gel).

1-Arylmethanamines 19 **or *N*-(Arylmethyl)carboxamides** 20**; General Procedure:**[31]
To a Biotage microwave vial were added $Pd(OAc)_2$ (0.6 mg, 2.5 μmol), XPhos (2.4 mg, 5 μmol), the methanesulfonate (0.25 mmol), the (ammoniomethyl)trifluoroborate (0.33 mmol) or the (carboxamidomethyl)trifluoroborate salt (0.33 mmol), and K_3PO_4 (382 mg, 1.80 mmol). The vial was sealed with a PTFE-lined septum and purged with N_2 (3 ×). To the reaction vessel was added a mixture of *t*-BuOH and H_2O (1:1; 2.5 mL), and the mixture was heated to 110 °C for 1–18 h. The mixture was allowed to cool to rt and extracted with EtOAc (3 × 2 mL), and the EtOAc extracts were then dried ($MgSO_4$). The combined organic extracts were concentrated under reduced pressure, and the crude product was purified by preparative chromatography (silica gel).

***N*-(*tert*-Butoxycarbonyl)-1-arylmethanamines** 21**; General Procedure:**[32]
To a sealed tube were added potassium {[(*tert*-butoxycarbonyl)amino]methyl}trifluoroborate (62 mg, 0.263 mmol, 1.05 equiv), an aryl or hetaryl chloride (0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (3 mg, 0.013 mmol, 5 mol%), SPhos (0.03 mmol, 10 mol%), and K_2CO_3 (104 mg, 0.75 mmol, 3.0 equiv). The mixture was purged with argon (3 ×) (liquid electrophiles were added after the argon purge). Toluene/H_2O (4:1; 1 mL) was then added to the tube, and the mixture was heated with stirring to 85 °C for 22 h. The mixture was allowed to cool to rt, a soln of pH 7 buffer (2 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 3 mL). The organic layers were combined, dried ($MgSO_4$), and filtered. The filtrate was concentrated and purified by column chromatography.

***N*-(Arylmethyl)arenesulfonamides** 22**; General Procedure:**[33]
To a microwave vial equipped with a stirrer bar were added $PdCl_2(NCMe)_2$ (1.3 mg, 2 mol%), RuPhos (4 mol%), Cs_2CO_3 (3 equiv), and the (sulfonamidomethyl)trifluoroborate (1–1.2 equiv). The vial was capped with a PTFE-lined septum and purged with N_2 (3 ×). The electrophile (0.25 mmol, 1 equiv) was then added using a microsyringe, and then *t*-BuOH and degassed distilled H_2O were added. The mixture was then placed into a preheated oil bath and heated at 100 °C for 14–16 h. The mixture was allowed to cool to rt, the vial was uncapped, and the mixture was diluted with EtOAc (5 mL) and H_2O (5 mL). The organic layer was passed through a Celite plug and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (silica gel or basic alumina).

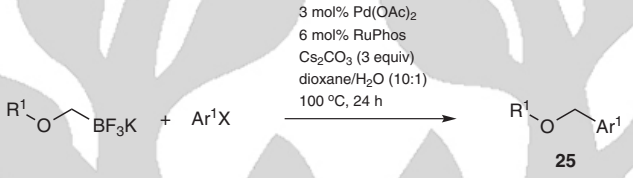
(Phthalimidomethyl)arenes 24**; General Procedure:**[34]
Into a Biotage microwave vial equipped with a stirrer bar were added potassium (phthalimidomethyl)trifluoroborate (**23**; 80.1 mg, 0.3 mmol), K_2CO_3 (104 mg, 0.75 mmol), $PdCl_2(NCMe)_2$ (4.9 mg, 7.5 mol%), and XPhos (17.9 mg, 15 mol%). The vial was capped with a PTFE-lined septum and purged with N_2 (3 ×). The electrophile (0.25 mmol, 1.0 equiv) was added using a microsyringe, and then *t*-BuOH (0.8 mL) and degassed distilled H_2O (0.2 mL) were added. The resulting mixture was stirred at 100 °C for 5–42 h. After the reaction was complete (monitored by TLC), the mixture was allowed to cool to rt, the vial was uncapped, and the mixture was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed

with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel).

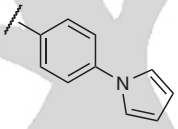
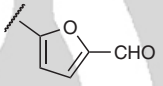
1.1.4.2.3.3.3 (Alkoxymethyl)trifluoroborates

The preparation of potassium (alkoxymethyl)trifluoroborates and their cross coupling with aryl and hetaryl halides can be performed to install alkoxymethyl groups on the arenes or hetarenes, giving (alkoxymethyl)arenes **25**.[35] Using palladium(II) acetate and RuPhos, a variety of substrates have been utilized in this context (Scheme 18).

Scheme 18 Cross Coupling of (Alkoxymethyl)trifluoroborates with Aryl and Hetaryl Halides[35]

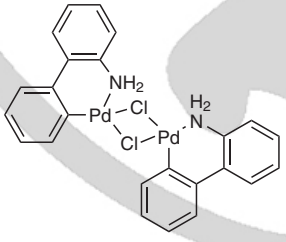


25

R^1	Ar^1	X	Yield (%)	Ref
Bn	2,6-$Me_2C_6H_3$	Cl	72	[35]
Bn		Cl	85	[35]
t-Bu	4-NCC_6H_4	Cl	67	[35]
$(CH_2)_2$TMS	4-NCC_6H_4	Cl	80	[35]
$(CH_2)_2$TMS		Cl	50	[35]
$(CH_2)_2$TMS	3-pyridyl	Br	70	[35]

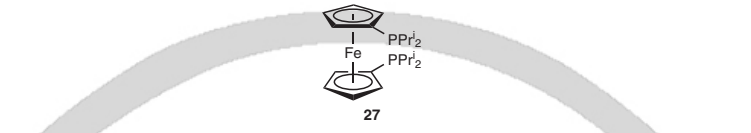
Alkoxymethyl groups can also be installed in molecules by the cross coupling of (alkoxymethyl)trifluoroborates with aryl and hetaryl methanesulfonates. This C—O activation provides the corresponding cross-coupled (alkoxymethyl)arenes **28** in high yields for a range of substrates (Scheme 19).[36]

Scheme 19 Cross Coupling of (Alkoxymethyl)trifluoroborates with Aryl and Hetaryl Methanesulfonates[36]

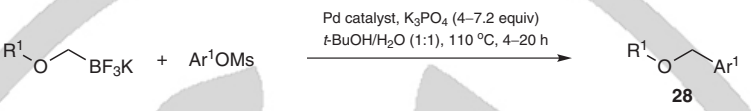


26

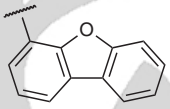
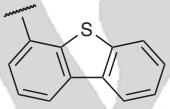
for references see p 357



27

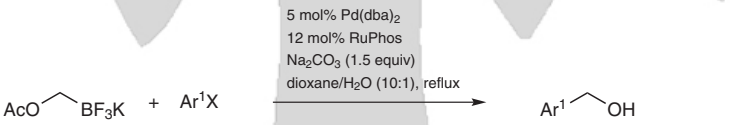


28

R^1	Ar^1	Pd catalyst (mol%)	**27** (mol%)	Yield (%)	Ref
Bn	1-naphthyl	$PdCl_2$(cod) (5)	10	82	[36]
t-Bu	1-naphthyl	$PdCl_2$(cod) (5)	10	87	[36]
$(CH_2)_2$TMS	1-naphthyl	$PdCl_2$(cod) (5)	10	91	[36]
Bn	6-quinolyl	**26** (3)	6	81	[36]
Bn		**26** (5)	10	69	[36]
Bn		**26** (3)	6	68	[36]

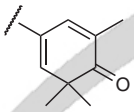
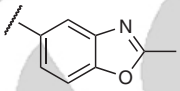
The cross coupling of potassium (acetoxymethyl)trifluoroborate with aryl halides and trifluoromethanesulfonates has also been described.[37] Using this strategy, a hydroxymethyl group can be directly installed onto an aromatic or heteroaromatic ring system to give alcohols **29** without a separate deprotection step to reveal the free alcohol. This transformation can be accomplished in good to excellent yields using 5 mol% of bis(dibenzylideneacetone)palladium(0) and 12 mol% of RuPhos (Scheme 20).

Scheme 20 Cross Coupling of Potassium (Acetoxymethyl)trifluoroborate with Aryl Halides and Trifluoromethanesulfonates[37]



29

Ar^1	X	Yield (%)	Ref
2-naphthyl	Cl	85	[37]
4-$H_2NCOC_6H_4$	Cl	82	[37]
4-$O_2NC_6H_4$	Br	62	[37]

Ar^1	X	Yield (%)	Ref
	OTf	76	[37]
6-quinolyl	Cl	81	[37]
	Cl	80	[37]

(Alkoxymethyl)arenes 25; General Procedure:[35]
Into a Biotage microwave vial were added the (alkoxymethyl)trifluoroborate (0.55 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), RuPhos (14 mg, 0.03 mmol), and Cs_2CO_3 (448 mg, 1.5 mmol, as reported). The vial was sealed with a PTFE-lined disposable septum and was purged with N_2. To the mixture was added the electrophile (0.5 mmol) and dioxane/H_2O (10:1; 2 mL), and the mixture was stirred at 100 °C. After 24 h, the mixture was allowed to cool to rt and extracted with EtOAc (3 ×). The combined organic layers were washed with brine and dried ($MgSO_4$), the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel).

(Alkoxymethyl)arenes 28; General Procedure:[36]
A Biotage vial was charged with $PdCl_2$(cod) (2.1 mg, 7.5 μmol) or (2′-aminobiphenyl-2-yl)chloropalladium(II) dimer (**26**; 7.7 mg, 12 μmol), dippf (**27**; 6.3 mg, 15 μmol or 10.5 mg, 25.0 μmol), the (alkoxymethyl)trifluoroborate (0.33 mmol), the methanesulfonate (0.25 mol), and K_3PO_4 (382 mg, 1.80 mmol). The vial was sealed with a PTFE-lined septum and purged with argon (3 ×). *t*-BuOH/H_2O (1:1; 2.5 mL) was added under argon, and the mixture was heated to 110 °C for 20 h and then allowed to cool to rt. The mixture was extracted with EtOAc (3 × 2 mL) and then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude product was purified by preparative chromatography (silica gel).

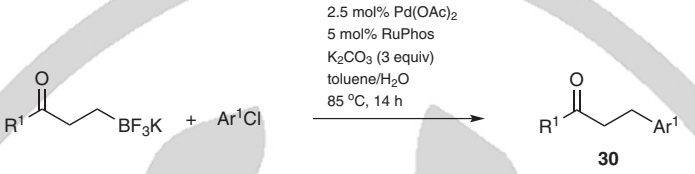
Benzylic Alcohols 29; General Procedure:[37]
A Biotage vial was charged with the electrophile (0.092 mmol), $Pd(dba)_2$ (2.65 mg, 0.005 mmol), RuPhos (5.44 mg, 0.012 mmol), Na_2CO_3 (14.6 mg, 0.138 mmol), potassium (acetoxymethyl)trifluoroborate (24.9 mg, 0.138 mmol), 1.4-dioxane (1.5 mL), and distilled H_2O (150 μL). The vial was sealed with a disposable cap, and the mixture was heated to reflux with stirring for 24 h under N_2, allowed to cool to rt, and then filtered and concentrated. The crude product was purified by preparative chromatography (silica gel).

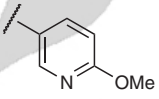
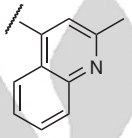
1.1.4.2.3.3.4 (3-Oxoalkyl)trifluoroborates

The cross coupling of (3-oxoalkyl)trifluororates provides an alternative route to the products obtained by Michael-type addition reactions to α,β-unsaturated carbonyl systems, and this is a particularly advantageous approach in instances where the functional groups on the substrates are incompatible with the reactive organometallic reagents traditionally employed in Michael-type transformations. Specifically, carbonyl-containing trifluoroborate substrates can be cross coupled to give 2-arylethyl ketones **30** using palladium(II) acetate and RuPhos (Scheme 21).[38,39]

for references see p 357

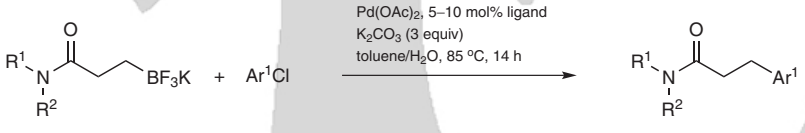
Scheme 21 Cross Coupling of (3-Oxoalkyl)trifluororates with Aryl and Hetaryl Chlorides[38,39]

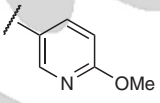


R^1	Ar^1	Yield (%)	Ref
$(CH_2)_2Ph$	$4\text{-}OHCC_6H_4$	94	[39]
$(CH_2)_2Ph$	$2\text{-}MeOC_6H_4$	88	[39]
$(CH_2)_2Ph$		87	[39]
$(CH_2)_2Ph$		65	[39]
$2,4\text{-}(MeO)_2C_6H_3$	$3,5\text{-}(MeO)_2C_6H_3$	87	[39]
$(CH_2)_8CH{=}CH_2$	$3,5\text{-}(MeO)_2C_6H_3$	81	[39]

The cross coupling of (3-amino-3-oxopropyl)trifluoroborates can also be accomplished using palladium(II) acetate and RuPhos (Scheme 22); however, in most cases this cross-coupling strategy requires twice as much ligand and catalyst to proceed as does the strategy outlined above for the 3-oxoalkyl substrates.[40] The cross coupling of these substrates with hetaryl chlorides to give 3-arylpropanamides **31** proceeds more effectively when SPhos is used as the ligand.

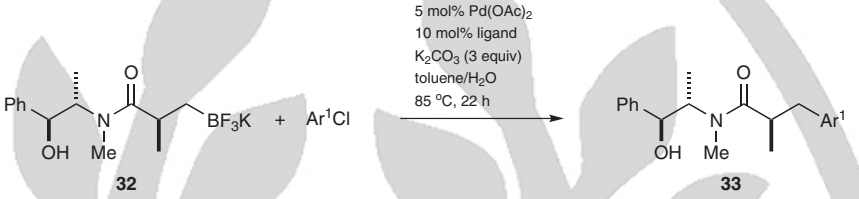
Scheme 22 Cross Coupling of (3-Amino-3-oxopropyl)trifluoroborates with Aryl and Hetaryl Chlorides[40]



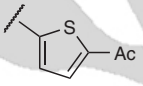
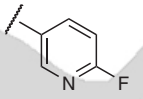
R^1	R^2	Ar^1	$Pd(OAc)_2$ (mol%)	Ligand (mol%)	Yield (%)	Ref
Me	Me	$4\text{-}OHCC_6H_4$	5	RuPhos (10)	87	[40]
Me	Me	$2,6\text{-}Me_2C_6H_3$	5	RuPhos (10)	76	[40]
Me	Me		2.5	SPhos (5)	87	[40]
Me	Me	2-thienyl	2.5	SPhos (5)	79	[40]
$(CH_2)_2O(CH_2)_2$		$2\text{-}MeOC_6H_4$	5	RuPhos (10)	65	[40]
Ph	H	$2\text{-}MeOC_6H_4$	5	RuPhos (10)	84	[40]

Enantiomerically enriched potassium trifluoroborate **32** can be prepared using pseudoephedrine as the chiral auxiliary in a diastereomeric ratio greater than 95:5. Once in hand, this substrate can undergo cross coupling with a variety of aryl and hetaryl chlorides to give 3-arylpropanamides **33** (Scheme 23).[41]

Scheme 23 Cross Coupling of an Enantioenriched (3-Amino-3-oxopropyl)trifluoroborate with Aryl and Hetaryl Chlorides[41]



32 **33**

Ar^1	Ligand	Yield (%)	Ref
Ph	RuPhos	70	[41]
4-$MeOC_6H_4$	SPhos	51	[41]
3,5-$(MeO)_2C_6H_3$	RuPhos	62	[41]
4-$O_2NC_6H_4$	RuPhos	75	[41]
	RuPhos	73	[41]
	RuPhos	84	[41]

The preparation of (4-oxoalkyl)trifluoroborates has been described, and the conditions used for the cross coupling of (3-oxoalkyl)trifluoroborates have been shown to also be suitable for the cross coupling of these substrates.[42]

2-Arylethyl Ketones 30**; General Procedure:**[39]
Into a flask were added the (3-oxoalkyl)trifluoroborate (2.02 mmol), the electrophile (2.0 mmol), K_2CO_3 (829 mg, 6 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), and RuPhos (46.7 mg, 0.1 mmol). The flask was purged with N_2 and toluene/H_2O (4:1; 10 mL) was added. The mixture was heated to 85 °C with stirring under a N_2 atmosphere. After 14 h, the mixture was allowed to cool to rt. A soln of pH 7 buffer (10.0 mL) was added and the resulting mixture was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel).

3-Arylpropanamides 31**; General Procedure:**[40]
To a mixture of the (3-amino-3-oxopropyl)trifluoroborate (2.02 mmol), the electrophile (2.0 mmol), K_2CO_3 (829.3 mg, 6.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), and RuPhos (93.3 mg, 0.2 mmol) under N_2 was added a mixture of toluene and H_2O (5:1; 10 mL). The mixture was heated to 85 °C with stirring under a N_2 atmosphere for 14 h, and then allowed to cool to rt. A pH 7 buffer soln (10 mL) was added and the mixture was extracted with EtOAc (3 × 6 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (silica gel).

for references see p 357

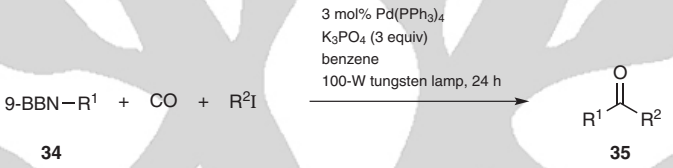
(*R*)-3-Aryl-*N*-[(1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-*N*,2-dimethylpropanamides 33; **General Procedure:**[41]

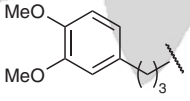
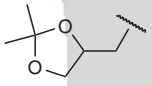
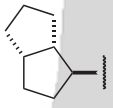
A flask was charged with potassium trifluoroborate **32** (90 mg, 0.263 mmol, 1.05 equiv), $Pd(OAc)_2$ (3 mg, 0.013 mmol, 5 mol%), RuPhos (12 mg, 0.025 mmol, 10 mol%), and K_2CO_3 (104 mg, 0.75 mmol, 3.0 equiv), and then purged with N_2 (3×). The electrophile (0.25 mmol, 1.0 equiv) and a mixture of toluene and H_2O (4:1; 1 mL) were added to the reaction flask. The mixture was heated to 85 °C for 22 h, and then allowed to cool to rt. A soln of pH 7 buffer (1 mL) was added and then the mixture was extracted with EtOAc (2 × 3 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (silica gel).

1.1.4.2.4 Carbonylative Cross-Coupling Reactions

One important application of the *B*-alkyl Suzuki–Miyaura reaction is the carbonylative cross coupling to generate unsymmetrical ketones. The cross coupling of trialkylboranes **34** and alkyl iodides can be carried out using tetrakis(triphenylphosphine)palladium(0) under a carbon monoxide atmosphere to give ketones **35** (Scheme 24).[43]

Scheme 24 Carbonylative Cross Coupling of Trialkylboranes with Aryl Iodides[43]



R^1	R^2	Yield (%)	Ref
$(CH_2)_7Me$	$(CH_2)_4Me$	67	[43]
$(CH_2)_7Me$	Cy	65	[43]
$(CH_2)_7Me$	CH_2t-Bu	69	[43]
		73	[43]
$(CH_2)_3CMe_2CO_2Me$		65	[43]
$(CH_2)_{10}CN$	$(CH_2)_3CO_2Me$	65	[43]

Dialkyl Ketones 35; **General Procedure:**[43]

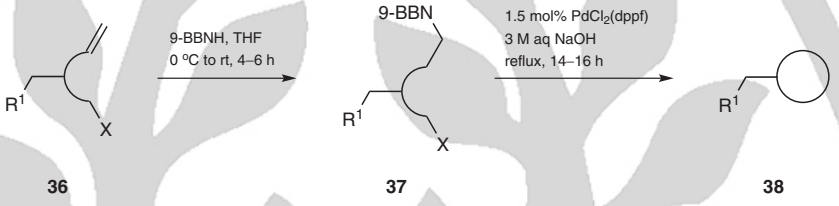
CAUTION: *Carbon monoxide is extremely flammable and toxic, and exposure to higher concentrations can quickly lead to a coma.*

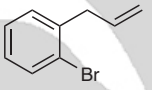
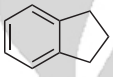
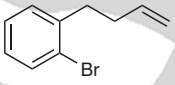
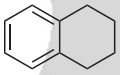
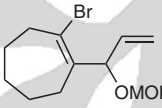
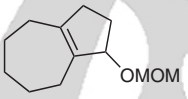
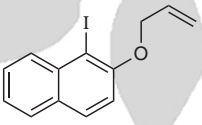
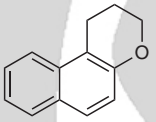
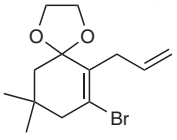
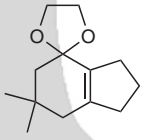
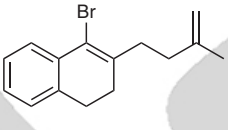
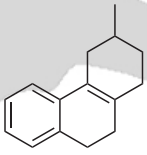
To a soln of the trialkylborane **34** (2 mmol) in THF was added benzene (12 mL) (**CAUTION:** *carcinogen*), $Pd(PPh_3)_4$ (0.06 mmol), powdered K_3PO_4 (6 mmol), and the alkyl iodide (2 mmol). The flask was flushed with 1 atm of CO, and the mixture was stirred at rt for 24 h under irradiation with a 100-W tungsten lamp.

1.1.4.2.5 Intramolecular Cross-Coupling Reactions

The intramolecular cross coupling of alkylborane substrates has been used extensively in synthetic strategies to bring about ring closure and generate carbocycles. The intramolecular cross coupling of 9-alkyl-9-borabicyclo[3.3.1]nonanes (e.g., **37**), obtained from the corresponding alkenes (e.g., **36**), with aryl and alkenyl halides to form five- and six-membered rings (e.g., **38**) can be achieved using [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Table 1).[44]

Table 1 Intramolecular Cyclization of Haloalkenes[44]



Starting Material **36**	Product **38**	Yield (%)	Ref
		86	[44]
		66	[44]
		68	[44]
		70	[44]
		84	[44]
		77	[44]

Carbocycles 38**; General Procedure:**[44]

To a soln of the haloalkene **36** (1.72 mmol) in THF (3 mL) was added a 0.5 M soln of 9-BBNH in THF (3.6 mL, 1.8 mmol) at 0 °C. The mixture was stirred for 5 h at rt to generate trialkylborane **37**, and then $PdCl_2$(dppf) (22 mg, 0.03 mmol) and 3 M aq NaOH (1.7 mL) were

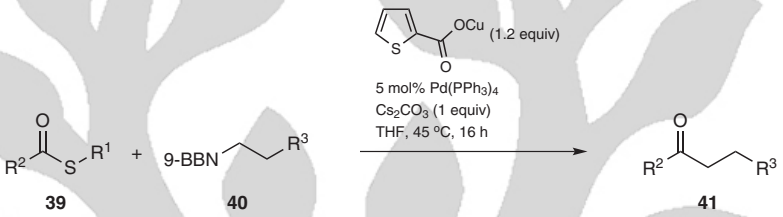
for references see p 357

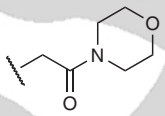
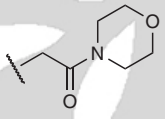
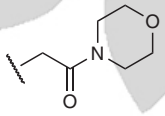
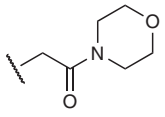
added. After heating at reflux for 14–16 h, the unreacted borane was oxidized with 30% aq H_2O_2 for 1 h. The product was extracted, and the extracts were washed with brine, dried ($MgSO_4$), and purified by column chromatography (silica gel, hexane/Et_2O).

1.1.4.2.6 Palladium-Catalyzed Coupling with Thioesters

Alkylboron species are also competent in the copper-mediated, palladium-catalyzed Liebeskind–Srogl reaction. Thioesters **39** and 9-alkyl-9-borabicyclo[3.3.1]nonane derivatives **40** undergo cross coupling in the presence of tetrakis(triphenylphosphine)palladium(0) and copper(I) thiophene-2-carboxylate (CuTC) to provide ketones **41** in moderate to excellent yields (Scheme 25).[45]

Scheme 25 Liebeskind–Srogl Cross Coupling of Alkylboranes with Thioesters[45]



R^1	R^2	R^3	Yield (%)	Ref
	Ph	$(CH_2)_8Me$	83	[45]
	Ph	Ph	82	[45]
	Ph	4-ClC_6H_4	76	[45]
	Ph	4-$MeOC_6H_4$	78	[45]
4-Tol	1-adamantyl	4-$MeOC_6H_4$	63	[45]

Ketones 41; General Procedure:[45]
Into a Schlenk tube were added the thioester **39** (0.40 mmol), CuTC (91 mg, 0.48 mmol), Cs_2CO_3 (130 mg, 0.40 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and the tube was degassed with argon. A 0.5 M soln of the 9-alkyl-9-BBN reagent **40** in THF (0.96 mL, 0.48 mmol) was then added via syringe, followed by anhyd, degassed THF (4 mL). The dark brown suspension was stirred under argon at 45 °C. After 16 h, Et_2O was added, and the reaction was quenched with 2 M HCl, 1 M aq NH_3, and then brine. The crude mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel) or preparative plate chromatography (silica gel).

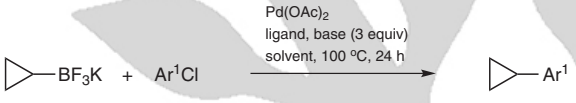
1.1.4.3 Cross Coupling of Secondary Alkylboron Derivatives

The cross coupling of secondary alkylboron derivatives is mechanistically more challenging than that of primary alkyl derivatives because the transmetalation step is more difficult for secondary derivatives, and the reductive elimination step competes with facile β-hydride elimination. Nonetheless, significant advances have been made in this area over recent years.

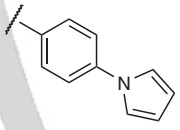
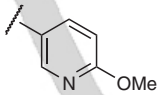
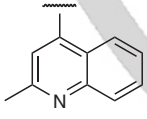
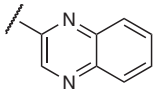
1.1.4.3.1 Cyclopropylboron Derivatives

The introduction of cyclopropyl moieties onto complex molecular scaffolds is of importance because of their prevalence in a number of biologically active molecules. The exceptional reactivity of cyclopropyl derivatives results from the partial sp^2 character of the constituent carbon atoms; thus, there are a number of strategies for their incorporation using organotrifluoroborates[46] and *N*-methyliminodiacetic acid (MIDA) boronates.[47] The cross coupling of potassium cyclopropyltrifluoroborate with aryl and hetaryl chlorides, to give cyclopropyl(het)arenes **42**, using two slightly different catalytic systems has been achieved (Scheme 26).[46]

Scheme 26 Cross Coupling of Potassium Cyclopropyltrifluoroborate with Aryl and Hetaryl Chlorides[46]



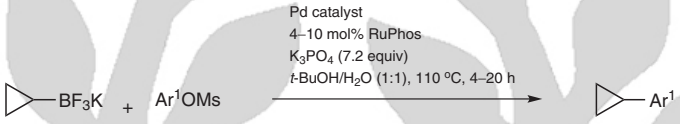
42

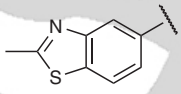
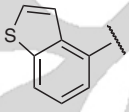
Ar^1	$Pd(OAc)_2$ (mol%)	Ligand (mol%)	Base	Solvent	Yield (%)	Ref
4-$MeOC_6H_4$	3	XPhos (6)	K_2CO_3	cyclopentyl methyl ether/H_2O (10:1)	75	[46]
3,5-$(MeO)_2C_6H_3$	3	XPhos (6)	K_2CO_3	cyclopentyl methyl ether/H_2O (10:1)	94	[46]
	3	XPhos (6)	K_2CO_3	cyclopentyl methyl ether/H_2O (10:1)	90	[46]
	2	di-1-adamantyl(butyl)phosphine (3)	Cs_2CO_3	toluene/H_2O (10:1)	85	[46]
	2	di-1-adamantyl(butyl)phosphine (3)	Cs_2CO_3	toluene/H_2O (10:1)	95	[46]
	2	di-1-adamantyl(butyl)phosphine (3)	Cs_2CO_3	toluene/H_2O (10:1)	79	[46]

for references see p 357

Although halides and trifluoromethanesulfonates are most often employed as the electrophilic partner in cross-coupling reactions with cyclopropyl derivatives, this reaction platform also extends to the cross coupling with methanesulfonylated phenol derivatives. Using palladium(II) acetate and RuPhos, potassium cyclopropyltrifluoroborate readily undergoes reaction with aryl methanesulfonates, and dichloro(cyclooctadiene)palladium(II) can be partnered with RuPhos for the reaction with hetaryl methanesulfonates to give the cyclopropylarenes and -hetarenes **43** (Scheme 27).[48]

Scheme 27 Cross Coupling of Potassium Cyclopropyltrifluoroborate with Aryl and Hetaryl Methanesulfonates[48]



Ar^1	Pd Catalyst (mol%)	RuPhos (mol%)	Yield (%)	Ref
1-naphthyl	$Pd(OAc)_2$ (2)	4	87	[48]
4-$MeOC_6H_4$	$Pd(OAc)_2$ (5)	10	96	[48]
3,4,5-$(MeO)_3C_6H_2$	$Pd(OAc)_2$ (2)	4	91	[48]
6-quinolyl	$PdCl_2$(cod) (2)	4	94	[48]
	$PdCl_2$(cod) (2)	4	85	[48]
	$PdCl_2$(cod) (2)	4	93	[48]

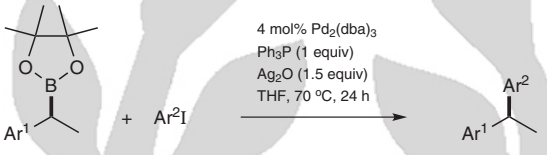
Cyclopropylhetarenes 42 (Ar^1 = Hetaryl); General Procedure:[46]
In a glovebox, into a Biotage microwave vial were added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), di-1-adamantyl(butyl)phosphine (5.3 mg, 0.015 mmol), potassium cyclopropyltrifluoroborate (81.8 mg, 0.55 mmol), and Cs_2CO_3 (480 mg, 1.5 mmol). The vial was sealed with a PTFE-lined cap and removed from the glovebox. The electrophile (0.5 mmol) and toluene/H_2O (10:1; 2 mL) were then added by syringe and the mixture was stirred at 100 °C. After 24 h, the mixture was allowed to cool to rt and diluted with H_2O (1.5 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel).

Cyclopropylarenes 43; General Procedure:[48]
Into a Biotage microwave vial were added $Pd(OAc)_2$ (1.1 mg, 5.0 μmol), RuPhos (4.7 mg, 10 μmol), the aryl methanesulfonate (0.25 mmol), potassium cyclopropyltrifluoroborate (47.2 mg, 0.33 mmol), and K_3PO_4 (382 mg, 1.80 mmol). The vial was sealed with a PTFE-lined septum and purged with argon (3 ×). *t*-BuOH/H_2O (1:1; 2.5 mL) was added under argon, and the mixture was then heated to 110 °C for 4–20 h, allowed to cool to rt, and then extracted with EtOAc (3 × 2 mL). The extracts were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the desired product was obtained after purification by preparative chromatography (silica gel).

1.1.4.3.2 Benzylic Alkylboron Reagents

The cross coupling of chiral secondary benzylic organoboronate esters with aryl iodides can be achieved using tris(dibenzylideneacetone)dipalladium(0), triphenylphosphine, and silver(I) oxide.[49] Using these conditions, good yields of 1,1-diarylethanes **44** are obtained with relatively high levels of stereoretention (Scheme 28).

Scheme 28 Cross Coupling of Secondary Benzylic Boronate Esters with Aryl Iodides[49]



Ar^1	Ar^2	Stereoretention (%)	Yield[a] (%)	Ref
Ph	4-$MeOC_6H_4$	92	65	[49]
Ph	4-ClC_6H_4	91	81	[49]
Ph	4-Tol	92	86	[49]
Ph	3,5-$Me_2C_6H_3$	93	86	[49]
4-ClC_6H_4	Ph	84	84	[49]
4-Tol	Ph	94	54	[49]

[a] Yield determined by ^1H NMR versus an internal standard.

1,1-Diarylethanes 44; General Procedure:[49]
Into a flask, under an inert atmosphere, were added the aryl iodide (0.10 mmol), the benzylic boronate ester (0.147 mmol), Ag_2O (34.5 mg, 0.15 mmol), $Pd_2(dba)_3$ (3.69 mg, 4.0 μmol), and Ph_3P (26.0 mg, 0.099 mmol). THF (1.9 g) was added, and the reaction vessel was sealed and heated to 70 °C. After 24 h, the reaction mixture was passed through a Celite plug and the filtrate was purified by column chromatography (pentane).

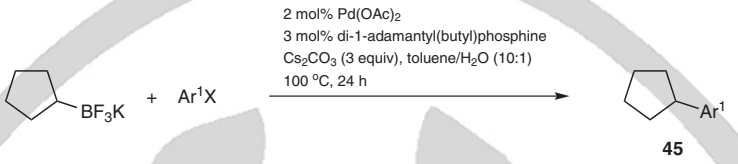
1.1.4.3.3 Non-benzylic Alkylboron Reagents

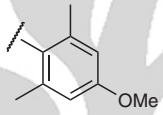
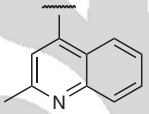
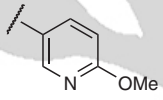
The first significant developments toward the cross coupling of non-benzylic secondary alkylboron reagents were described independently by the van den Hoogenband[50] and Molander[51] groups.

The cross coupling of symmetric cyclic secondary alkyltrifluoroborates with aryl chlorides and bromides can be accomplished using palladium(II) acetate and di-1-adamantyl(butyl)phosphine (Scheme 29).[51] This reaction proceeds readily to give products such as cyclopentylarenes **45**; however, the reaction with acyclic secondary organoboron species is complicated by a β-hydride elimination/reinsertion process that provides a significant quantity of an isomerized primary alkylated product.

for references see p 357

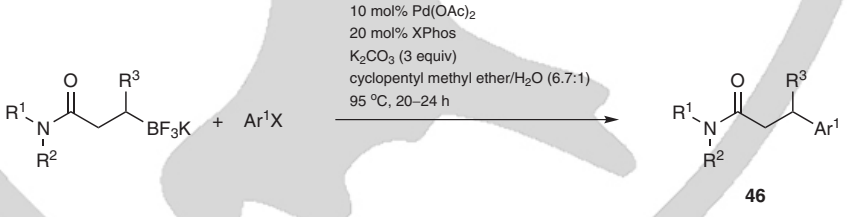
Scheme 29 Cross Coupling of Potassium Cyclopentyltrifluoroborate with Aryl and Hetaryl Halides[51]



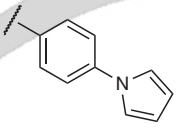
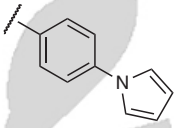
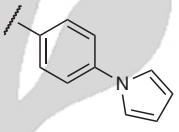
Ar^1	X	Yield (%)	Ref
2-$MeOC_6H_4$	Cl	87	[51]
3-$MeO_2CC_6H_4$	Cl	89	[51]
	Cl	82	[51]
	Cl	88	[51]
	Cl	92	[51]
3-quinolyl	Br	72	[51]

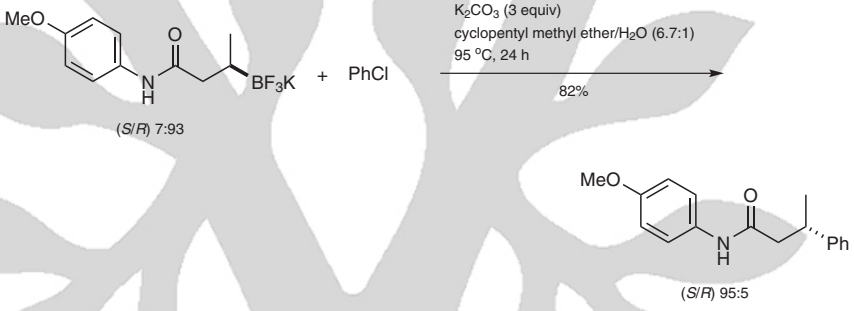
More recently, advances have been described in which stereodefined secondary β-carbamoylalkyl trifluoroborates undergo cross coupling with aryl electrophiles with complete inversion of configuration (Scheme 30).[11] These reactions employ palladium(II) acetate, SPhos or XPhos, and cesium carbonate or potassium carbonate as the base. In a similar fashion to the results described by Suginome and coworkers,[10] the origin of this inversion process most likely derives from an intramolecular coordination of the carbonyl group that inhibits the *syn*-coplanar orientation required for β-hydride elimination and creates a coordinatively unsaturated palladium species that is unable to interact agostically with the β-hydrogens.

Scheme 30 Cross Coupling of (3-Amino-3-oxoalkyl)trifluoroborates with Aryl Halides[11]



R^1	R^2	R^3	Ar^1	X	Yield (%)	Ref
Cy	H	Me	2-$MeOC_6H_4$	Cl	90	[11]
Cy	H	Me	4-NCC_6H_4	Cl	76	[11]
Cy	H	Me	4-$MeO_2CC_6H_4$	Br	92	[11]

R^1	R^2	R^3	Ar^1	X	Yield (%)	Ref
$(CH_2)_4$	Me			Cl	92	[11]
Me	Me	Me		Cl	72	[11]
$(CH_2)_4$	Ph			Cl	94	[11]



Cyclopentylarenes 45; **General Procedure:**[51]
In a glovebox, into a Biotage microwave vial were added $Pd(OAc)_2$ (2.2 mg, 0.01 mol), di-1-adamantyl(butyl)phosphine (5.4 mg, 0.015 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), potassium cyclopentyltrifluoroborate (96.8 mg, 0.55 mmol), and the aryl halide (0.50 mmol). The vial was sealed with a PTFE-lined cap and removed from the glovebox. Toluene (2.5 mL) and H_2O (0.25 mL) were added by syringe and the mixture was stirred at 100 °C. After 24 h, the mixture was allowed to cool to rt, and GC/MS analysis showed complete conversion of the aryl halide. The organic layer was separated and the aqueous layer was washed with EtOAc (3 × 1 mL). The combined organic phases were concentrated under reduced pressure and purified by column chromatography (silica gel).

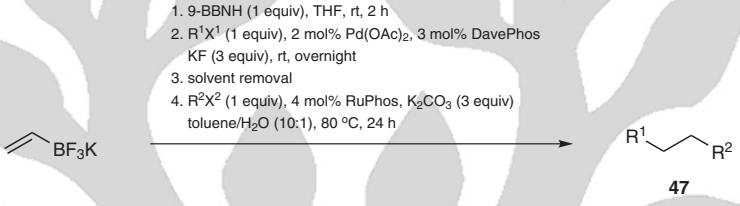
3-Arylalkanamides 46; **General Procedure:**[11]
To a Biotage microwave vial were added $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), XPhos (0.05 mmol, 20 mol%), K_2CO_3 (0.75 mmol, 3 equiv), the aryl electrophile (0.25 mmol, 1 equiv), and the potassium trifluoroborate (0.25 mmol, 1 equiv). The vial was sealed and purged with N_2 (3 ×), cyclopentyl methyl ether (1.0 mL) and H_2O (0.15 mL) were added, and the mixture was heated to 95 °C for 20–24 h. The mixture was allowed to cool to rt and was then quenched with H_2O (1 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, concentrated, and purified by column chromatography (silica gel).

for references see p 357

1.1.4.4 Cross Coupling of Diborylalkane Species

In recent years, a number of strategies have been described that incorporate two boron groups into a molecule and subsequently selectively react one over the other. One strategy exploits the use of potassium trifluoro(vinyl)borate as a 1,2-dianion equivalent. This substrate readily undergoes hydroboration with 9-borabicyclo[3.3.1]nonane, and the intermediate species contains two orthogonally reactive boron species. The trialkylborane moiety can be chemoselectively reacted with a variety of aryl electrophiles using palladium(II) acetate and DavePhos, and the resulting (2-arylethyl)trifluoroborate species readily undergoes further cross coupling with aryl, hetaryl, and alkenyl electrophilic species to give 1,2-diarylethanes **47** (Scheme 31).[52]

Scheme 31 One-Pot Generation/Cross Coupling of a 1,2-Diborylethane[52]

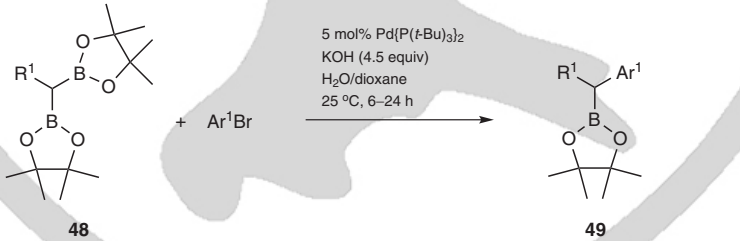


47

R^1	X^1	R^2	X^2	Yield (%)	Ref
4-NCC_6H_4	Br	4-AcC_6H_4	Br	77	[52]
4-NCC_6H_4	Br	3-$MeO_2CC_6H_4$	Br	82	[52]
4-$F_3CC_6H_4$	Br	4-$MeO_2CC_6H_4$	Br	76	[52]
3,5-$(MeO)_2C_6H_3$	Cl	4-AcC_6H_4	Cl	78	[52]
3,5-$(MeO)_2C_6H_3$	Cl	4-$OHCC_6H_4$	Cl	81	[52]
4-AcC_6H_4	Cl	4-$OHCC_6H_4$	Cl	79	[52]

1,1-Diborylalkanes **48** can be utilized in the Suzuki–Miyaura cross-coupling reaction. Once prepared, the boron moieties are symmetrically reactive; however, reaction at one center provides a secondary alkylboronate ester which is unreactive under the reaction conditions. Thus, even in the presence of excess amounts of the electrophilic partner, the second boron moiety is left intact in benzylic boronate esters **49** and can be used for further chemical transformations (Scheme 32).[53]

Scheme 32 Cross Coupling of 1,1-Diborylalkanes and Aryl Bromides[53]

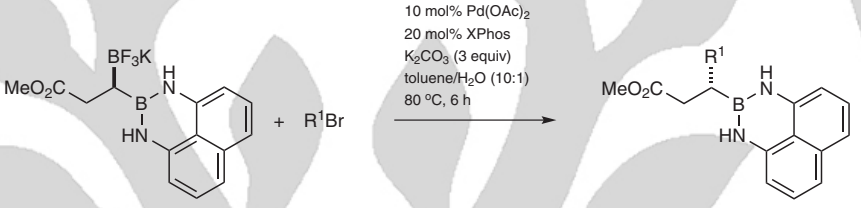


48 **49**

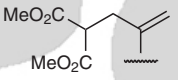
R^1	Ar^1	Yield (%)	Ref
$(CH_2)_4Ph$	Ph	74	[53]
$(CH_2)_4Ph$	4-$MeOC_6H_4$	75	[53]
$(CH_2)_4Ph$	2-$iPrC_6H_4$	61	[53]
Me	4-$MeOC_6H_4$	68	[53]
Bn	4-$MeOC_6H_4$	65	[53]
$(CH_2)_2OBn$	4-$MeOC_6H_4$	42	[53]

In another example, diboryl carboxylic acid ester **50** undergoes selective reaction at the organotrifluoroborate moiety in the presence of aryl and alkenyl bromides in good yields with inversion of configuration in the monoboryl esters **51** (Scheme 33).[54]

Scheme 33 Selective Cross Coupling of a 3,3-Diboryl Ester[54]



50 99% ee (1.2 equiv) **51**

R^1	ee (%)	Yield (%)	Ref
2-Tol	99	83	[54]
4-ClC_6H_4	99	85	[54]
4-$MeOC_6H_4$	99	88	[54]
2-thienyl	97	71	[54]
	99	81	[54]
(*E*)-CH=CHTMS	91	51	[54]

1,2-Diarylethanes 47; **General Procedure:**[52]

In a glovebox, into a 10-mL Biotage microwave vial were added potassium trifluoro(vinyl)-borate (33.5 mg, 0.25 mmol) and 9-BBNH (31.0 mg, 0.25 mmol). The reaction vial was sealed with a rubber septum and then removed from the glovebox. Under a N_2 atmosphere, THF (2 mL) was added, and the mixture was stirred at rt for 2 h. Into a separate 10-mL Biotage microwave vial, fitted with a rubber septum, were added $Pd(OAc)_2$ (1.12 mg, 5 μmol), DavePhos (2.95 mg, 7.5 μmol), KF (43.6 mg, 0.75 mmol), and the electrophile R^1X^1 (0.25 mmol). The septum-sealed vial was purged with N_2, and the THF mixture containing the diboryl species was added dropwise via a double-ended needle. The resulting mixture was stirred overnight at rt and then the solvent was removed under reduced pressure. Then, into the same 10-mL Biotage tube were added RuPhos (4.70 mg, 0.010 mmol) and K_2CO_3 (104 mg, 0.75 mmol). The tube was sealed with a cap lined with a disposable PTFE septum, evacuated, and purged with N_2 (3×). The second electrophile (R^2X^2; 0.25 mmol) and toluene/H_2O (10:1) were added to the vial, and the mixture was heat-

for references see p 357

ed to 80 °C for 24 h and then allowed to cool to rt. The organic layer was separated, and the aqueous layer was washed with EtOAc (3 × 1 mL). The combined organic phases were concentrated and purified by column chromatography (silica gel).

2-(1-Arylalkyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes 49**; General Procedure:**[53]
To a soln of the 1,1-diborylalkane **48** (0.3 mmol, 1.5 equiv), the aryl electrophile (0.2 mmol, 1 equiv), and Pd{P(*t*-Bu)$_3$}$_2$ (5 mol%) in dioxane (1 mL) was added 8 M aq KOH (112 μL, 0.9 mmol). The mixture was stirred at 25 °C for 6–24 h, and then filtered through a pad of silica gel, eluting with Et_2O. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel).

3-Substituted Methyl 3-(1*H*-Naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanoates 51**; General Procedure:**[54]
$Pd(OAc)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.30 mmol), the electrophile (0.10 mmol), and the 3,3-diboryl ester **50** (0.12 or 0.15 mmol) were stirred in toluene (1.0 mmol) and H_2O (0.10 mL) at 80 °C. After 6 h, the mixture was cooled and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

1.1.4.5 Conclusions

Since the first report of the cross coupling of an alkylboron derivative, there have been significant advances in the scope of the cross-coupling reaction with respect to the diversity of reagents that can be employed as the nucleophilic partner, and the variety of electrophilic partners that can be utilized in this context. The efforts to date have led to promising progess toward achieving the holy grail of alkylboron coupling: the cross coupling of secondary enantioenriched derivatives with complete stereochemical control.

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