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Cross-Coupling

Stereospecific Couplings of Secondary and Tertiary Boronic Esters

Daniele Leonori and Varinder K. Aggarwal**

boron · cross-coupling · homogeneous catalysis · palladium · synthetic methods

This Minireview highlights advances in the Suzuki–Miyaura cross-coupling of secondary boron reagents for the creation of C–C bonds with control of stereochemistry. It also includes non-transition-metal coupling of secondary and tertiary boronic esters to electron-rich aromatics.

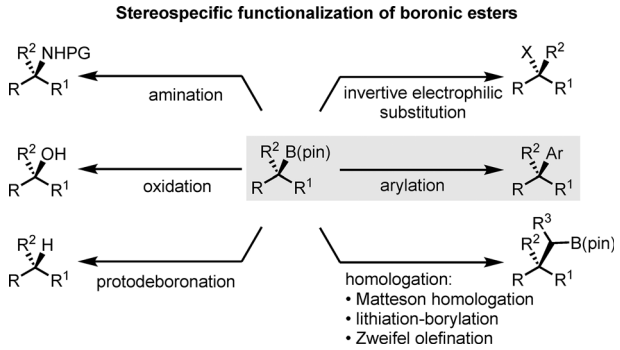
1. Introduction

Chiral boronic esters and their derivatives are powerful building blocks in asymmetric synthesis. They can be easily prepared in high yields and selectivity, and they display a high degree of chemical stability. The fact that boronic esters exhibit greater configurational stability than any other chiral organometallic reagents (e.g. organolithiums, organomagnesiums, organocoppers, organotins)[1] makes them very useful synthetic intermediates. Furthermore their stereospecific conversion into other useful functional groups is a continually expanding and contemporary area of research.

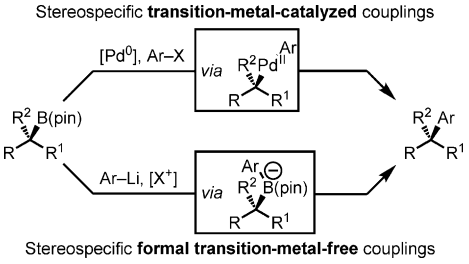
Although the most common transformation of this class of substrates is their oxidation to alcohols, many other protocols have now been reported and have significantly expanded their synthetic utility (Scheme 1).

In particular, the recent stereospecific arylation of secondary and tertiary boronic esters provides a new method for the synthesis of well-defined three-dimensional molecules, an area which has received significant attention in recent years. Based on the mechanism involved, this field of research can be divided into classical transition-metal-catalyzed couplings and formal non-transition-metal couplings (Scheme 2).

In this review, we present stereospecific coupling reactions of chiral, nonracemic boronic esters. The scope and limitations of those methods are described with particular emphasis on the mechanistic aspects.



Scheme 1. pin = pinacol.



Scheme 2.

2. Transition-Metal-Catalyzed Couplings

2.1. Pioneering Mechanistic Studies

The transition-metal-catalysed coupling of organoborons, the Suzuki–Miyaura cross-coupling, is one of the most versatile methods for the formation of C–C bonds.[2,3]

The development of a stereospecific Suzuki cross-coupling of chiral organoborons is directly related to the possibility of achieving full chirality transfer from the chiral organoboron to the aryl-alkyl-Pd^{II} intermediate by B→Pd^{II}

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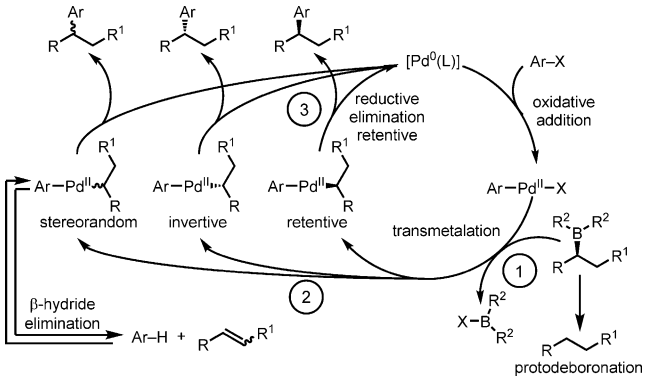
transmetalation.[4] After reductive elimination, a well-established retentive process,[5] the desired enantioenriched product is delivered.

In looking at the mechanism for the palladium(0)-catalyzed Suzuki cross-coupling, three key aspects need to be simultaneously fulfilled (Scheme 3):



Scheme 3.

1. The chiral organoboron reagent has to be sufficiently reactive to undergo the transmetalation process, but at the same time sufficiently stable not to undergo protodeboronation or other decomposition pathways.
2. The B→Pd^{II} transmetalation should be stereospecific (either retention or inversion). If a combination of both pathways takes place or if a radical (e.g., not chiral) intermediate is involved, a detrimental erosion of enantiopurity will be observed in the final product.
3. The aryl-alkyl-Pd^{II} intermediate needs to undergo the reductive elimination step at a faster rate than β-hydride elimination to avoid isomerized products and the formation of olefin by-products.

The first mechanistic study aimed at evaluating the stereochemical outcome of the palladium(0)-catalyzed cross-coupling of chiral organoborons was reported independently by the groups of Woerpel[6] and Soderquist (Scheme 4).[7] In their seminal work, these authors took advantage of a method developed by Whitesides and co-workers to access the configurationally stable alkylboranes.[8] This method requires the use of racemic but configurationally defined *syn* and *anti* α,β-deuterated primary alkyl organometallics. By taking advantage of the preferential population of the anti-periplanar conformation for bulky 1,2-disubstituted alkanes, this method relies solely on ^{1}H NMR analysis of the vicinal *J* constants to determine the stereochemistry of the products. In addition, the incorporation of D atoms, while making the products diastereomeric, does not perturb the reaction in terms of steric bias.

These initial mechanistic studies showed that deuterated alkyl BBN-boranes undergo palladium(0)-catalyzed cross-coupling with vinyl and aryl halides with retention of configuration at the boron-bearing carbon atom (Scheme 4 A,B). More recently Taylor and Jarvo reported a similar study for the nickel(II)-catalyzed coupling of alkylboranes with primary alkyl halides. Also in this case, ^{1}H NMR analysis of the reaction products confirmed the retentive nature of the transmetalation process under nickel(II) catalysis (Scheme 4 C).[9]

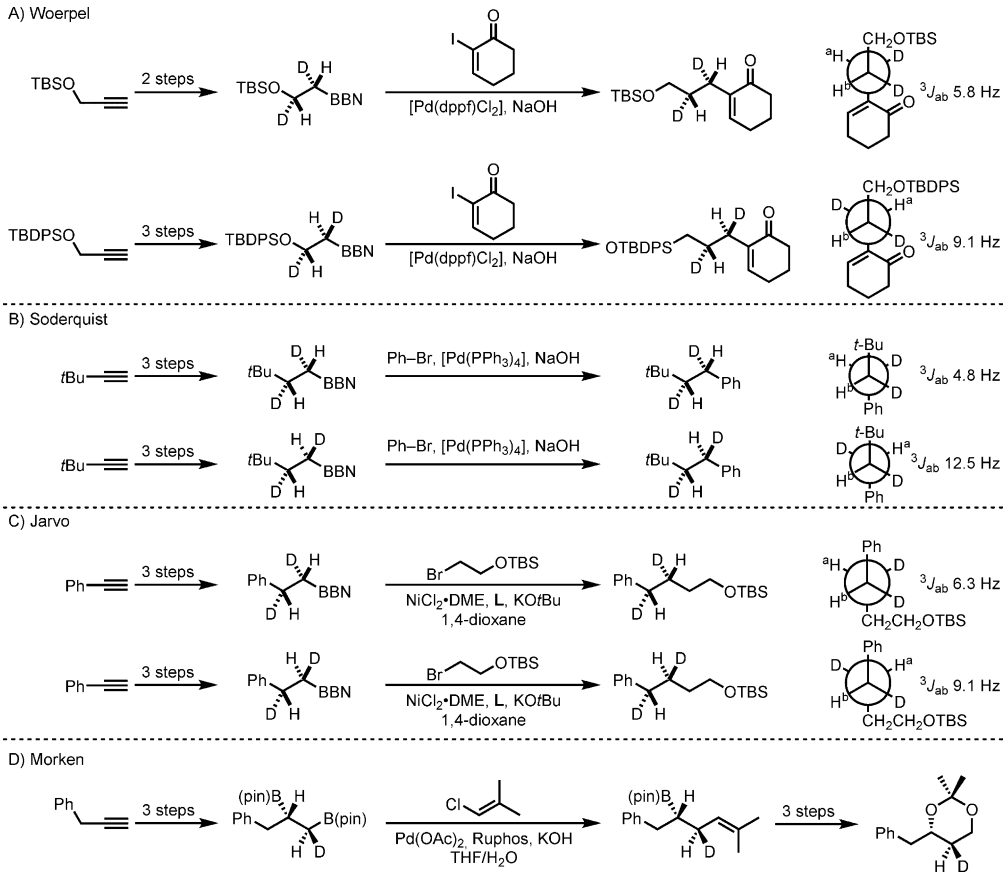
In 2014 Morken and co-workers disclosed a similar mechanistic study for the Suzuki–Miyaura cross-coupling of 1,2-diboryl ester substrates.[10] Also in this case the palladium(0)-catalyzed coupling with vinyl halides was found to be retentive. This finding is consistent with an inner-sphere transmetalation (Scheme 4 D).

Additional mechanistic studies by Soderquist revealed a significant difference in the nature of the catalytic cycle based on the nature of the boron reagent employed (Scheme 5).[7] In fact, while the use of boranes (e.g. R-BBN) resulted in very fast couplings, the use of borinic esters (e.g., R-OBBD) was characterized by considerably slower rates. In the case of boranes, the reaction rate was found to be independent of [R-BBN] but it displayed a first-order dependence on [Ph-Br], thus making the oxidative addition of palladium(0) into the aryl halide the rate-determining step (RDS) for this coupling process (Scheme 5 A). Following activation of the borane by the hydroxide base results in fast B→Pd^{II} transmetalation via the initial Pd^{II}-oxo complex **1**.

In the case of borinic esters, the reaction rate was found to be independent of both [R-OBBD] and [Ph-Br] but it displayed a first-order dependence on [HO$^-$]. After extensive kinetic studies the authors identified the hydrolysis of the Ph-

Daniele Leonori (left) was born in Italy in 1982, studied Medicinal Chemistry at the Università degli Studi di Perugia, and completed his Ph.D. in 2010 at the University of Sheffield with Prof. Iain Coldham. After postdoctoral studies with Prof. Magnus Rueping (RWTH Aachen University) and with Prof. Peter H. Seeberger (Max Planck Institute of Colloids and Interfaces) he joined the group of Prof. Varinder K. Aggarwal as a Research Officer (University of Bristol, 2012–2014). He is now a Lecturer in Organic Chemistry at the University of Manchester.

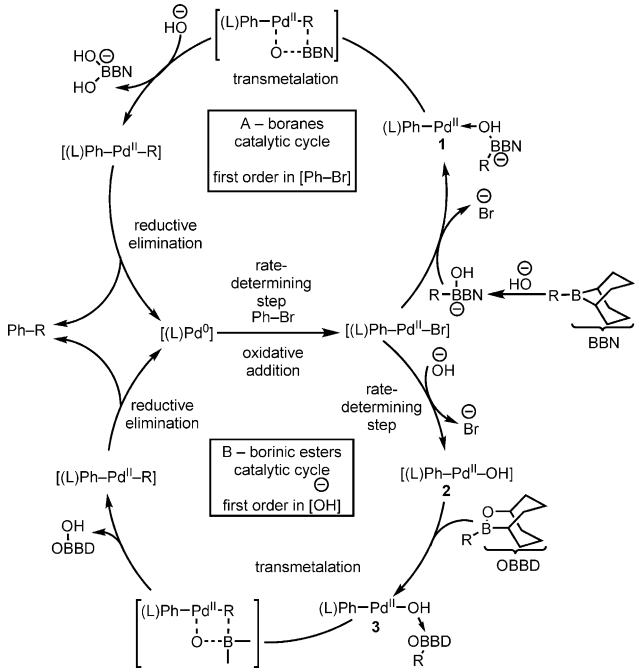
Varinder K. Aggarwal (right) studied chemistry at Cambridge University and received his Ph.D. in 1986 under the guidance of Dr. Stuart Warren. After postdoctoral studies (1986–1988) with Prof. Gilbert Stork, Columbia University, he returned to the UK as a Lecturer at Bath University. In 1991 he moved to Sheffield University, and was promoted to Professor in in 1997. In 2000 he moved to Bristol University where he holds the Chair in Synthetic Chemistry. His current research interests center on the development of new catalytic processes for asymmetric synthesis.



Scheme 4. DME = dimethoxyethane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, Ruphos = 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

Pd^{II}-Br complex to the Ph-Pd^{II}-OH complex **2** to be the RDS (Scheme 5B). The complex **2** was proposed to be the active palladium(II) species which interacted with the borinic ester and initiated the B→Pd^{II} transmetalation via the initial complex **3**.

These pioneering mechanistic studies have helped the development of the field of stereospecific Suzuki–Miayura cross-couplings by delineating some of the critical factors that affect the key B→Pd^{II} transmetalation. This aspect will be discussed further in the following sections.



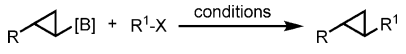
Scheme 5.

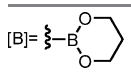
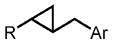
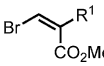
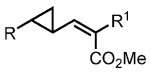
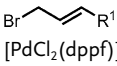
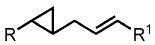
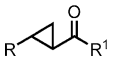
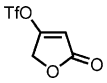
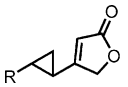
2.2. Couplings of Cyclopropyl Boronic Esters

Cyclopropyl-based organoborons were the first class of chiral secondary boron-containing compounds that were successfully employed in stereospecific Suzuki–Miayura cross-couplings. Because of the partial p character of the cyclopropyl exocyclic bonds,[11] the transmetalation process is less problematic. In addition these substrates are less prone to undergo β-hydride elimination, and this minimizes the formation of by-products.

Initial work by the groups of Marsden,[12] Charette,[13,14] Deng,[15–22] and Soderquist[23] revealed that geometrically pure (racemic) cyclopropylborons could be coupled under palladium(0) catalysis with a broad array of activated coupling partners in good yields and complete retention of configuration (Table 1). Both boronic esters (entries 1–3), boronic acids (entries 4–8), potassium trifluoroborate salts (entry 9),

Table 1:

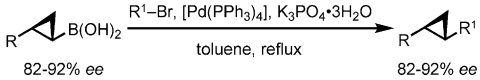


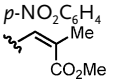
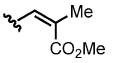
Entry	Conditions	Product	Ref.
[B]= 			
1	Ar-Br $[Pd(PPh_3)_4]$, KO*t*Bu, DME, reflux		[12]
2	 $Pd(OAc)_2$, PPh_3, KO*t*Bu, DME, 80 °C		[13]
3	 $[PdCl_2(dppf)]$, Ag_2O, KOH THF, reflux		[22]
[B] = $B(OH)_2$			
4	Ar-Br $[Pd(PPh_3)_4]$, $K_3PO_4 \cdot 3\,H_2O$, toluene, 100 °C		[16]
5	 $[Pd(PPh_3)_4]$, $K_3PO_4 \cdot 3\,H_2O$, toluene, 100 °C		[20,21]
6	 $[PdCl_2(dppf)]$, Ag_2O, KOH, 1,4-dioxane, 80 °C		[18]
7	R^1-COCl $[PdCl_2(dppf)]$, Ag_2O, K_2CO_3 toluene, 80 °C		[19]
8	 $[Pd(MeCN)_2Cl_2]$, $AsPh_3$, Ag_2O, THF, 70 °C		[17]
[B] = BF_3K			
9	Ar-Br $[Pd(PPh_3)_4]$, $K_3PO_4 \cdot 3\,H_2O$, toluene-H_2O, reflux		[14,15]
[B] = BBN			
10	Ar-Br $[Pd(PPh_3)_4]$, NaOH, THF, reflux		[23]

and boranes (entry 10) could be used with sp^2-based and activated sp^3-based electrophiles. However attempts at using the bench-stable pinacol boronic esters were unsuccessful.

The first example of a stereospecific Suzuki–Miyaura cross-coupling of a geometrically defined and enantioenriched cyclopropylboron was reported by Deng and coworkers in 1998.[24] The required enantioenriched boronic acids were prepared by substrate-controlled cyclopropanation of a boronic ester tartaramide followed by hydrolysis. The boronic acids efficiently coupled with sp^2-type coupling partners in high yield and retention of configuration (Table 2). The scope of this coupling protocol was investigated and found to be compatible with a range of aryl bromides (entries 2–4). Activated vinyl bromides could also be employed (entries 5 and 6). Unfortunately, the direct use of the boronic ester only gave the arylated product in poor yield.

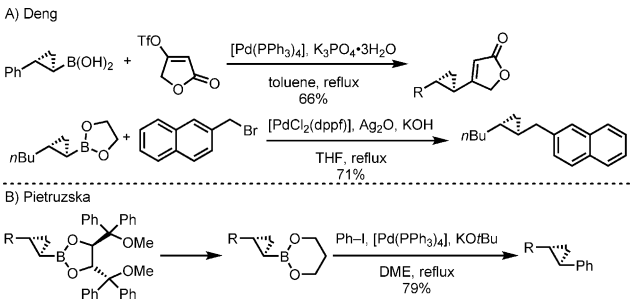
Table 2:



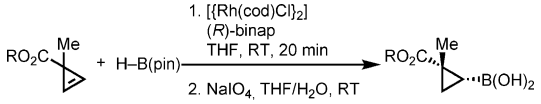
Entry	R	R^1	Yield [%]
1	Ph	Ph	77
2	Ph	*o*-$MeOC_6H_4$	90
3	Ph	*o*-AcC_6H_4	83
4	Ph	*p*-$NO_2C_6H_4$	87
5	Ph		81
6	*n*-hex		76

Later reports from the same authors expanded the range of coupling partners to vinyl triflates and benzylic bromide (Scheme 6A).[17,22] However, to promote the stereospecific cross-coupling with benzylic bromides, glycol boronic esters needed to be used. Similar results were also obtained by Luithle and Pietruzska during the evaluation of new enantiopure cyclopropyl boronic esters building blocks in cross-coupling protocols.[25] Also in their case the bulky taddol-like group needed to be exchanged for a less sterically hindered diol to facilitate the transmetalation process (Scheme 6B).

In 2003 Gevorgyan and co-workers demonstrated the first stereospecific coupling of trisubstituted enantioenriched cyclopropyl boronic acids.[26] The required starting materials were prepared by asymmetric hydroboration of ester functionalized cyclopropenes with pinacol borane under rhodium(I) catalysis, followed by $NaIO_4$-mediated hydrolysis of the pinacol group (Scheme 7). Under these reaction conditions the boronic acids were obtained as single *cis* diastereoisomers in very high yields and almost perfect levels of enantioselec-



Scheme 6.

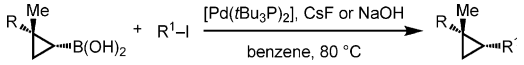


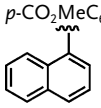
Scheme 7. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene.

tivity. The direct use of pinacol boronic esters only resulted in inefficient coupling, hence the need for hydrolysis to the boronic acid.

Exposure of the boronic acids to aryl and vinyl iodides in the presence of $[Pd(tBu_3P)_2]$,[27] gave the desired products in high yields and complete retention of configuration (Table 3).

Table 3:



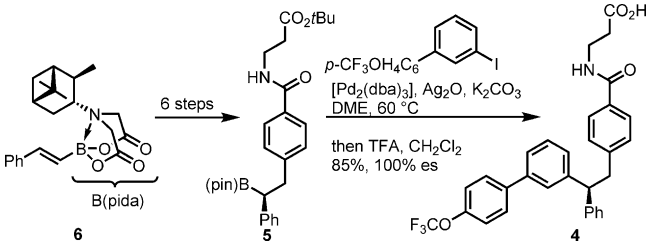
Entry	R	R^1	Yield [%]
1	CO_2Me	Ph	76
2	CO_2Me	*p*-$MeOC_6H_4$	77
3	CO_2Me	*p*-$CO_2MeC_6H_4$	64
4	CO_2Me		85
5	CO_2Me		65
6	CH_2OMe	Ph	85

2.3. Couplings of Secondary Benzylic Boronic Esters

The stereospecific coupling of secondary benzylic boronic esters with aryl halides constitutes not only the first reaction wherein the proof-of-concept of stereospecific couplings was established, but also the largest field of application resulting from the relevance of chiral diarylmethane motifs in many pharmaceuticals and natural products.

In 2009 Crudden an co-workers reported that $[Pd_2(dba)_3]\cdot PPh_3$ was an active catalyst for the coupling of aryl iodides with enantioenriched 1-arylethylboronic esters, which were readily available by asymmetric hydroboration[28–30] of styrene (Table 4).[31,32] Importantly, the choice of the base proved to be critical and only Ag_2O provided the desired products in good yields and high levels of enantiospecificity (es).[33,34] The use of this particular base was believed to assist the slow transmetalation step by simultaneously swapping the halide on palladium for the oxo-species (see Section 2.1, Scheme 5).[35,36] In accordance with the mechanistic studies by the groups of Soderquist and Woerpel,[6,7] all the substrates reacted with retention of configuration. The scope of the aryl iodide partner was evaluated and both electron-poor and electron-rich groups were tolerated (Table 4, entries 1–6). However, substitution at the aryl group of the boronic ester gave the desired products in lower levels of es (entries 7 and 8). Aryl bromides could also be used but they generally provided the desired products in diminished yields.

Recently the application of this new coupling protocol has been demonstrated by Li and Burke in a short total synthesis of **4**, a glucagon receptor antagonist (Scheme 8).[37] The highly



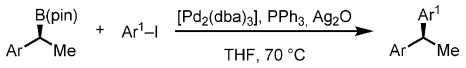
Scheme 8. TFA = trifluoroacetic acid.

enantioenriched benzylic pinacol boronic ester **5** was prepared in six steps using the pinene-derived iminodiacetic acid (pida)-based boronic ester building block **6**. Exposure of **5** to the Crudden coupling conditions gave the desired arylated product, which after acidic treatment provided **4** in 85% yield and 100% es.

Building on their initial discovery Crudden and co-workers have expanded the stereospecific arylation of chiral boronic esters to substrates bearing two different aryl groups.[38] In this case, neopentyl boronic esters were used (prepared using a modified Aggarwal lithiation–borylation reaction)[39,40] because of the difficulties in the generation of highly enantioenriched pinacol boronic esters. Exposure of these substrates to the reaction conditions analogous to the ones developed before, gave chiral triarylmethanes in high yield and almost complete enantiospecificity with retention of configuration (Table 5). While modification of electronics was well tolerated, increased steric bulk gave lower enantiospecificity (entry 4).

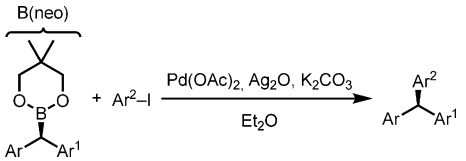
Recently, Ohmura, Awano, and Suginome reported the first example of a Suzuki–Miyaura cross-coupling that proceeded with inversion of stereochemistry at the boron-bearing carbon atom (Table 6).[41] This impressive result was demonstrated with α-(acylamino)benzyl boronic esters, which

Table 4:



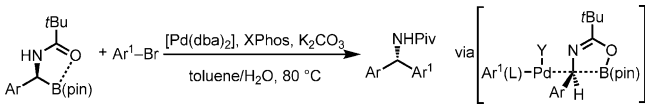
Entry	Ar	Ar^1	Yield [%]	es [%]
1	Ph	*p*-AcC_6H_4	63	92
2	Ph	*p*-ClC_6H_4	62	91
3	Ph	*p*-MeC_6H_4	60	92
4	Ph	3,5-$(Me)_2C_6H_3$	64	93
5	Ph	*p*-$MeOC_6H_4$	48	93
6	Ph	*o*-MeC_6H_4	48	93
7	*p*-ClC_6H_4	Ph	64	84
8	*p*-MeC_6H_4	Ph	38	84

Table 5:

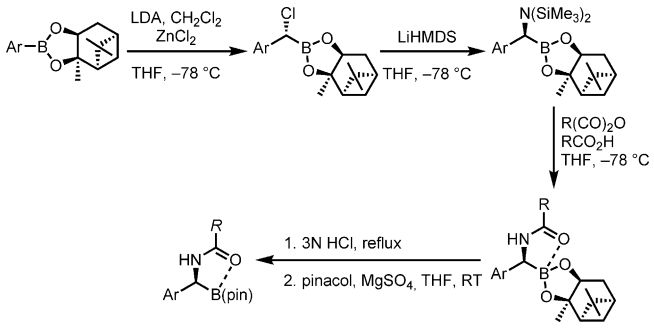


Entry	Ar	Ar^1	Ar^2	Yield [%]	es [%]
1	*m*-$MeOC_6H_4$	*p*-AcC_6H_4	*p*-EtC_6H_4	80	90
2	*m*-$MeOC_6H_4$	*p*-AcC_6H_4	*p*-FC_6H_4	69	93
3	*m*-$MeOC_6H_4$	*p*-$CHOC_6H_4$	Ph	66	92
4	2-naphthyl	*o*-MeC_6H_4	Ph	60	78

Table 6:



Entry	Ar	Ar^1	Yield [%]	es [%]
1	Ph	*p*-$MeOC_6H_4$	76	97
2	Ph	*p*-$CO_2EtC_6H_4$	87	97
3	Ph	*p*-$CF_3C_6H_4$	85	96
4	Ph	*p*-$CHOC_6H_4$	84	98
5	Ph	2-naphthyl	76	96
5	Ph	*o*-MeC_6H_4	79	95
7	Ph	3-thienyl	80	96
8	Ph	3-pyridyl	83	92
9	*p*-$MeOC_6H_4$	Ph	79	98
10	2-naphthyl	Ph	68	95
11	*p*-MeC_6H_4	Ph	55	82



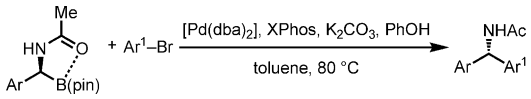
Scheme 9. HMDS = hexamethyldisilazide, LDA = lithium diisopropylamide.

were prepared in five steps using a Matteson homologation of (−)-pinanediol-based aryl boronic esters (Scheme 9).[42]

During the optimization process, the authors discovered that the selectivity was dependent on the nature of the N-acyl group, the base, and the phosphine. After extensive screening of reaction conditions, the use of the sterically demanding pivaloyl (Piv) group in combination with K_2CO_3 as the base and XPhos as the phosphine ligand was found to be optimal, thus providing excellent yields and almost perfect enantiospecificities with inversion of configuration. The substrate scope for the cross-couplings was very broad and differentially functionalized aryl bromides, and both electron-rich and electron-poor heterocyclic bromides were successfully employed (Table 6). The inversion of the stereochemistry has been rationalized by the authors on the basis of an amide-chelated transition state (TS) during the key B→Pd^{II} transmetalation event. The strong and observable intramolecular coordination of the carbonyl oxygen atom to the boron atom (^{11}B NMR $\delta = 14–16$ ppm) is believed to play a key role making the empty orbital on boron unavailable for coordination to palladium(II). As such, the palladium approaches from the opposite side of the boron atom (S_E2inv pathway).

Later reports by the same authors demonstrated that the stereochemical outcome of this process could be controlled by the careful addition of Brønsted or Lewis acid additives.[43] In particular, after a survey of many acidic additives, phenol (2.5 equiv) was found to be the best Brønsted acid to promote the invertive coupling. With this additive the use of the Piv group was not necessary and the synthetically more useful N-Ac derivatives could be coupled in high yields and very high levels of enantiospecificity with inversion of configuration (Table 7).

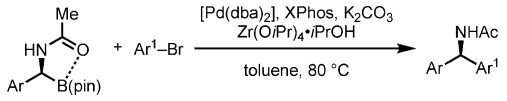
Table 7:



Entry	Ar	Ar^1	Yield [%]	es [%]
1	Ph	*p*-MeC_6H_4	67	98
2	Ph	*p*-$MeOC_6H_4$	60	99
3	Ph	*p*-$CF_3C_6H_4$	83	94
4	Ph	*o*-MeC_6H_4	69	91
5	*p*-$MeOC_6H_4$	Ph	75	98

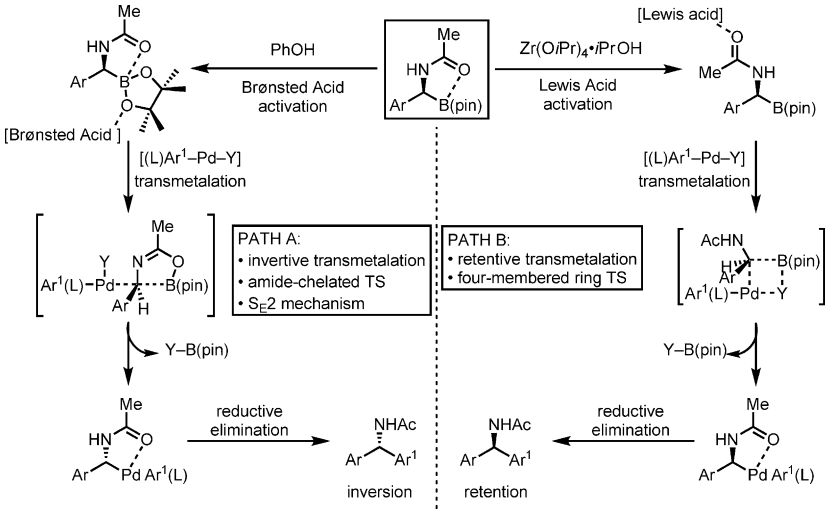
Impressively, when the Lewis acid $Zr(OiPr)_4{\cdot}i$PrOH[44] (1–0.5 equiv) was used, a dramatic switch to retention (instead of inversion) was observed and the products were now formed in high yields and enantiospecificities (Table 8).

Table 8:



Entry	Ar	Ar^1	Yield [%]	es [%]
1	Ph	*p*-$MeOC_6H_4$	67	78
2	Ph	*p*-$CF_3C_6H_4$	96	83
3	Ph	*o*-MeC_6H_4	73	86
4	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	71	85

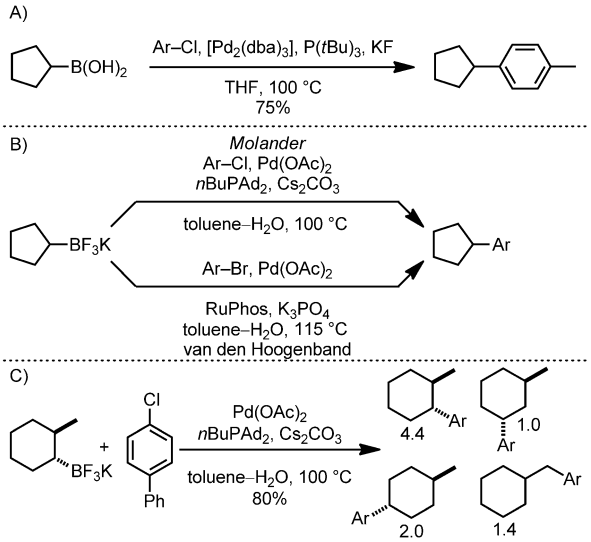
The opposite stereochemical outcomes have been explained by the authors considering the different abilities of phenol and $Zr(OiPr)_4{\cdot}i$PrOH to activate the starting α-(acylamino)benzyl boronic ester. In the absence of any additive, the boronic ester displays a strong C=O→B interaction. Phenol was proposed, acting as a Brønsted acid, to protonate the pinacol group and reinforce the C=O→B interaction. This arrangement would lead to an inversion for the transmetalation via an amide-chelated TS (Scheme 10, Path A). In the $Zr(OiPr)_4{\cdot}i$PrOH process, the Lewis acid was expected to disrupt the C=O→B interaction by competitive coordination with the C=O group. This arrangement would form an electropositive boron species which could undergo the transmetalation via a cyclic four-membered-ring TS and form the intermediate aryl,alkyl-Pd^{II} complex with retention of configuration (Scheme 10, Path B). These findings make this protocol a rare example of a enantiodivergent cross-coupling process, where starting from one enantiomer of the boronic ester, either enantiomer of the final product can be obtained depending on the reaction conditions.



Scheme 10.

2.4. Couplings of Secondary Nonbenzylic Boronic Esters

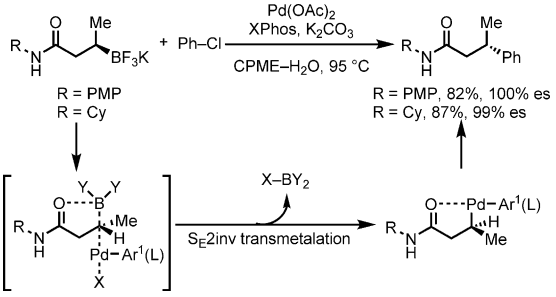
The development of Suzuki–Miayura cross-couplings of secondary nonbenzylic boronic esters has historically been a much more difficult challenge because of the lower reactivity of these substrates compared to that of the secondary benzylic ones. In an isolated example, Fu and co-workers had demonstrated the ability of cyclopentyl boronic acid to undergo efficient coupling with *p*-tolyl chloride without competing protodeboronation (Scheme 11 A).[45] In



Scheme 11. Ad = adamantyl.

2008 the groups of Molander[46] and van den Hoogenband[47] independently reported the successful Suzuki–Miyaura cross-coupling of symmetrical secondary potassium trifluoroborate with aryl halides (Scheme 11 B). However, when applied to unsymmetrical systems the coupling reaction led to mixtures of isomers arising from competing β-hydride elimination/isomerization/re-addition pathways (Scheme 11 C).[46] Such processes may also have occurred in examples shown in Schemes 11 A and B but they are not observable.

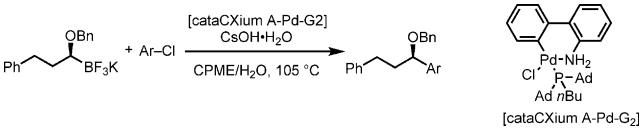
In an attempt to address these limitations, Molander and co-workers first demonstrated that enantioenriched secondary nonbenzylic potassium trifluoroborate salts were efficient coupling partners in stereospecific Suzuki–Miyaura cross-couplings (Scheme 12).[48] However, to display sufficient

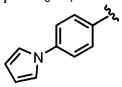
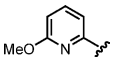


Scheme 12. PMP = *para*-methoxyphenyl.

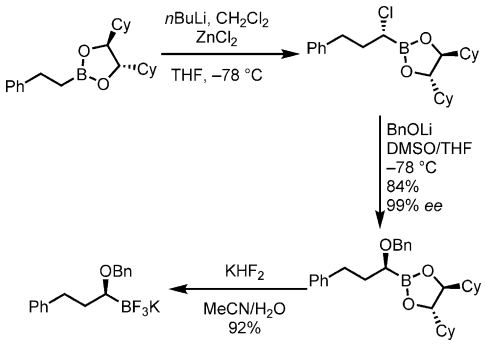
reactivity an ancillary group able to 1) coordinate the boron atom, 2) assist in the transmetalation step, and 3) stop the β-hydride elimination needed to be present. The substrates that were successful in this novel coupling protocol were β-BF_3 amides (β-BF_3 esters and ketones did not work) and exposure to reaction conditions similar to those developed by Ohmura, Awano, and Suginome[41] [$Pd(OAc)_2$, XPhos, K_2CO_3] gave the desired products in good yields and almost perfect enantiospecificities with inversion of configuration. Also in this case the authors rationalized the invertive stereochemical outcome on the basis of the ability of the ancillary carbonyl group to coordinate the B atom and thus allow only a $S_E2$inv transmetalation process. This coordination was also proposed to restrict the conformation of the aryl,alkyl-Pd^{II} intermediate, thus inhibiting a syn-periplanar arrangement between the palladium and the α-C=O hydrogen atoms. This arrangement minimizes β-hydrogen elimination pathways.

Table 9:



Entry	R	Yield [%]	es [%]
1	*p*-$CF_3C_6H_4$	81	100
2	*p*-$CO_2MeC_6H_4$	62	100
3	*p*-$BocHNC_6H_4$	70	100
4		86	100
5	*p*-FC_6H_4	75	100
6*	*p*-FC_6H_4	77	98
7*		78	98
8*		65	98

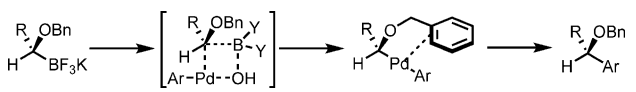
More recently Molander and Wisniweski further extended the scope of the reaction to enantioenriched α-alkoxy organoborons with a broad range of aryl chlorides (Table 9).[49] In this case the potassium trifluoroborates were employed to facilitate the otherwise difficult transmetalation step. The required starting material was prepared with excellent enantioselectivity through Matteson homologation chemistry (Scheme 13).



Scheme 13. DMSO = dimethylsulfoxide.

The authors found that the highly active Buchwald precatalyst [cataCXium A-Pd-G2] and $CsOH{\cdot}H_2O$ were effective for the cross-coupling process. The [cataCXium A-Pd-G2] complex has the advantage that a very active palladium(0) catalyst is generated by fast reductive elimination of carbazole[50] while CsOH·OH has been identified by Carrow and Hartwig as an effective base for cross-couplings where the hydrolysis of the [Ar-Pd^{II}-Br] complex to the [Ar-Pd^{II}-OH] complex is the RDS.[51,52] In contrast to the previous couplings of β-amido trifluoroborate salts, the desired products were formed with retention of configuration.

The stereochemical outcome of this process has been rationalized on the basis of a cyclic four-membered ring TS resulting from the noncoordinating nature of the OBn (Scheme 14). By analogy to what has been found by



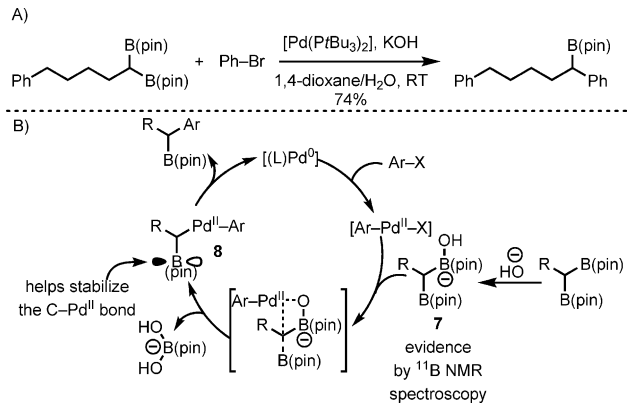
Scheme 14.

Soderquist on the coupling of borinic esters (Section 2.1, Scheme 5),[7] the B atom is most probably activated by the OH group of the palladium(II) complex. Once formed, the aryl,alkyl-Pd^{II} is believed to benefit from stabilization by the OBn group, thus limiting β-hydride elimination.

Hall and co-workers also reported the coupling of secondary potassium trifluoroborate salts.[53] Taking advantage of the seminal reports from the groups of Molander[48] and Endo and Shibata,[54] the authors reported a stereospecific coupling of enantiopure 1,1-diborylated compounds (see Table 10).

In 2010 Endo and Shibata[54] reported the chemoselective cross-coupling of achiral 1,1-diboronyl esters to afford racemic aryl boronic esters in high yields (Scheme 15 A). Computational studies revealed the significant ability of one boronyl group to (i) activate the other boronyl group, thus allowing the formation of the monoboronate complex **7**, and (ii) to stabilize the aryl,alkyl-Pd^{II} species **8** with its empty p orbital (Scheme 15 B). These synergistic effects are believed to increase the rate of transmetalation and diminish competitive β-hydride elimination.

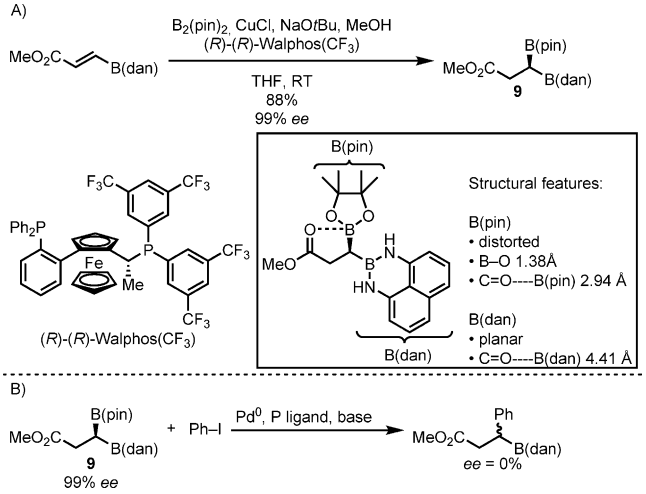
Based on these observations, Hall[53] prepared an enantioenriched 1,1-diboryl species by copper(I)-promoted asymmetric 1,4-addition of $B_2(pin)_2$ to a [B(dan)]-containing α,β-unsaturated ester. The desired product **9** was obtained in excellent yield and enantioselectivity using (*R*)-(*R*)-Walphos-(CF_3) as the chiral ligand (Scheme 16 A). The X-ray structure showed that (i) the [B(pin)] distance from the C=O was considerably shorter than that for [B(dan)], (ii) the [B(pin)] group was distorted while the [B(dan)] was trigonal-planar, and (iii) the activation of the [B(pin)] by the C=O resulted in a longer B–O bond length in the [B(pin)] group (Scheme 16 A). This arrangement would render the [B(pin)] moiety more reactive towards the Suzuki–Miyaura cross-coupling. However, when **9** was used in the cross-coupling reaction under various reaction conditions the desired arylated



Scheme 15.

product was obtained in good yield, but as a racemate (Scheme 16B). This result led the authors to postulate the intermediacy of a transient intermediate which lost its stereochemical integrity in the catalytic cycle.

Based on the work of the group of Molander,[46,48,49] **9** was then converted into the corresponding trifluoroborate **10**, which after exposure to Molander's conditions,[48] led to the formation of the desired arylated product in high yields and almost perfect enantioselectivity with inversion of configuration (Table 10). The scope of the coupling was very broad



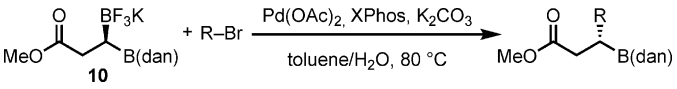
Scheme 16.

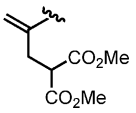
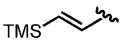
and included electron-rich (entries 1, 4, and 8) and electron-poor (entries 2, 3, 5 and 7) aromatics, heterocycles (entry 9), and it was also extended to vinyl bromides (entries 10–13). By analogy with the work of the groups of Suginome[42] and Molander,[48] the stereochemical outcome was explained on the basis of an S_E2inv transmetalation process promoted by both the internal coordination of the C=O to boron and the neighboring [B(dan)] group.

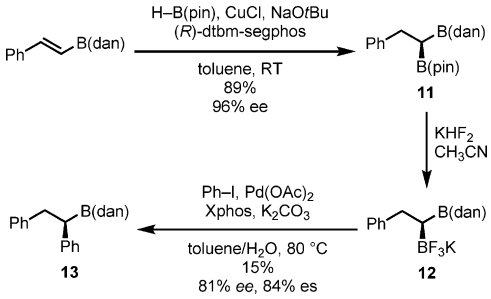
More recently Yun[55] has reported a copper(I)-catalyzed asymmetric hydroboration of borylalkenes to give 1,1-diboraalkanes carrying a gem B(pin)–B(dan) moiety (Scheme 17). The phenyl-substituted substrate **11** does not contain an ancillary group (i.e., a carbonyl group) but after conversion into the corresponding trifluoroborate salt **12**, can be engaged in Suzuki–Miyaura cross-couplings with retention of configuration. Although the product **13** was obtained in low yield and with a diminished *ee* value, this example represents the first stereoretentive coupling of enantioenriched 1,1-diboraalkanes lacking an additional coordinating group.[55]

A highly enantioselective Suzuki–Miyaura cross-coupling of achiral gem pinacol boronic esters has been reported by Morken and co-workers using monodentate taddol-based phosphoramidite ligand (Table 11).[56] The coupling protocol tolerated electron-rich aryl iodides (entries 1, 2, 6, and 7) and substrates with increased steric bulk, although in lower yields (entries 3 and 4). However, the coupling of electron-poor substrates (e.g., *p*-IC_6H_4CN/CO_2Et) was not possible, the

Table 10:



Entry	R	Yield [%]	es [%]
1	*o*-MeC_6H_4	83	100
2	*p*-FC_6H_4	86	100
3	*p*-ClC_6H_4	85	100
4	*p*-$MeOC_6H_4$	88	100
5	*p*-$CF_3C_6H_4$	84	99
6	*m*-$(EtO)_2CHC_6H_4$	85	98
7	*p*-CNC_6H_4	0	–
8	2-naphthyl	79	98
9	2-thienyl	71	98
10		66	96
11		81	100
12		51	92
13		33	89



Scheme 17. dtbm-segphos = 5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole.

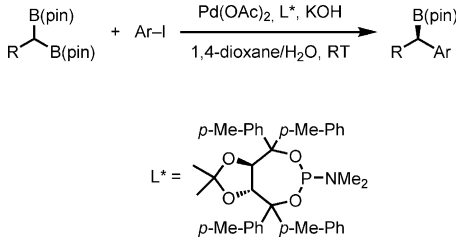
exception being a substrate with a *p*-F substituent (entry 5), because of the in situ protodeboronation of the product. Mechanistic studies performed by the authors suggested that the transmetalation process was the stereodetermining step.

2.5. Couplings of Secondary Allylic Boronic Esters

Allylic boronic esters are a particularly powerful class of chiral building block in asymmetric synthesis. Their prototypical transformation is the 1,2-addition to carbonyl-type functionalities (aldehydes, ketones, imines) and allows the synthesis of functionalized homoallylic alcohols/amines with exquisite control of regio- and stereochemistry.

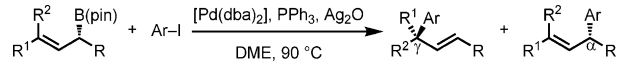
The first Suzuki–Miyaura cross-coupling of racemic allylic boronic esters was described by Crudden and co-workers in 2012.[57] The authors showed that the substrates react with several aryl iodides, preferentially at the γ-position (Scheme 18A). In analogy to the well-understood coupling of allyl silanes,[58,59] the high γ-selectivity was explained on the basis

Table 11:



Entry	R	Ar	Yield [%]	e.r.
1	CH_2Bn	*p*-$MeOC_6H_4$	82	94:6
2	CH_2Bn	*m*-$MeOC_6H_4$	62	93:7
3	CH_2Bn	*o*-$MeOC_6H_4$	55	84:16
4	CH_2Bn	*o*-PhC_6H_4	53	95:5
5	CH_2Bn	*p*-FC_6H_4	82	91:9
6	pentyl	*p*-$MeOC_6H_4$	81	92:8
7	Cy	*p*-$MeOC_6H_4$	43	88:12

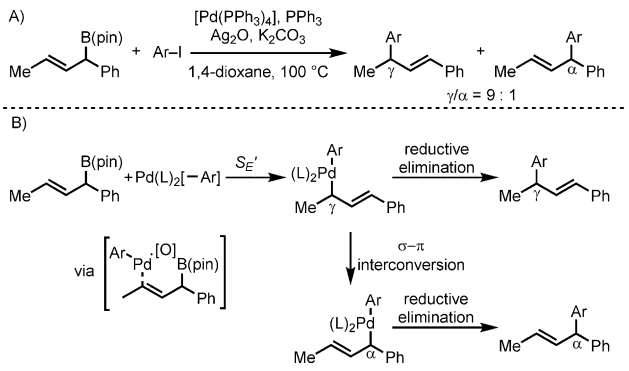
Table 12:



Entry	R^1	R^2	Ar	γ/α	*E*/*Z*	Yield [%]	es [%]
R = CH_2CH_2Ph							
1	H	Me	Ph	83:17	94:6	75	96
2	Me	H	Ph	94:6	78:22	81	100
R = Ph							
3	*n*Pr	H	Ph	98:2	99:1	78	100
R = *i*Pr							
4	H	Me	Ph	90:10	99:1	77	96
5	*n*Pr	H	Ph	92:8	99:1	71	100
6	H	Me	*p*-MeC_6H_4	91:9	99:1	72	93
7	H	Me	*p*-$MeOC_6H_4$	85:15	99:1	72	96
8	H	Me	*p*-BrC_6H_4	90:10	99:1	42	93
9	H	Me	*p*-$CF_3C_6H_4$	90:10	99:1	42	93

of an S_E' transmetalation and a fast reductive elimination. The authors rationalized the formation of the α-arylated product on the basis of a competing σ–π interconversion of the aryl-allyl-Pd^{II} intermediate prior to reductive elimination (Scheme 18B).

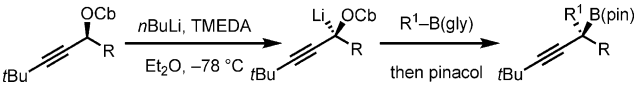
More recently Aggarwal, Crudden, and co-workers examined the cross-coupling of enantioenriched allylic boronic esters with aryl iodides which gave high γ-regioselectivity and high retention of chirality (Table 12).[60] The desired enantioenriched allylic boronic esters were prepared using the Aggarwal lithiation–borylation methodology.[39,61] High enantiospecificity was observed regardless the geometry of the olefin but *Z*-allylic boronic esters tended to give γ-products with higher *E* selectivity (compare entries 1 and 2). Different *p*-substituted aryl iodides were evaluated and whilst electron-poor coupling partners resulted in lower yields (entries 8 and 9), they all reacted with very high stereospecificity. The retentive stereochemical outcome was rationalized by the authors on the basis of a *syn*-S_E' transmetallation. The $A^{1,3}$ strain in this step governs the *E*/*Z* ratio and accounts for the decrease of *E* selectivity when using *E*-allylic boronic esters.



Scheme 18.

2.6. Coupling of Tertiary Propargylic Boronic Esters

The stereospecific Suzuki–Miyaura cross-couplings of enantioenriched tertiary propargylic pinacol boronic esters was reported by Aggarwal and co-workers in 2012.[62] The desired starting materials were synthesized by lithiation-borylation of propargylic carbamates (Scheme 19). Only *tert*-butyl-functionalized propargylic substrates could be used because of the inherent configurational instability of alternative propargylic lithiated carbamates.



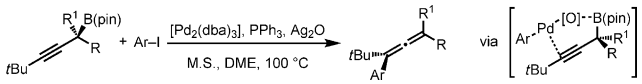
Scheme 19. gly = ethylene glycol, OCb = *N*,*N*-diisopropyl carbamate, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

As with allylic boronic esters, the cross-coupling of propargylic boronic esters can give rise to mixtures of products arising from reaction at either the α or γ position.[57,58,63,64] However, exposure of these substrates to aryl iodides under reaction conditions similar to those developed by Crudden provided the desired tetrasubstituted allene products in good yields and excellent enantiospecificities with retentive transfer of chirality (Table 13). The competing protodeboronation of the starting materials was however observed in few cases (entries 2 and 3). The regio- and stereochemical outcome was rationalized by the authors on the basis of a palladium(II)-hydroxy activated boronic ester. This interaction would result in a favorable six-membered ring TS during the key transmetalation process.

3. Non-Transition-Metal-Catalyzed Couplings

As mentioned in the preceding sections, the palladium(0)-catalyzed stereospecific Suzuki–Miyaura cross-coupling of

Table 13:

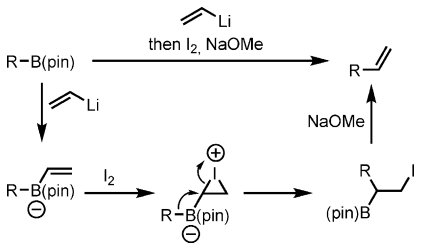


Entry	R	R^1	Ar	Yield [%]	es [%]
1	CH_2Bn	Et	Ph	83	98
2	CH_2Bn	Et	*p*-BrC_6H_4	65	98
3	CH_2Bn	Et	*p*-AcC_6H_4	80	98
4	CH_2Bn	Et	*p*-$MeOC_6H_4$	72	98
5	Me	*i*Pr	*p*-AcC_6H_4	70	98
6	*i*Bu	Et	*p*-AcC_6H_4	71	100
7	CH_2PMB	Et	*p*-AcC_6H_4	75	98

chiral boronic esters is affected by the challenging B→Pd^{II} transmetalation step.[4] This step can lead to unwanted side reactions (e.g., protodeboronation) that make many of these coupling processes still very difficult. However, the use of highly reactive organotrifluoroborates equipped with ancillary groups (e.g., β-carbonyl, α-boryl…) and structurally designed phosphine ligands has addressed a number of examples and enhanced the scope of this transformation. However, the coupling of even more challenging tertiary boronic esters in the absence of ancillary groups is beyond the current capabilities of transition metals.

An alternative approach which employs easy-to-make pinacol boronic esters (and one that does not require transition-metal catalysts) has recently been developed by Aggarwal and co-workers.[65] This stereospecific arylation protocol is based on the Zweifel olefination reaction (Scheme 20), but now extended to electron-rich aromatics.[40,66] Because there is no transmetalation step, unfunctionalized secondary and tertiary boronic esters can be used.

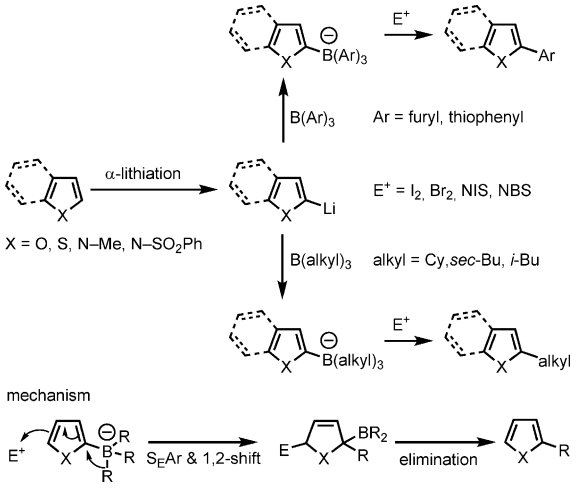
This last section will describe relevant background examples and will then illustrate the scope of the process by discussing relevant mechanistic features.



Scheme 20.

3.1. Pioneering Work

The earliest applications of transition-metal-free couplings can be found in pioneering work from the groups of Levy,[67–69] Negishi,[70,71] Suzuki,[72–74] Ishikura,[75–80] and others.[81–83] These examples showed that aryl and alkylboranes can undergo arylation processes by treatment with electron-rich aryllithiums (e.g., 2-lithiofuran, 2-lithiothiophene) followed by electrophilic trapping (Scheme 21). The mechanism of these coupling reactions is analogous to the Zweifel olefination reaction[84] and comprises a sequence of electrophilic aromatic substitution, 1,2-metallate rearrangement, and elimination[85,86] from the in situ formed aryl-substituted boronate complex. A more detailed mechanistic discussion is presented later.



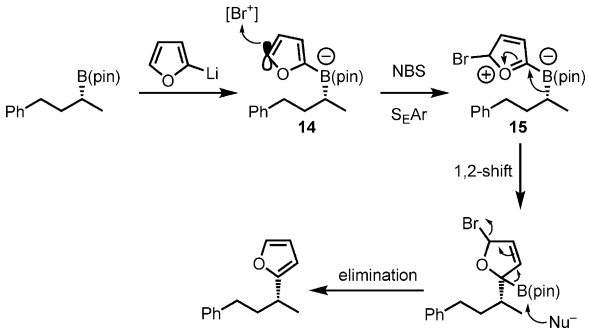
Scheme 21.

However, these protocols have found scarce application in organic synthesis, probably because of the combined difficulties associated with handling air-sensitive boranes, creating stereodefined boranes, and in particular, issues of which group would migrate in nonsymmetrical boranes.

3.2. Couplings of Secondary and Tertiary Boronic Esters

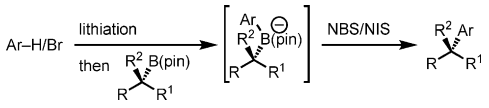
Aggarwal[65] recently reported an alternative method for coupling secondary and tertiary boronic esters. In this process, addition of an electron-rich aryllithium reagent (e.g., 2-lithiofuran) to a chiral boronic ester gave the intermediate boronate complex **14** which, upon reaction with a suitable electrophile, generated the stabilized cation **15** (Scheme 22). The optimum electrophile was NBS but occasionally NIS was the reagent of choice to avoid further halogenation of the aromatic ring. The cation **15** triggered a 1,2-migration, and, following elimination, gave the aryl-coupled product stereospecifically (Scheme 22).

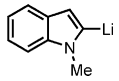
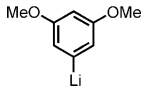
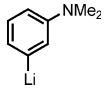
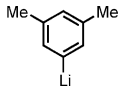
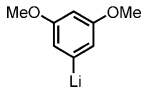
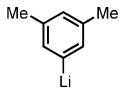
As illustrated in Table 14, the scope of this coupling reaction required the use of highly electron-rich aromatics, such as furan (entries 1–3), thiophene (entry 4), and indole



Scheme 22. NBS = *N*-bromosuccinimide.

Table 14:



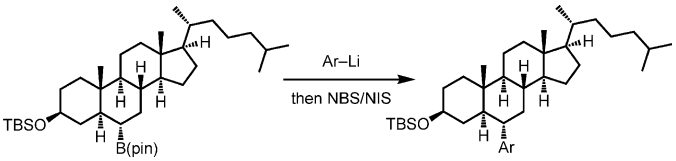
Entry	Ar-Li	R	R^1	R^2	Yield [%]	es [%]
Secondary boronic esters						
1		CH_2Bn	Me	H	91	100
2		CH_2Bn	$(CH_2)_2CO_2tBu$	H	90	100
3		Ph	Me	H	93	100
4		CH_2Bn	Me	H	92	100
5		CH_2Bn	Me	H	89	100
6		CH_2Bn	Me	H	83	100
7		CH_2Bn	Me	H	65	100
8		CH_2Bn	Me	H	89	100
9		CH_2PMP	Me	H	83	100
Tertiary boronic esters						
10		CH_2Bn	Me	Et	89	100
11		Ph	Me	*i*Bu	76	100
12		Ph	*p*-BrC_6H_4	Me	53	100
13		CH_2Bn	Me	Et	63	100
14		CH_2Bn	Me	Et	75	100
15		CH_2Bn	Me	Et	66	100

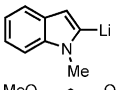
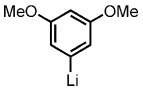
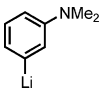
(entry 5), and was also extended to more challenging six-membered aromatics (entries 6–9) with the bis(*m*-methyl)-phenyl substrate representing the lower limits tolerated by the process in terms of aryl group nucleophilicity (entry 9). The power of this methodology was demonstrated by extending it to the arylation of tertiary boronic esters (entries 10–15), thus creating the challenging all-carbon quaternary centres in excellent stereospecificity.

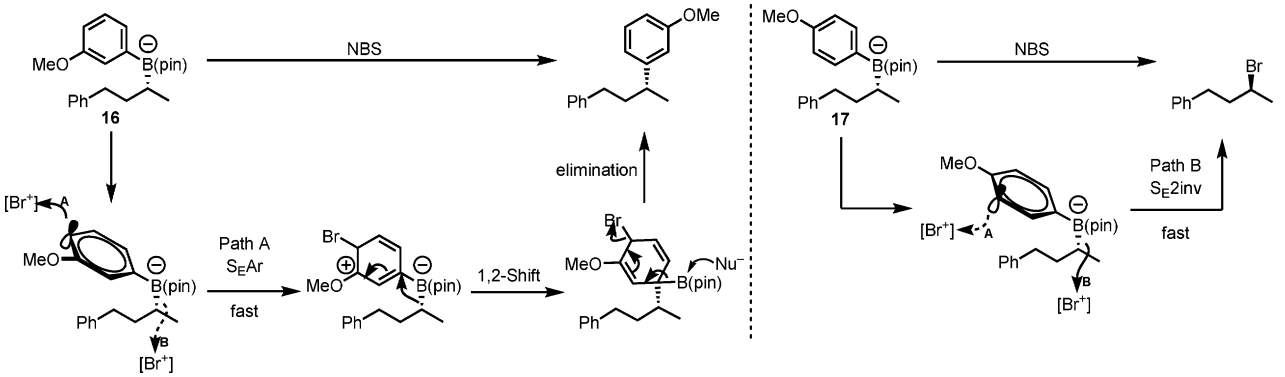
The authors have applied this novel arylation method to the diastereoselective arylation of steroids (Table 15). After hydroboration of cholesterol, the boronic ester derivative was coupled to various aromatics in good to high yields.

Since aryl-substituted boronate complexes display enhanced nucleophilicity at both the aromatic ring and at the boron-bearing sp^3-carbon atom,[87] not all electron-rich aromatics can be used in this protocol. This aspect is illustrated by the two apparently similar substrates **16** and **17** (Scheme 23). While addition of NBS to the ate complex **16** led to complete arylation (Scheme 23, Path A), addition of NBS to **17** gave the alkyl bromide in excellent yield and enantiospecificity with inversion of configuration (S_E2inv; Scheme 23, Path B). The complete switch in selectivity can be rationalized by looking at the juxtaposition of the substituents around the aromatic ring. Because boronate functionalities

Table 15:



Entry	Ar-Li	Yield [%]
1		78
2		75
3		91
4		68



Scheme 23.

are strong electron-donating groups (EDGs),[88] in the case of **16**, the methoxide and the boronate group reinforce each other and promote reaction at the sp^2-carbon center. In the case of **17**, this synergistic effect is not present and the substrate undergoes preferential bromination at the sp^3-carbon center.

4. Summary and Outlook

The Suzuki–Miyaura cross-coupling is one of the most versatile and widely employed reactions for the formation of C–C bonds. Traditionally used for Csp^2–Csp^2 couplings, growing interest in creating biomolecules with three-dimesional architectures has fuelled interest in expanding the process to Csp^2–Csp^3 couplings in which the sp^3 coupling partner is a boron reagent. Primary organoboron reagents work well in Suzuki–Miyaura cross-coupling, but only certain secondary boron reagents bearing specific features can be employed. Such features must enhance the otherwise slow transmetalation step and inhibit β-hydride elimination and are summarized in Scheme 24.

Ultimately, there may be a ligand/metal/base combination which does not require any specific features on the sp^3-boron

Classes of Substrates	HO, B, OH	B, O, O	B, O, O	BF_3K	Transmetalation Step: *ret/inv*	Transmetalation Step: key features	β-Hydride Elimination Step: key features
R, B	✓	✓	X		*ret*	facilitated by increased p character	disfavored by strain in cyclopropene
Ar, B, R			✓		*ret*	more reactive benzylic system	fast reductive elimination
R, B, R			✓		*ret*	• more reactive allylic system • γ-transmetalation	fast reductive elimination
R, B, R			✓		*ret*	• more reactive propargylic system • γ-transmetalation	fast reductive elimination
R, B, O, NR_2				✓	*inv*	facilitated by coordination from amide	conformationally restricted due to coordination from amide
Ar, N, H, B, O, R			✓		*ret* or *inv*	• more reactive benzylic system • facilitated by coordination from amide	not possible
R, B, Ph, O				✓	*ret*	more reactive α-O system	conformationally restricted due to coordination from Ph group
B, R, B			✓		*ret*	assisted by neighboring boron	fast reductive elimination due to stabilization from neighboring boron
B, O, OR, B			X	✓	*inv*	• assisted by neighboring boron • facilitated by coordination from ester	• conformationally restricted due to coordination from ester • fast reductive elimination due to stabilization from neighboring boron

Scheme 24.

substrate, thus enabling fast transmetallation and avoiding β-hydride elimination, but so far this has not been found. However, such a process is quite likely to be highly sensitive and would need optimization with different substrates. An alternative and very promising stereoconvergent protocol has recently been described in which a secondary racemic benzylic trifluoroborate salt was coupled to an aryl halide in the presence of $[Ni(cod)_2]$ and a bisoxazoline ligand.[89] This novel photoredox process goes through a radical intermediate and moderate enantioselectivity was observed. No doubt the enantioselectivity can be improved. More importantly, this process potentially offers broader scope of boron reagents which can be employed than the traditional Suzuki–Miyaura reaction.

An alternative to transition-metal-catalyzed cross-couplings is the new electrophile-triggered coupling reaction. Here, an electron-rich aryllithium is added to a secondary boronic ester and following addition of an electrophile, 1,2-migration and elimination occurs, thus leading to the coupled product. The methodology shows broad substrate scope in terms of both the boronic ester and the electron-rich aromatic, and shows complete stereospecificity. It can even be applied to tertiary boronic esters including benzylic and nonbenzylic substrates. Indeed, unlike the Suzuki–Miyaura cross-coupling of secondary boron reagents, there are no specific requirements on the nature of the boronic ester which can be employed. If its use could be expanded to include electron-neutral or even electron-poor aromatics this would significantly expand its scope. However, as it uses organolithiums it is more limited in functional-group tolerance than the traditional Suzuki–Miyaura reaction.

Addendum

Biscoe et al.[90] have recently reported the stereospecific coupling of unfunctionalized secondary alkyl boronic acids and trifluoroborates with aryl halides using conditions similar to that reported in Table 9.

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