REVIEW

Suzuki–Miyaura cross-couplings for alkyl boron reagent: recent developments—a review

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Abstract

In the history of catalysis and organic synthesis, boric chemistry has been developed into one of the most varied and practical disciplines. Several useful Suzuki–Miyaura cross-coupling (SMC) reactions as well as hydroborylation reactions are regarded the essential tools inside the chemical synthesis toolkit accompanied by researchers of the industry or the academia. Novel synthesis of the less electrically and sterically ongoing carbon–boron synthetic reagents is carried out to ensure a unique coupling reaction utilizing metals along with these reagents which draws considerable interest in accelerating the discovery of creative uses for otherwise difficult organic adducts in many disciplines. This article details the noteworthy advancements in the use of traditional metal-catalyzed carbon–carbon coupling processes with cutting-edge coupling partners such as carbon–boron reagents often the beta-alkyl Suzuki–Miyaura coupling since 2001. The current review covers alkylboranes, organotrifluoroborates, 9-BBN, alkylboronic acids and boronic esters as useful reagents in SMCs that will help synthetic chemists in developing new compounds.

Keywords Suzuki–Miyaura, Metal catalyzed, Boron reagents, Organic synthesis, Cross-couplings
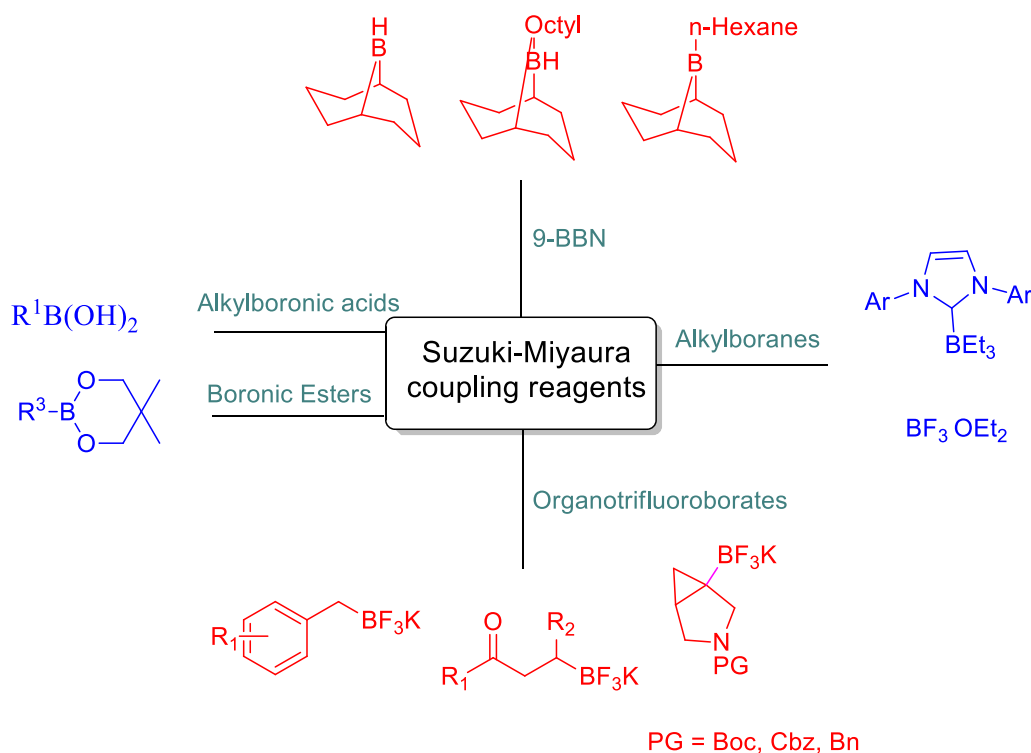
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Graphical Abstract

Background

The chemical intricacy of the unique metalloid boron is remarkable. The three valence electrons of boron, which are readily ripped away, promote metallicity and make it electron-deficient, are responsible for its peculiar features. Because boron is sufficiently localized and strongly bonded to its nucleus, the insulating states may form as a result [1]. Particularly because of boron's relatively small atomic mass, boron compounds have undergone extensive research for use as energy storage devices. High-energy fuels for cutting-edge aircraft and gaseous storage equipment such as hydrogen gas in fuel cells are only two examples of energy-rich applications containing compounds of boron [2]. Most prestigious noble prizes (2 of them) in the field of chemistry were awarded consecutively in the year 1976 with another being awarded in 1979 because of the extensive, groundbreaking research on boron [3, 4].

Typically, at least one carbon–boron link exists in compounds with the name organoboron (Scheme 1A) [5–8]. It was 60 years ago that the first organoboron compounds were utilized in chemical synthesis [9, 10]. Since then, chemistries containing these substances have developed, making them one of the most varied, extensively researched and used families in organic synthesis and catalysis [10–12]. In situ characterization of SMCs in the formulation of various nanoparticles has garnered a significant attraction in organometallic chemistry. They are now involved in a variety of well-known and significant reactions, including Suzuki–Miyaura, and hydroborations among others [13–16]. To perform the SMC reaction, an organic halide and an organoboron reagent are often combined with palladium (the main catalyst and the base used) to activate all compounds containing B (Scheme1A)[5–7]. Various pharmaceutical items have also used organoboron chemicals. Boron-based medicines represent a unique family of chemicals with several biological uses, including neutron capture treatment uses, neutron capture treatment agents and molecular imaging agents [17]. Similarly, boron-based chemicals' usefulness and widespread use have aided the advancement of material sciences and agriculture [18, 19]. Battery electrolytes and electroactive materials have all been explored using organoborane polymers [20, 21].

Metal catalysis has significantly influenced several scientific areas, including the production of pharmaceutical adducts, environmental protection, biomass and energy [22–34]. In the case of organometallics, the metal ligand
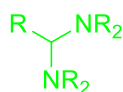
(A) SMC reaction

$$R^1\text{-BXn} \quad + \quad R^2\text{-Y} \xrightarrow[\text{Base}]{\text{metal/ligand catalytic system}} R^1\text{-}R^2$$
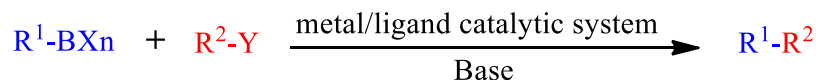
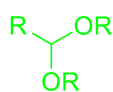R^1, R^2= Alkyl, Alkenyl, Aryl

Xn= $(OH)_2$, $(OR)_2$, F_3K, etc.

Y= Cl, Br, I, OTf, etc.

Metal catalysis = [Pd], [Ni] (more common)

[Co], [Ru], [Fe], [Ag], etc. (less common)

(B) Selected examples of organoboron compounds

Boronamides   Boronicester   Boronicacid   Organotrifluoroborates

Scheme 1 **A** Suzuki–Miyaura cross-coupling reaction, **B** examples of organoboron

interaction, which often has a highly covalent character, is crucial in defining their variety of properties and complex chemistry, which combines elements of conventional organic and inorganic chemistry. These metal–ligand complexes for SMC's are more stable for various transition metals including Pd, Ni and Cu. Accordingly, the extensive study of metal catalysis has resulted in substantial advancements in the borylation of unfunctionalized hydrocarbons' main carbon–hydrogen linkages, opening the door to a range of carbon–boron reagents and leading to innovations in carbon–carbon cross-couplings. The creation of a powerful sp^2–sp^2 SMC has been well studied; however, reports on sp^3–sp^3 or sp^3–sp^2 variations are significantly less common [35–42]. The usage of boron-containing compounds having alkyl substituents was restricted among the several hybridized boron reagents used in Suzuki–Miyaura coupling because of competing side reactions [43, 44]. Alkyl–palladium complexes are formed when organometallic compounds with metallated carbon atoms, particularly those that also include hydrogen atoms, are eliminated by hydride rather than reductive means [45]. Boronic acids may be extracted by crystallization and chromatography

and are generally stable at room temperature, but in SMC circumstances, they promote other side reactions such as protodeboronation [46]. N-methyliminodiacetyl boronates, tetrahedral boronates or palladium catalysts loaded stoichiometrically are the main methods used to avoid undesirable breakdown routes in boron couplings. On the other hand, separation issues, a lack of atom economy and air sensitivity hinder the usage of alkylborane in Suzuki reactions. This reaction has also used trialkylboranes in their construction [47, 48].

In 2017, a recent review of the alkyl–alkyl Suzuki–Miyaura couplings was published [49]. As a result, we will concentrate on the most recent advancements in Suzuki–Miyaura that use carbon and boron reagents. The cross-coupling between enol phosphate or triflate, a vinyl or aryl halide, and an alkyl borane sets it apart from other Suzuki–Miyaura couplings. Electron-rich and electron-deficient coupling partners often exhibit the highest reactivity with B-alkyl Suzuki–Miyaura couplings. Notably, the halide partner's nature, as well as the kind of solvent, base, organoborane and metal catalyst, have a significant impact on this form of coupling. The review on B-alkyl Suzuki–Miyaura couplings by Danishefsky et al. in 2001
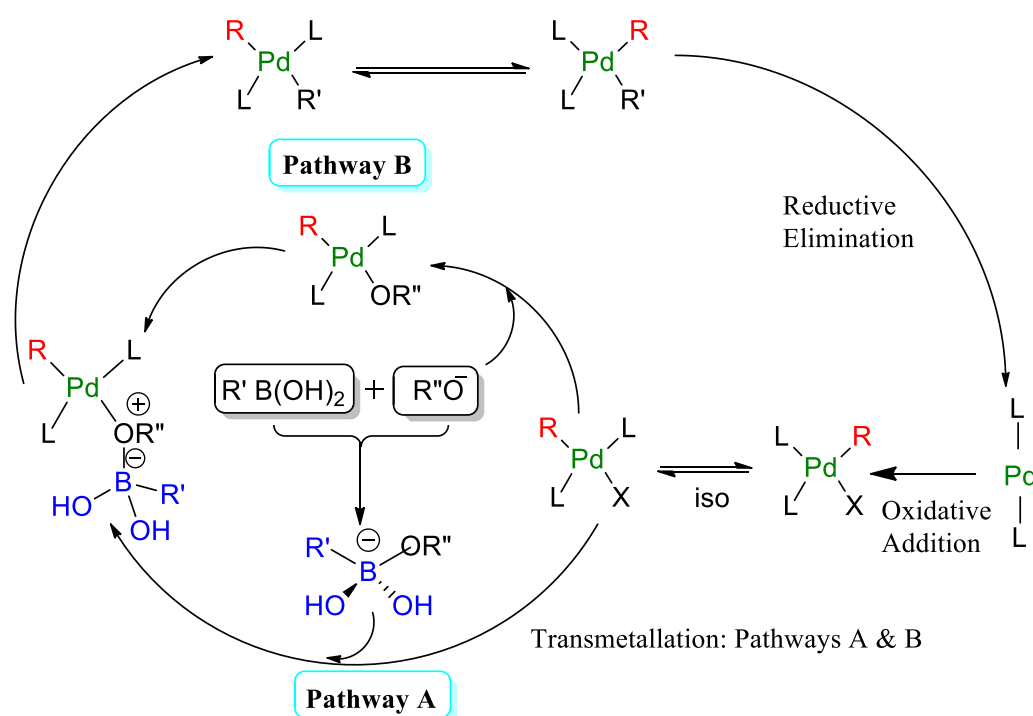
Scheme 2 Suzuki–Miyaura cross-coupling's basic working principle

Main text

A brief overview of Suzuki couplings

included a full description of the implications of these factors [37]. The developments in stereo-specific sp^3–sp^2 Suzuki–Miyaura couplings are beyond the range of this summary. It is important to note that many forms that continue with either configuration inversion or retention have a solid history [50, 51]. Although they were recently examined in great detail in the literature, acyl Suzuki–Miyaura couplings, Liebeskind–Srogl cross-linkages and decarbonylative Suzuki–Miyaura couplings were not discussed in detail [52–56].

Suzuki–Miyaura couplings, as noted in the introduction, are activated by combining reagents of carbon–boron with carbon halides and Pd, which acts as a base as well as a catalyst (Scheme 1A) [5–7]. Palladium's effectiveness has aided in the rapid advancement of catalysis, allowing for the performance of coupling processes like Suzuki–Miyaura couplings at parts per billion molar catalyst loadings today [57]. As an alternative to the pricey palladium catalyst, nickel has been shown to have effective catalytic activity for Suzuki–Miyaura couplings [58, 59]. Nickel catalysts are not only less costly but they can also be taken out of the reaction mixtures with more ease due to their economic viability [60]. Various other metal catalytic systems, including Ag, Cu, Co, Fe Ru, etc., have been studied in Suzuki reactions. However, compared to Pd and Ni catalysts, their uses are much diminished [60–62].

The Suzuki–Miyaura reaction, discovered in 1979 [63], has probably grown to be among the most extensively utilized, and adaptable transition metal (Pd, Ni, etc.) catalyzed processes for the synthesis of carbon–carbon linkage [60, 64]. The general mechanistic process begins with addition through the oxidative process, transmetalation via metals and lastly the elimination by reduction process (Scheme 2). SM coupling is distinct in nature from transition metal couplings due to the boron reagent activation or transmetalation. Mechanistic studies, in addition to the metal, successfully demonstrated various functions exhibited by different reaction reagents. Some mechanistic insights are still being actively researched, including how boron is activated in the presence of the base, while others like the need for electron donor ligands, base and protic solvents are already well established [65, 66]. As may be seen, there are two primary analytical pathways. (A) Boronate pathway: In situ generation of the tetra-coordinate nucleophilic boronate species III replaces Pd intermediate I halide ligands produced by addition through oxidation that came after transferring palladium species V organic moiety by removing $B(OH)_2OR$ from former resultant intermediate IV. (B) Oxo-palladium pathway: Nucleophilic action directed to boronic

acid entities and producing geometrically, (tetracoordinate) species IV, Oxo-palladium II is produced when the palladium core interacts with the RO substitution ligand X. This is because the Suzuki–Miyaura coupling is often accelerated by using inorganic bases in alcohol or aqueous solvents, which may generate either alkoxy or hydroxy ligands. Pathway A is supported by both electrospray ionization–mass spectrometry analyses and density functional theory [67, 68], which found boronate species but no oxo-palladium species [69–71]. The notion of route B is supported by research that includes experimental observations and kinetic analysis of the absence of activities in certain circumstances when lithium salts of boronic species or organic Lewis bases are present. Even though pathways **A** and **B** are in direct competition with one another, the Maseras group argued that approach **A** had lower energy barriers [72]. So, (**A**) the boronate route is the more efficient one. Furthermore, they claimed that the experimental data they replicated are in agreement with their theoretical report [67].

More research is required to determine whether or not the two pathways are mutually exclusive in each catalytic cycle. There is still some evidence to analyze that is consistent with option **A**. It is less probable for the palladium center to react to the strongest nucleophile like alkoxy and hydroxyl moieties when the center is electron-rich, and to react more often with a weaker nucleophile and a boronate $[R-B(OH)_3]$.

The SMC strategy has been so fruitful because it combines modest catalytic loadings with unusually mild reaction conditions and strong stereo- and regioselectivity. The used conditions are amenable to both aqueous and heterogeneous environments, are tolerant of steric hindrance and can accommodate a broad variety of functional groups. Typically materials that begin with boron are resistant to heat, water and other common solvents. Both they and their byproducts tend to be reasonably safe for the environment. This makes them simple to work with and isolate from reaction mixtures [73–76].

Thanks to its special properties, Suzuki reactions has been put to use in several fields of study, ranging from the polymeric materials creation to the creation of complicated organic adducts. Large-scale synthesis of medicines and the manufacturing of fine compounds and novel materials like medicinal chemistry and organic light-emitting diodes all rely heavily on Suzuki–Miyaura coupling [77–79]. Many textbooks and articles focus on the practical uses of this reaction. Table 1 of our review (reaction partners and circumstances) summarizes the reports of C–C linkages in the order in which they are described.

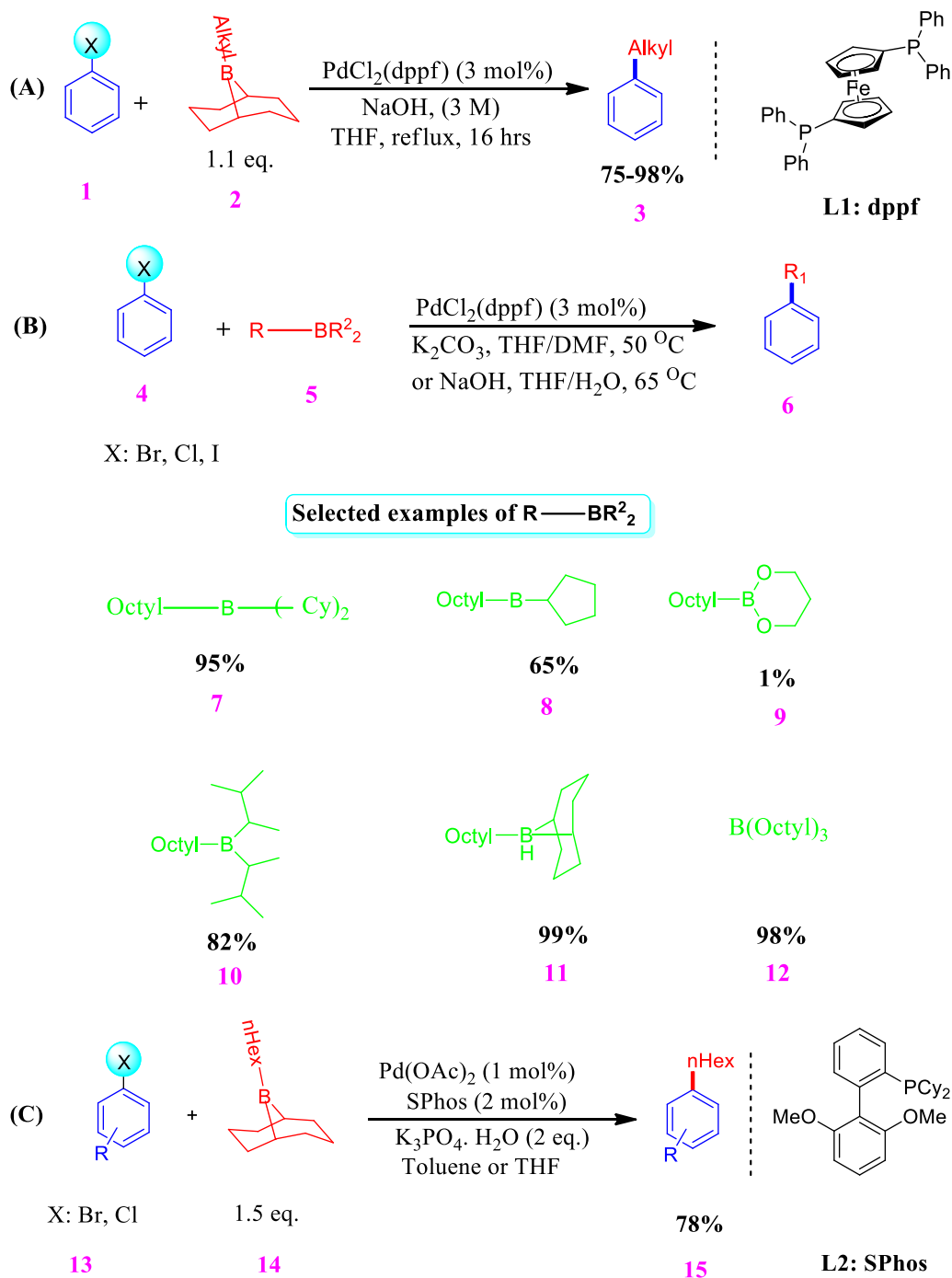## Initial reports on beta-alkyl SMCs and approaches utilizing 9-BBN derivatives

Using $PdCl_2$(dppf), a base such as NaOH or MeO, and trialkylboranes (R_3B) or B-alkyl-9-BBN **2**, Suzuki and Miyaura discovered the alkylboron coupling in 1986 (Scheme 3A). Excellent yields of 75–98% of alkenes and alkylated arenes **3** were obtained as a result of the reaction, which proceeded smoothly. However, when sec-butyl boranes were employed, no coupling was seen [80]. The reaction rate of several alkyl borons while Beta-alkyl couplings were first highlighted in 1989 by the same group is schematically illustrated (Scheme 3B). When compared to 9-BBN derivatives, pinacolborane **10** exhibited almost little reactivity (1% yield). The Sequences of 9-BBN derivatives coupled to haloarenes by hydroboration **4** (intra and inter-molecular) or haloalkenes were used to produce functionalized cycloalkenes arenes and alkenes. Many different functions on either coupling partner were successfully carried out, resulting in high yields of geometrically pure arenes and alkenes. Alternatively, base-sensitive compounds may be subjected to the reaction using K_2CO_3 instead of NaOH [81–83].

A novel ligand with finely honed steric and electrical characteristics was claimed to have been designed by the group Buchwald in 2004. Two methoxy groups are attached to one of the phenyls in phosphone ligands (L2, Scheme 3C). By boosting the electron density on the biaryl, the oxygen lone pairs aid in the stability of the Pd complex. In addition to preventing cyclometalation, the MeO groups also boost steric bulk. The intended function of this ligand was as a general-purpose catalyst for both C-H activation processes and cross-coupling. It finally became available commercially under the name of SPhos that now functions as a vital key element for contemporary catalyst reactions. This newly available ligand was stable and included a variety of aryl boronic acids. Beta-alkyl derivative couplings of 9-BBN utilizing $K_3PO_4 \cdot H_2O$ as a key base were also successful (Scheme 3C). The project's range of work included testing the stability of aryl halides such as aryl chlorides and 3-dimethylamino-2-bromoanisole [84].

Through the use of palladium tetrakis and cesium carbonates in clean water, Wu et al. (2013) created an SMC between chloroenynes **16** and **17** and B-benzyl-9-BBN **18** in creating a wide variety with high precision and yield of derivatives (1,5-diphenylpent-3-en-1-yne) with excellent regioselectivity such as isomerism (E/Z) (Scheme 4) [85]. Substrates to be a mixture of electron-withdrawing and electron-donating groups were successful under these circumstances. It is important to note that these compounds have anti-inflammatory properties and may be extracted from plants, although in very small amounts.

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Table 1 A general overview of the pertinent reports on carbon (sp^3)-carbon (sp^2) cross-couplings included in this study

| Substrates	Boron reagents	Reaction conditions	Schemes	References
Aryl iodides	Ttrialkylboranes and B-alkyl-9-BBN	PdCl2(dppf), NaOH, THF, reflux,	3A	[80]
Aryl iodides and bromides	Alkylboranes	PdCl2(dppf), NaOH, THF, 65 °C	3B	[81–83]
Aryl halides	B-boronic acids and a B-alkyl-9-BBN	Pd(OAc)2, SPhos, K3PO4.H2O, THF/Toluene	3C	[84]
Chloroenzynes	B-benzyl-9-BBN	Pd(PPh3)4, Cs2CO3, water	4	[85]
CAr-O electrophiles	B-alkyl-9-BBN	Ni(COD)2, IPr.HCl, CssCO3, iPr$_2$O, 110 °C , 12 h	5A	[89]
Aromatic and alkenyl ethers	B-alkyl-9-BBN	Ni(COD)2, PCy3, base, iPr2O, 110 °C ,	5B, C	[90]
Aryl halides	9-BBN and 1,3-dienes	Pd(dppf)Cl2 or Pd(dppb)Cl2N	6	[91]
β-triflyl enones	B-alkyl-9-BBN	Pd(dppf)Cl2, Cs2CO3, DMF:THF:H2O, 60 °C , 16 h	7A	[92]
Halogenated pyridine	9-BBN derivatives of L-aspartic acid	Pd(PPh3)4, K3PO4 (aq.), THF 50 °C ,	7B	[93]
Aromatic esters	Alkyl organoboron reagents	Ni(COD)2, dcype, CsF, toluene	8A	[95]
Aroyl fluorides	Alkyl organoboron reagents	Ni(COD)2, dppe, CsF,	8B	[96]
Aryl halides/triflates and vinyl triflates	Potassium alkyltrifluoroborates	PdCl2(dppf)CH2Cl Cs2CO3, THF: H2O, reflux, 6–72 h	10B	[48, 98]
Aryl and heteroaryl chlorides and bromides	Tertiary trifluoroborate salts	CatacXium-A-Pd G3, Cs2CO3, tol/water, 90 °C , 18 h	10C	[104]
Aryl bromides	Secondary alkyl β-trifluoroboratoketones and esters	Ir[dFCF3ppy]2(bpy)PF6, NiCl2 dme, dtbbpy, Cs2CO3, 2,6-lutidine, 1,4-dioxane, hv	11A	[10]
Aryl bromides	α-alkoxyalkyl- and α-acyloxyalkyltrifluoroborates	Ir[dFCF3ppy]2(bpy)PF6, Ni(COD)2, dtbbpy, K2HPO4, dioxane, hv	11B	[106]
Aryl bromides	Tertiary organotrifluoroborates reagents	Ir[dFCF3ppy]2(bpy)PF6, Ni(TMHD)$_2$ or Ni(dtbbpy)(H2O)4Cl2, K2HPO4 or Na2CO3, no additive or ZnBr$_2$, dioxane/DMA or DMA, hv, 12–72 h	11C	[107]
Aryl bromides	Trialkylboranes	PdCl$_2$(dppf), THF, reflux, 2–6 h	13B	[111, 112]
Aryl halides and triflates	NHC–borane complexes	[Pd], Ligand, tol-H$_2$O or THF-H$_2$O, heat or microwave	13C	[113]
Alkenyl and aryl halides	Trialkyl- and triaryl-boranes (generated in situ)	Pd(OAc)2, n-BuAd2P or RuPhos, K3PO4, tol-H2O, 100 °C	13D	[114]
Alkenyl and aryl Halides and triflates	*n*-alkylboronic acids	PdCl2(dppf), K2CO3, Ag2O, THF, 80 °C , 6–10 h	14A	[118]
Alkenyl halides	*n*-alkylboronic acids	PdCl(C3H5)dppb, Cs2CO3, toluene	14B	[119]
2-Bromoalken-3-ol derivatives	Primary and secondary alkylboronic acids	Pd(OAc)2,LBPhos.HBFK2CO3, toluene, 110 °C , 3–27 h	14C	[120]
Di-ortho-substituted arylhalides	Cyclic secondary alkylboronic acids	Pd(OAc)2, AntPhos, K3PO4, toluene, 110 °C , 12–24 h	14D	[121]
Aryl and alkenyl triflates	Acyclic secondary alkylboronic acids	[Pd(cinnamyl)Cl]$_2$, Ligand, K3PO4.H2O, toluene, 110 °C , 12 h	14E	[122]
Aryl methyl ethers bearing ortho-carbonyls	Boronic esters	RuH2(CO)(PPh3)3, toluene, 110 °C	16A	[123]
Aryl and heteroarylbromides	MIDA boronates	PdCl2(dppf).CH2Cl2, Cs2CO3, THF:H$_2$O, 80 °C, 24–48 h	17	[47]
Alkenyl bromide	Alkyl iodide and 9-MeO-9BBN (*t*BuLi for in situ generation)	Pd(OAc)$_2$, Aphos-Y	18B	[133]
Aryl bromide	OBBD derivatives	Pd(dtbpf)Cl$_2$ Et3N or K3PO4, TPGS-750-M/H2O 45 °C , Ar, 16–21 h	18D	[134]
Styrene	9-BBN	THF, SPhos and Pd(OAc)2 at 50 °C, 24 h	9	[97]
Aldehydes/ketones	Benzyl Trifluoroborates	4Cz-IPN, r.t. DMSO	12	[108]
Allyl bromides	Arylboronic acids	S-Catalyst and weak base	15	[122]

Scheme 3 First reports of B-alkyl Suzuki–Miyaura cross-coupling (**A**–**C)** and the reactivity of alkylborances (**C**)

As an alternative to halides, C–O electrophiles are a promising class of compounds. However, aryl methyl ethers were seen as difficult coupling equivalents, therefore research on cross-couplings with these compounds

lagged behind phenol-protected electrophiles that of carbamates, sulfonates and benzyl groups. The carbon–methoxy bond may be broken with an activation energy of much larger since the OMe group is harder to break
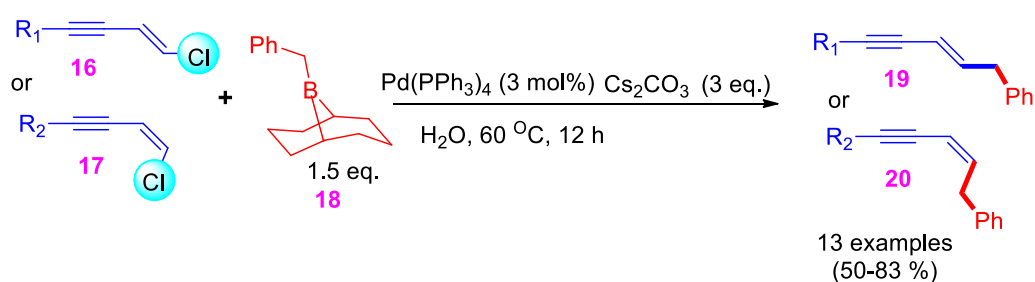
Scheme 4 B-alkyl SMC of chloroentnes
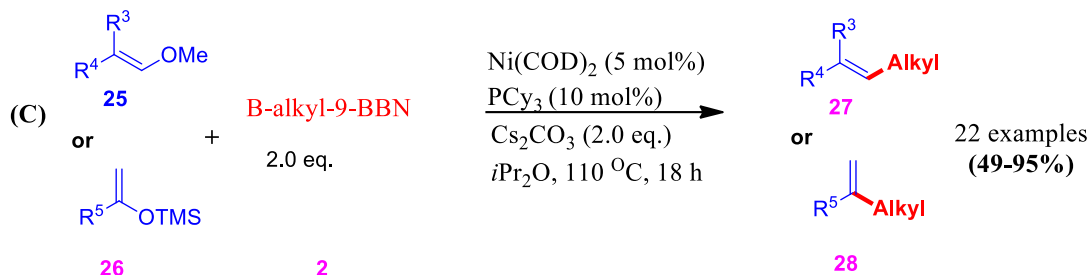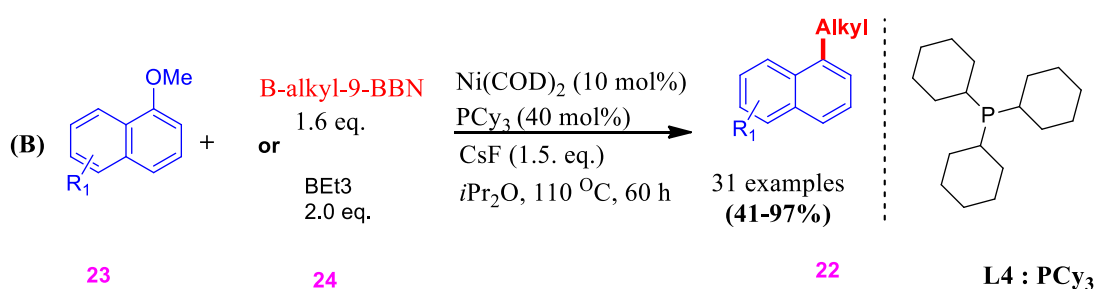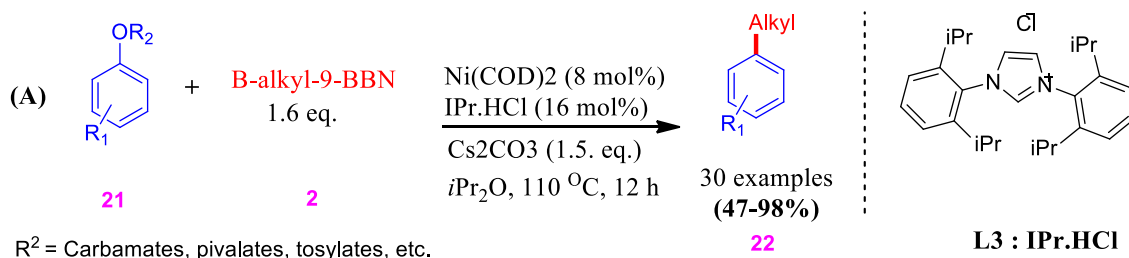
Scheme 5 Ni-catalyzed alkylation of C_{Ar-o} electrophiles (including aromatic methyl ethers) (**A**, **B**) and methyl enol ethers (**C**)

apart and the methyl group is less amenable to oxidative addition. Interestingly, nickel catalysis predominates in C−O electrophile cross-couplings, as shown in Scheme 5, which illustrates the Rueping group's work in this area. This illustrates nickel's greater activity with such difficult substrates [86–88].

A successful nickel-catalyzed alkylation of carbon−oxygen electrophiles (carbonates, pivalates, tosylates, sulfamates and carbamates) **21** was reported (back in 2016)

by a team headed by Rueping using an available 9-BBN reagent. The ideal circumstances included Cs_2CO_3 in diisopropyl ether, an IPr•HCl ligand and $Ni(COD)_2$ (Scheme 5A). This innovative technique avoided the limitation of β hydride elimination and was tolerant to several crucial synthetic functional groups of alkylboranes and phenol pivalates [89]. Following this, the same group published the first 25 and 26 methyl enol ethers as well as the aromatic polycyclic methyl ethers alkylation
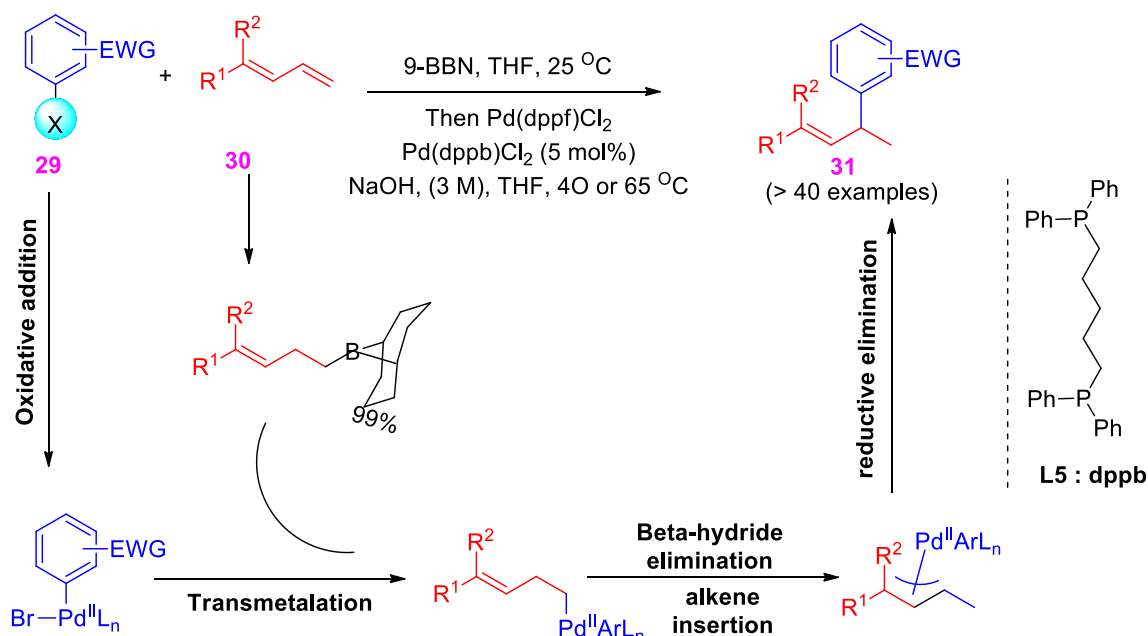
Scheme 6 Hydroboration/Pd-catalyzed migrative SMC of 1,3-dinese aryl halides

23 that calls for breaking a very inert carbon–methoxy bonds and utilizes carbon–boron reagents in wide FG (functional groups) absorbance (Scheme 5B, C). It might be predicted, the choice of ligand and base is important in reactions that break C–O bonds. Since the conditions given for carbon–oxygen electrophiles did not work, PCy3 had to be used in lieu of IPr•HCl to get the best results. When coupling alkenyl ethers, Cs_2CO_3 was often employed; however, when coupling aromatic methyl ethers, CsF and Cs_2CO_3 may both be used. Instead of 1:2 Ni/L, a 1:4 ratio was used, and a reaction duration of 60 h rather than 12 h was used. In Scheme 5, the ideal circumstances for these unique transformations are listed [90].
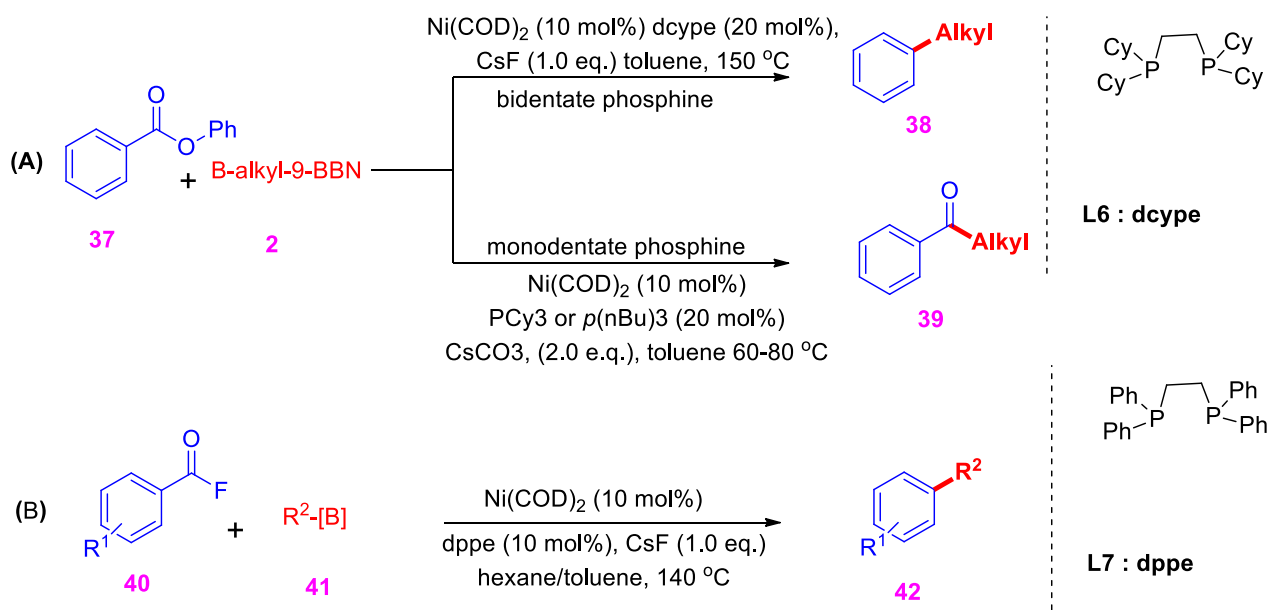
The 1,3-dienes 30 and aryl halides 29 hydroboration/Pd-catalyzed migrative SMC was the subject of a comprehensive report (> 40 examples) published by Zhang et al. in 2018. Through this process, branched allylarenes may be directly synthesized using primary homoallylic alkylboranes. It was discovered that the ligand choice might change how selectively branched coupling behaves in comparison to linear coupling. It was discovered that a large angle of 1.5:dppb with that of a ligand usually a bidentate was more advantageous for the branch-selective coupling. Their review included early mechanistic investigations that demonstrated palladium movement during the allyl palladium species production. Alkenes were partly dissociated and then partially reinserted as traveling progressed through a hydride removal (beta-hydride) series along with the insertion of alkene steps (Scheme 6) [91].

Newhouse and the team recently worked on the beta-alkyl coupling reactions consisting of catalyst, i.e., $Pd(dppf)Cl_2$ in 2.5 mol% concentration with Cs_2CO_3 by the usage of enones 32 to create FG absorbance as illustrated in Scheme 7a. With high to outstanding yields (10 examples), difficult aromatic, 33 enones (disubstituted) were produced using high degree triflate in chromatography or light than electronegative analogs [92]. Using palladium tetrakis and tripotassium phosphate in tetrahydrofuran, the team of Usuki demonstrated L-aspartic acid SMC by borylation 35 and a halogenated pyridine derivative 34. This final obtained yield provided information about electronegative elements' location as well as reactivity order that was discovered in this series: as well as C2, C4 < C3 < and Cl < I < Br [93].

Even though this review does not address decarbonylative and acyl cross-coupling processes [52–56, 94], it is important to note two relatively recent unique studies from the Nishihara and Rueping groups. They demonstrated (Scheme 8A) the exquisite nickel-catalyzed SMC using alkyl organoboron reagents (6 examples with triethylboron and majorly 9-BBN 2) and aromatic esters that were ligand-controlled and site-selective. Simple substitution of monodentate phosphine for bidentate phosphine (L6: dcype) as the ligand allowed ester substrates 37 to be converted into ketone products 39 and alkylated arenes 38. DFT analyses justified the regioselectivity, and the disclosed approach has revealed extensive tolerance to functional groups and a broad substrate range. Using a less expensive $NiCl_2$ catalyst, the process

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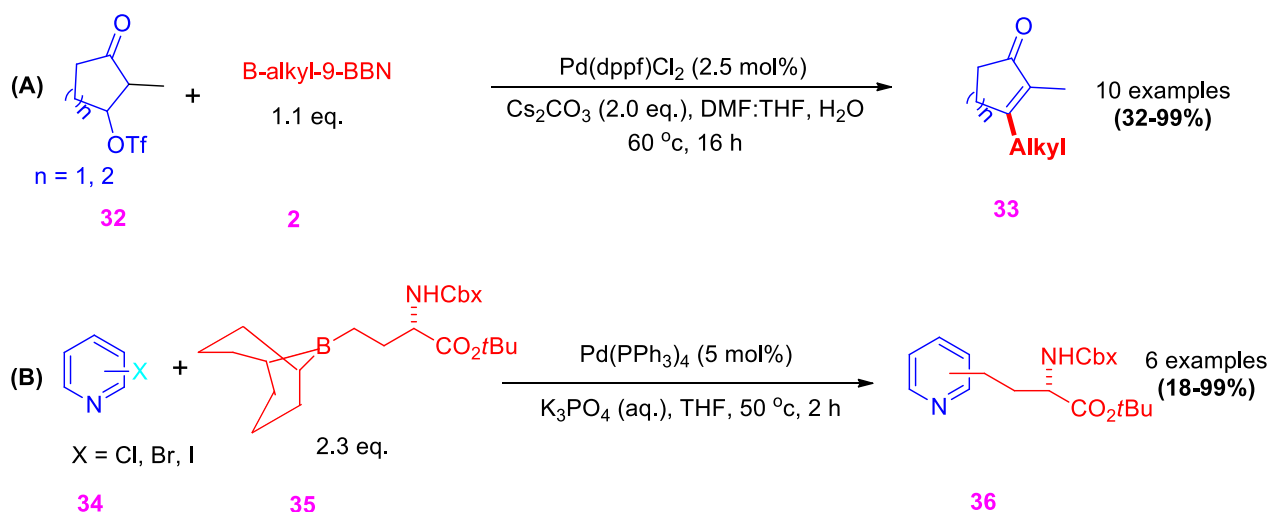
Scheme 7 Latest reports of SMCs using 9BBN (**A** and **B**)

Scheme 8 Novel decarbonlative cross-coupling reactions with alkyboranes (**A** and **B**)

was successfully tested on a wide scale [95]. The conditions for the excellent Ni-catalyzed decarbonylative carbon–fluorine alkylation (aroyl fluorides bond) **40**, as reported by the Nishihara group, are also shown schematically in 8B [96].

When styrene was hydroborated with 9-BBN (THF, rt), the resulting B-phenylethyl-9-BBN was produced. This compound was then in situ processed with Cs_2CO_3 and 1a while being exposed in THF to SPhos

and $Pd(OAc)_2$ at 50 °C, 24 h, yielding the expected cross-linkaged product 86% of the time. Similarly, reacting B-phenylethyl-9-BBN with 4a, it was easy to synthesize the tetrasubstituted alkene in 90% yield [97].

Organotrifluoroborates as reagents in sp³–sp² SMCs
It has been discovered that the unfavorable reactions characteristic of trivalent organoboron are inhibited by
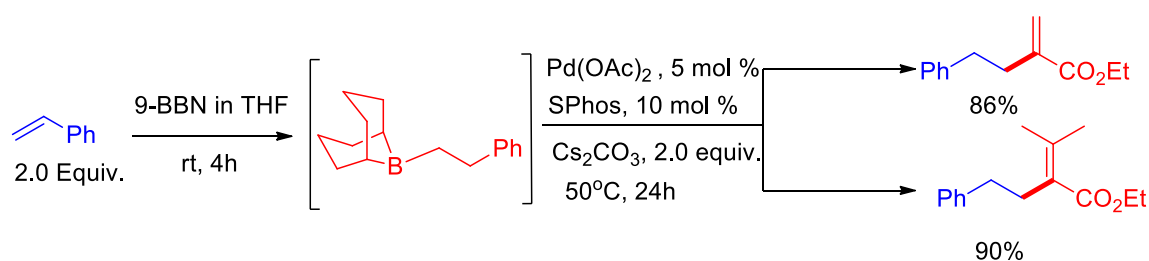
Scheme 9 Boron alkyl SMCs

the boron's tetracoordinate nature in organotrifluoroborates strengthened by strong boron–fluorine interactions. These complexes can all be kept on the shelf forever since they are all crystalline solids that are both stable in water and air. Additionally, it is possible to manipulate distant functional groups within the organotrifluoroborates while still maintaining the important C–B link. Organodiaminoboranes boronic esters/acids, and organodihaloboranes, are just a few examples of the several organoboron intermediates that may be readily converted into borates (RBF_3K) **45** on a wide scale by adding affordable fluoride sources to them (Scheme 9A) [98]. The K-alkylBF_3 first usage **45** was as a linkage supporter to vinyl BF_3 **46/47**. These arylhalides/ triflates were made by Molander and colleagues utilizing catalysts of $PdCl_2$. CH_2Cl_2 in tetrahydrofuran-water with cesium carbonate acting as base as illustrated schematically (Scheme 9B). By reporting on more than **50** instances with acceptable to very excellent yields in two subseque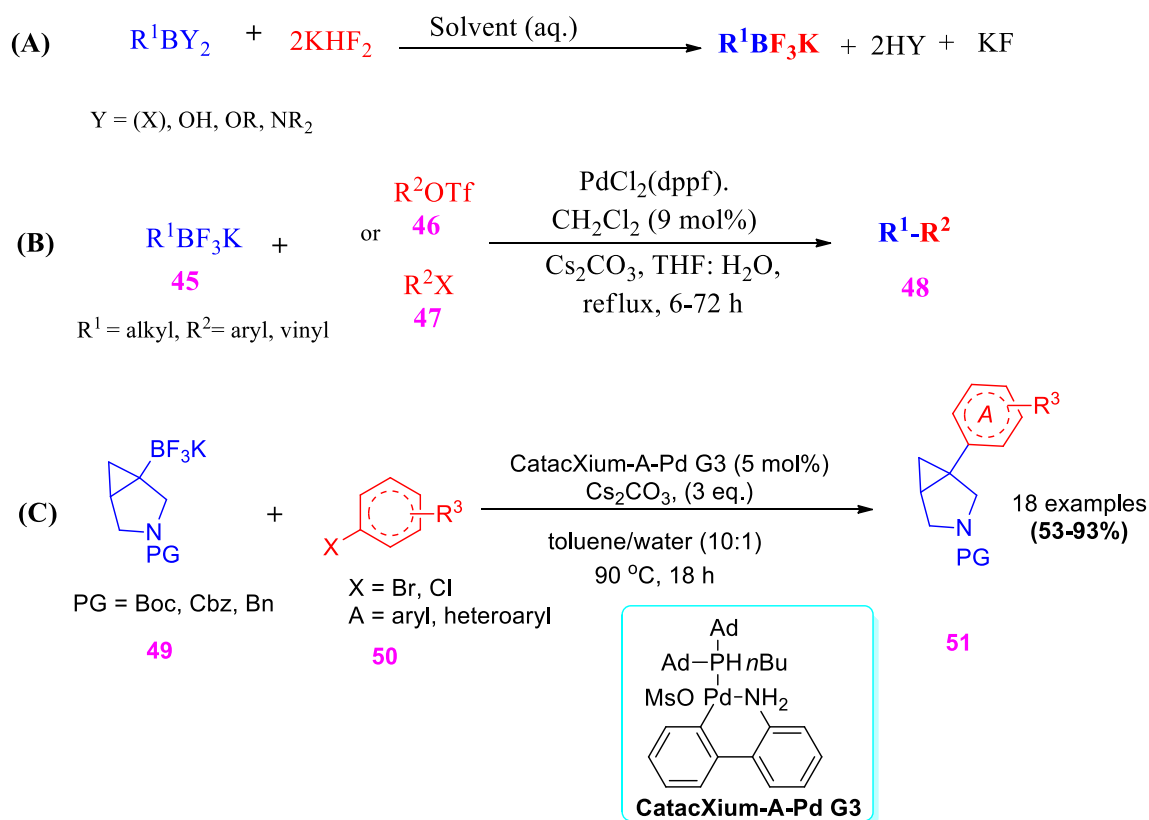nt publications from 2003 and 2001, the breadth of this B-alkyl SMC was investigated, demonstrating a potentially universal approach to a broad variety of functionalities [48, 98, 99]. Later, the same group developed several catalytic systems to detail the first thorough investigation of 2^0 alkylboron coupling with benzyl halides using microscale parallel experiments [38]. Numerous articles that followed and were thoroughly examined by other research teams, including the one by Molander in 2015, supported the use of trifluoroborates in Suzuki–Miyaura coupling [83, 100–103].

Using tertiary trifluoroborate salts **49** and a Pd-catalyzed SMC reaction, Harris and his team recently synthesized a versatile compound **51** with the name of 1-heteroaryl-3-azabicyclo[3.1.0] hexanes, an intriguing moiety for medical investigations having multiple synthetic options. With a diversity of bromides **50**, heteroaryl and aryl chlorides, the SMC procedure proved functional (Scheme 9C) [104]. The synthesis of 18 samples was carried out under the optimized circumstances using an instrument, cesium carbonates dissolved in water, with good to outstanding yields.

Following their study [103], the Molander group expanded the use of c–c SMCs widely for the fluorine and borates to exhibit resistance with palladium metal standard reactions through a double mechanism using a catalyst as illustrated in Scheme 10. This involved employing Ir-based nickel/photoredox dual catalysis to couple esters **52** and secondary alkyl -trifluoroboratoketones to aryl bromides **53** (Scheme 10A). Unlike traditional SMCs, which process dually in nature, the current double mechanism uses simple transmetalation using a single electron offering the corresponding toolset. Considering the significance of this transmetalation reaction and mechanism, the involvement of nickel as a catalyst provided a way for fragmentation via oxidation and the formation of benzyl halides as the matching partners. In 1,4-dioxane, they found optimal conditions for a mechanism to operate that composed of photocatalysts starting with iridium and palladium as the main constituent and utilizing dtbbpy in 2.5 molar concentration (Scheme 10A) [105]. The second study proposed a photoredox palladium-catalyzed SMCs with aryl (or heteroaryl) bromides **53** and acyloxyalkyltrifluoroborates 55. The benzyl, N, N-diisopropylcarbamoyl and pivaloyl protecting groups and several functional groups were all suitable with this technique (Scheme 10B) [106]. The development of quaternary structures (sterically demanding in nature) lacks a coherent approach and is severely constrained by the predominance of metal-catalyzed procedures now in use, which was advanced by their third work on dual catalysis. Different settings discovered the critical dependency for various functional moieties when coupling various tertiary organotrifluoroborates reagents along with light intensities. This technique could only be used on electron-deficient or neutral systems, limiting its applicability to linked aryl bromides [107].

This process produces benzyl radicals from the oxidation of benzyl trifluoroborates by excited-state 4Cz-IPN, and the resultant boron trifluoride functions as a Lewis acid to decrease the ability of carbonyl compounds to reduce. The reaction of benzyl trifluoroborates with ketone esters, diketones, ketones and aldehydes produces

(A) R^1BY_2 + $2KHF_2$ $\xrightarrow{\text{Solvent (aq.)}}$ $\mathbf{R^1BF_3K}$ + $2HY$ + KF

$Y = (X), OH, OR, NR_2$

(B) R^1BF_3K + or R^2OTf **46** / R^2X **47** $\xrightarrow[\text{reflux, 6-72 h}]{\begin{array}{c}PdCl_2(dppf).\\CH_2Cl_2 \text{ (9 mol\%)}\\Cs_2CO_3, THF: H_2O,\end{array}}$ $\mathbf{R^1\text{-}R^2}$ **48**

45

$R^1 = $ alkyl, $R^2 = $ aryl, vinyl

(C) [BF₃K substituted pyrrolidine with N-PG] **49** + [X—aryl—R³] **50** $\xrightarrow[\begin{array}{c}\text{toluene/water (10:1)}\\90\ ^oC, 18\ h\end{array}]{\begin{array}{c}\text{CatacXium-A-Pd G3 (5 mol\%)}\\Cs_2CO_3, (3\ eq.)\end{array}}$ [A—R³ substituted pyrrolidine] 18 examples **(53-93%)** **51**

PG = Boc, Cbz, Bn

X = Br, Cl
A = aryl, heteroaryl

Ad
Ad—PH*n*Bu
MsO Pd-NH₂

CatacXium-A-Pd G3

Scheme 10 Alkyltrifluoroborates salts: General synthesis and first report in sp³–sp.² SMC (**A** and **B**)

a variety of sterically hindered alcohols thanks to the dual functions of benzyl trifluoroborates [108].

Alkylborane reagents in carbon–carbon SMCs
Boron trifluoride and Grignard reagents etherate [109] provide a simple route to produce tri-n-alkylboranes (R_3B) (Scheme 11A). Rare reports about such a family consisting solely of boranes being used inside beta-carbon Suzuki–Miyaura coupling may be attributed to their flammability, oxygen sensitivity and the inefficiency with which complete three groups of alkyl nature can be transferred to keep a distance from the center [110]. A team by Wang in 2009 reported fast as well as selective palladium–metal coupling reactions of bromoarenes **59** with R_3B **60**, employing cesium carbonates (a weak base) in a moderate environment with unmasked acidic or basic functionalities (Scheme 11B). In more than 30 cases, the circumstances allowed primary alkyls, mainly lower n-alkyls like ethyl groups, as well as least protected base and highly protected TBS nitriles, chlorinated derivatives and phenols unprotected and base-labile phenols [111, 112].

The activation was accomplished by employing N-heterocyclic carbenes, and Lacôte et al. successfully transferred R_3B and Ar_3B completely in Suzuki coupling in excellent yields without the need for bases as illustrated in Scheme 11C. This NHC–borane multiplexes with triflates and aryl iodides, chlorides, bromides and triflates were used in 11 instances of the $C(sp^2)$-$C(sp^3)$ scope utilizing palladium acetate or palladium chlorides with a ligand under microwave irradiation or conventional heating [113]. Trialkyl boranes **66** and unactivated symmetrical triaryl are used in SMC by Li et al. (2015) as part of a broad, atom-economic technique (Scheme 11D). A one-pot procedure was used to link the relevant alkenyl and aryl halides **65** with the trialkylboranes **66** after terminal alkene hydroboration was completed. This method proved to be the most effective in the heterocyclic chemistry of boranes[114].

R-boronic acids as reagents for Suzuki couplings (sp3–sp2)
The R group (alkyl group) boronic acids and their boroxines are proven as effective SMCs collaborators inside coupling reactions and are in equilibrium with one

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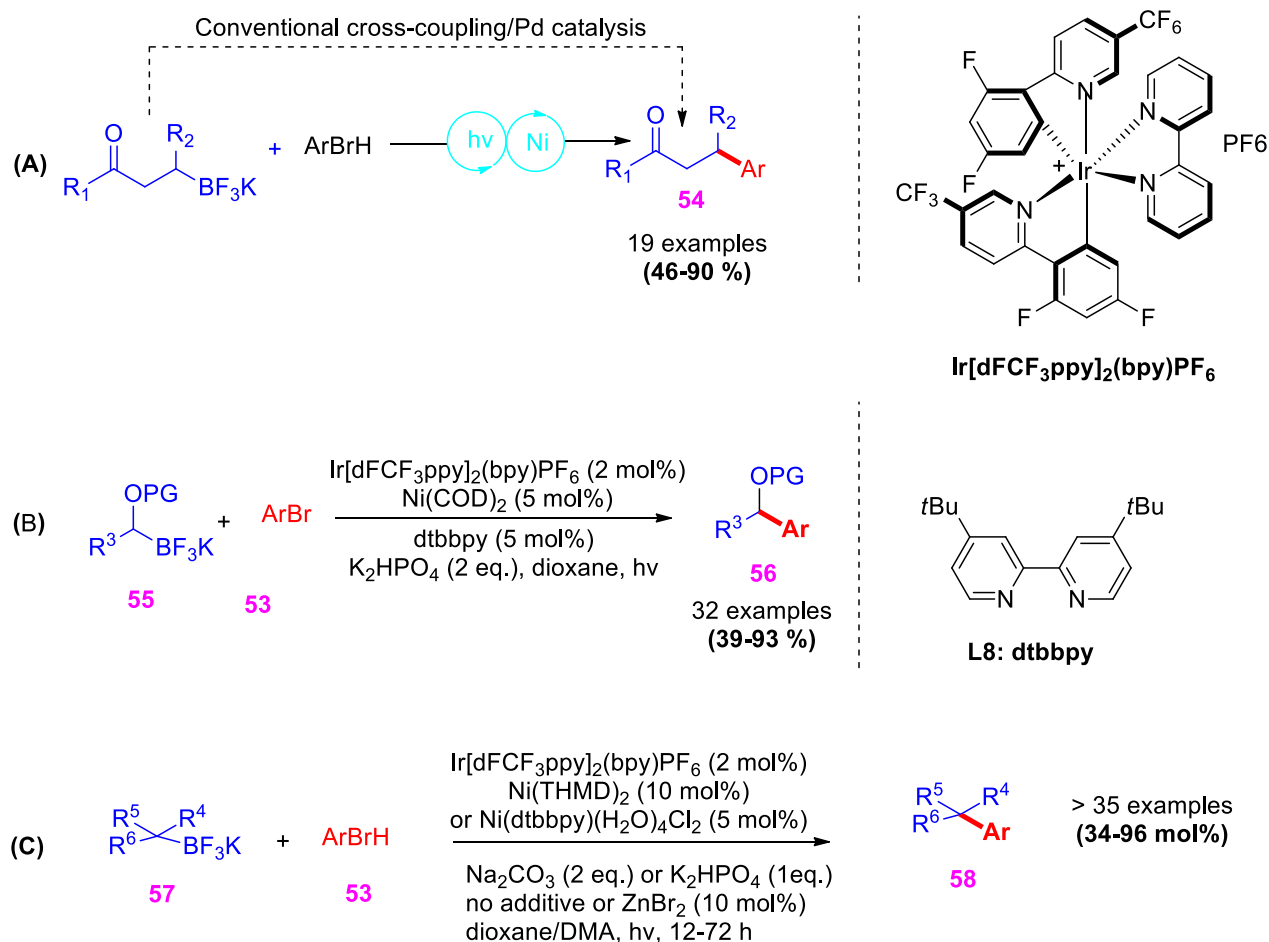
Scheme 11 Photoredox/metal dual catalysis of organotrifluoroborates by the Molander group (**A**–**C**)

Scheme 12 Boron triflouride as reagent

another [115]. Because of this, determining the ratio of boronic acid to boroxine in the catalytic process may be challenging, necessitating the use of extra boronic acid to guarantee the reaction's success [116]. Alkylboronic acids were used for the first time in 1995 by Gibbs et al. as coupling partners with alkenyl triflates [117]. By disclosing a productive Suzuki coupling of n-alkylboronic acids **68** that was boosted by Ag(I), the Falck group expanded the field of study (Scheme 12A) [118]0.2

In 2008, the development of the use of alkylboronic acids was evaluated [116]. Using the air-stable catalysts Cs_2CO_3 and $PdCl(C_3H_5)$ and the solvents xylene

or toluene, the SMC of primary alkenyl halides **73** with alkylboronic acids **72** was then described (Scheme 12B) [119]. To effectively link 2-bromoalken-3-ol **76** with primary and secondary alkylboronic acids 75 derivatives in 2012, Ma et al. employed palladium acetate with potassium carbonates and an air-stable monophosphine **fluoroboric acid** salt as the ligand (Scheme 12C) [120]. A Pd-AntPhos catalyst with strong reactivity allowed for a reduction in the β-hydride elimination. The team of Tang (2014) reported an alkyl–benzyl Suzuki coupling (sterically demanding) for cycloalkylboronic acids **78** and di-ortho-substituted arylhalides **79** as illustrated in

(A) $3RX$ + $3Mg$ + $BF_3.OEt_2$ $\xrightarrow{Et_2O}$ R_3B + $3FMgX$

(B)

R^1—Br + $Alkyl_3B$ $\xrightarrow[\text{THF, reflux, 2-6 h}]{\substack{PdCl_2(dppf)\ (2\ mol\%) \\ Cs_2CO_3\ (2\ eq.)}}$ R^1—Alkyl

59   **60**
1-3 eq.

61

R^1= OH, CO_2H, OPG, CO_2Me
R^2= Cl, NH_2, CHO, etc.

> 30 examples
(57-99%)

(C)

R^3—Br + Ar–N⌒N–Ar with BEt_3 $\xrightarrow[\substack{60\text{-}80\ ^oC/\ 24\ h \\ \text{or MW, }140\ ^oC\ 30\ min}]{\substack{[Pd]\ (5\text{-}10\ mol\%) \\ L\ (10\text{-}20\ mol\%) \\ THF\text{-}H_2O,\ \text{or toluene-}H_2O,}}$ R^1—Et

62   **63**
0.3-1 eq.

64

X = Br, Cl, I, OTf   Ar = 2,6-iPrC$_6$H$_3$

11 examples
(65-99%)

(D)

R^5 alkene | $BH_3.THF$
1.2 eq. | 0.45 eq.

R^4—X + R^5⌒⌒(R^5)⌒R^5 $\xrightarrow[\text{One pot}]{\substack{Pd(OAc)_2\ (2.5\ mol\%) \\ n\text{-}BuAd_2P \\ \text{or RuPhos}\ (5\ mol\%) \\ K_3PO_4,\ \text{toluene-water, }100\ ^oC}}$ R^4—R^5

65   **66**

77

X = Br, Cl,
R^4= Alkenyl, aryl

18 examples
(52-98%)

Scheme 13 Synthesis of alkylborances (**A** and **B**) and their uses as coupling partners in sp^3–sp.^{2} SMCs (**A**–**D**)

Scheme 12D. This process included new compounds of a sterically hindered nature, such as derivatives of highly substituted anthracene, naphthalene and benzene [121]. Acyclic secondary alkylboronic acids **81** and aryl/alkenyl triflates **82** were cross-coupled with acceptable to exceptional yields, according to the same group. By preventing the secondary alkyl coupling partner's isomerization (for example, iPr vs. nPr), it was shown that the large sterically affected P=O were essential for attaining selectivity and getting high yields.

Cross-coupling reactions between carbon with sp^3 and carbon with sp^2 hybridization are crucial for the synthesis of organic compounds. Transition metals have been widely used in these reactions to encourage the creation of beneficial carbon–carbon bonds. Using a custom thioether catalyst, an organocatalytic cross-coupling of arylboronic acids with allyl bromides was created. Initial mechanistic studies revealed that a crucial sulfoxonium ylide, which links to the Ar-boronic acid that causes 1,2-aryl migration, was involved [122].

Boronic esters and MIDA boronates as reagents in sp3–sp2 SMCs

A robust Ru-catalyzed Suzuki coupling of boronic esters **85** with benzyl alkyl ethoxide **84** showed fancy compounds discovered through chelates aid before Rueping's

work on further widespread cross-coupling techniques of difficult carbon–oxygen electrophiles with organoboron reagents (Scheme 13A) [88, 123]. It has been suggested that aromatic ketones **85** with the carbonyl in an ortho position might help break up C-OMe bonds. Of all the boronic esters that were examined, **85** were the very reactive compound. All the alkyl or benzyl boron-containing compounds were linked under similar circumstances utilizing catalysis as the main process. In a mechanism similar to that of alkyl as illustrated in Scheme 13B, this carbon–methoxy bond's breakdown uniquely coordinated with the C–O groups. Employing low-valent Ru complexes to separate an aryl carbon–oxygen bond's oxidative addition complex [88, 123] subsequently provided more evidence in favor of the proposed chelation-assisted process **91** (Scheme 13C). In contrast to the C-H functionalization, which happened quickly at normal temperatures, the C-O bond breakage happened at high temperatures (Scheme 13C). An ortho-directing group must still be present at the reactive site [88, 124, 125] for ruthenium-catalyzed Suzuki couplings proceeded for ethers. Aryl boranes were used, rather than a wide range of alkyl boranes, in the more widely reported directing groups for coupling reactions utilizing nickel [88, 123–126].

Burke, Yudin and other groups created the use of N-methyliminodiacetic acid (MIDA) boronates **92** in straight and iterative Suzuki coupling reactions [127–129], drawing inspiration from Wrackmeyer's groundbreaking work on protected boronic acids by iminodiacetic acids [130]. MIDA boronates have the advantage that their mild hydrolysis to liberate the corresponding boronic acids does not need the extreme conditions needed in the case of sterically bulky boronic esters. This is in addition to their chromatographic compatibility and stability. This class has a variety of applications in synthesis, and in 2015, a study of the effective iterative assembly of the MIDA building blocks was published [127]. Scheme 14 presents a direct Suzuki coupling between heteroaryl and aryl bromides and MIDA boronates [47].

Samson Lai and his team created alkylated benzophenones because MIDA esters are more soluble in organic solvents than their trifluoroborate counterparts and, in some ways, are thought to be more receptive to Suzuki–Miyaura coupling [131].

B-alkyl SMCs based on BBN variants (9-MeO-9-BBN and OBBD derivatives)
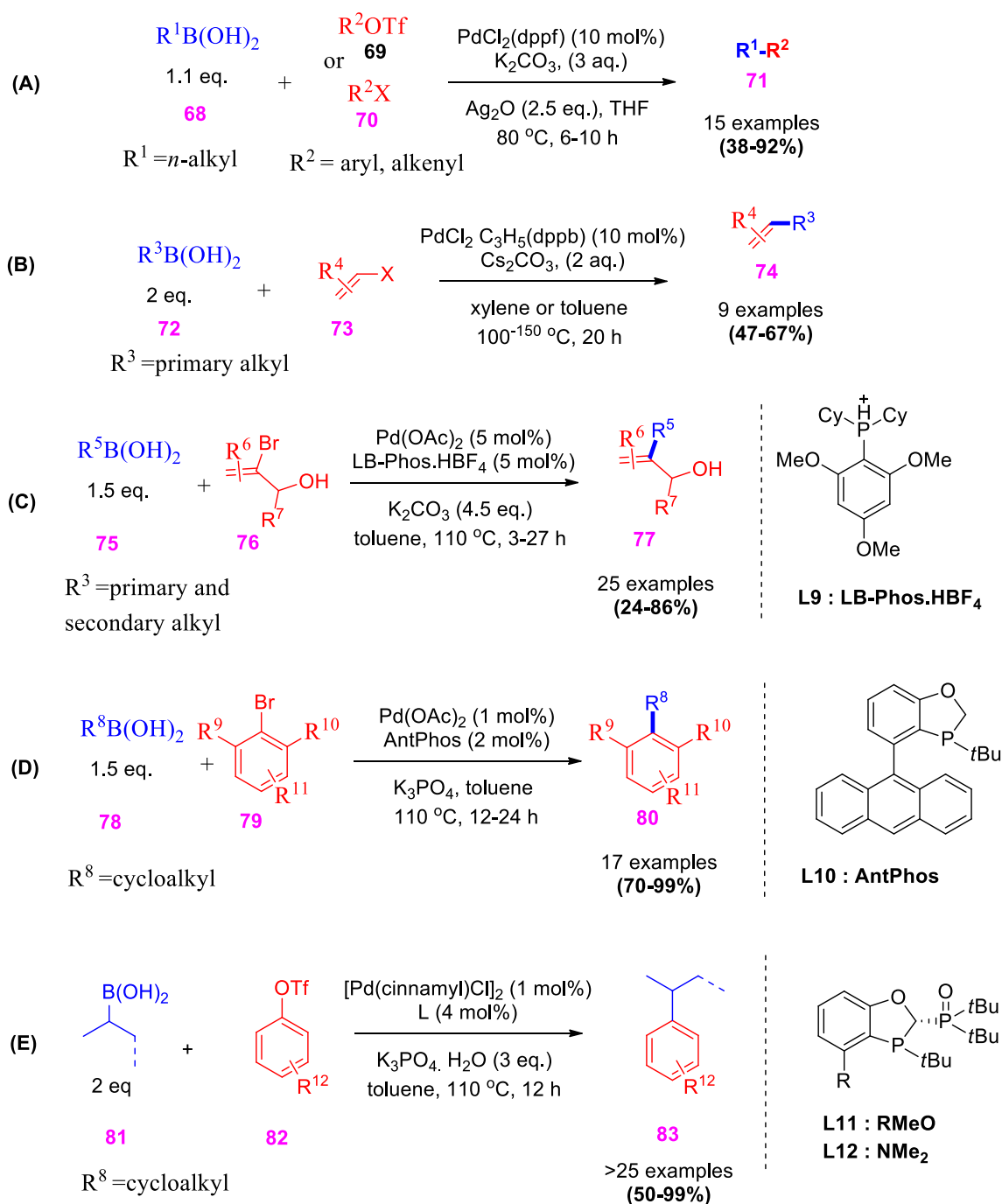
The SMC's fundamental configuration has largely not changed throughout the years. The "9-MeO-9-BBN variant" is one of the other forms for this transformation, however, that has allowed the sp^3–sp^2 coupling process to be used in more sophisticated applications (Scheme 15A, B). This approach is distinct because it lacks the critical base that functions as a promoter in standard SMC. Instead, the R-M (sp, sp^3 or sp^2) is first stopped by 9-MeO-9-BBN, producing the matching borinate complex. The R-group is subsequently transferred to an organopalladium complex generated in situ as the electrophilic partner by these borinate complexes **97** (Scheme 15A). In 2011, Seidel and Fürstner examined the 9-MeO-9-BBN version [132]. The 9-MeO-9-BBN variant approach described by Dai et al. in 2013 is shown in Scheme 15B. Alkenyl bromide **100** and alkyl iodide **99** are coupled under moderate reaction conditions utilizing a hemilabile P, O-ligand, Aphos-Y L13 and Pd(OAc)$_2$. By employing an organic solvent and one ligand, this innovative method improves upon the Johnson procedure, which typically uses two ligands and two organic solvents (tetrahydrofuran) in the Suzuki coupling stage of the total synthesis of structurally complicated natural compounds [133].
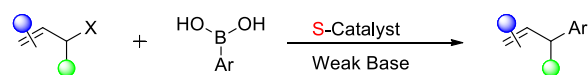
Another variation of 9-BBN is represented by OBBD derivatives **104**/**105** (Scheme 15C, D). Under moderate aqueous micellar catalysis conditions, B-Alkyl SMC was effectively carried out using OBBD reagents **104**/**105**. Scheme 15 illustrates the easy fabrication of OBBD.

In SMCs, OBBD derivatives exhibited comparable reactions owing to their reactivity, but a large benefit was being more stable. This reaction can occur at an optimal condition due to SMCs optimized conditions as illustrated in Scheme 15D, which included supporting ligands such as dtbpf. More than 34 instances with high to exceptional yields demonstrated the substrate range **108**. The circumstances were restricted to secondary OBBD reagents, and lower yields were seen when steric hindrance was present adjacent to the boronate group. A four-step one-pot synthesis was used to show the methodology's synthetic applicability, and the reaction media was successfully recycled [134].

Nowadays, it is uncommon to discover a complete synthesis without at least one cross-coupling reaction like Suzuki–Miyaura coupling [6]. Heravi et al. [135, 136] have written a comprehensive study of the usage of SMC in total synthesis; B-alkyl Suzuki coupling in precise was used in the synthesis of useful chemicals [137–139]. Cytochalasin Z8 and ieodomycin D are two examples of secondary fungal metabolites with diverse biological activity that target cytoskeletal processes [140–142], which are presented in Scheme 16. Michellamine, an inhibitor of AIDS (a viral cause), is a complicated compound that was produced using various methods utilizing SMCs and carbon–boron reagents Scheme 16 [142, 143].

(A) $R^1B(OH)_2$ 1.1 eq. **68** + R^2OTf or **69** / R^2X **70** → PdCl$_2$(dppf) (10 mol%), K$_2$CO$_3$, (3 aq.) / Ag$_2$O (2.5 eq.), THF 80 °C, 6-10 h → R^1-R^2 **71** 15 examples **(38-92%)**

$R^1 = n$-alkyl R^2 = aryl, alkenyl

(B) $R^3B(OH)_2$ 2 eq. **72** + R^4=X **73** → PdCl$_2$ C$_3$H$_5$(dppb) (10 mol%), Cs$_2$CO$_3$, (2 aq.) / xylene or toluene 100^{-150} °C, 20 h → R^4=R^3 **74** 9 examples **(47-67%)**

R^3 =primary alkyl

(C) $R^5B(OH)_2$ 1.5 eq. **75** + R^6 Br / OH / R^7 **76** → Pd(OAc)$_2$ (5 mol%), LB-Phos.HBF$_4$ (5 mol%) / K$_2$CO$_3$ (4.5 eq.) toluene, 110 °C, 3-27 h → R^6 R^5 / OH / R^7 **77** 25 examples **(24-86%)**

R^3 =primary and secondary alkyl

L9 : LB-Phos.HBF$_4$

(D) $R^8B(OH)_2$ 1.5 eq. **78** + R^9 Br R^{10} / R^{11} **79** → Pd(OAc)$_2$ (1 mol%), AntPhos (2 mol%) / K$_3$PO$_4$, toluene 110 °C, 12-24 h → R^9 R^8 R^{10} / R^{11} **80** 17 examples **(70-99%)**

R^8 =cycloalkyl

L10 : AntPhos

(E) B(OH)$_2$ 2 eq **81** + OTf / R^{12} **82** → [Pd(cinnamyl)Cl]$_2$ (1 mol%), L (4 mol%) / K$_3$PO$_4$. H$_2$O (3 eq.) toluene, 110 °C, 12 h → R^{12} **83** >25 examples **(50-99%)**

R^8 =cycloalkyl

L11 : RMeO
L12 : NMe$_2$

Scheme 14 Alkylboronic acids as coupling partneres in sp^3–sp.^{2} SMCs (**A**–**E**)

$\bullet$ =CH–X + HO–B(–OH)–Ar → S-Catalyst / Weak Base → $\bullet$ =CH–Ar

Scheme 15 Arylbromides as reagent in SMCs

Conclusion

The emphasis of the current study was on the application of carbon organoboranes as cross-coupling partners in reactions supported by transition metal catalysis
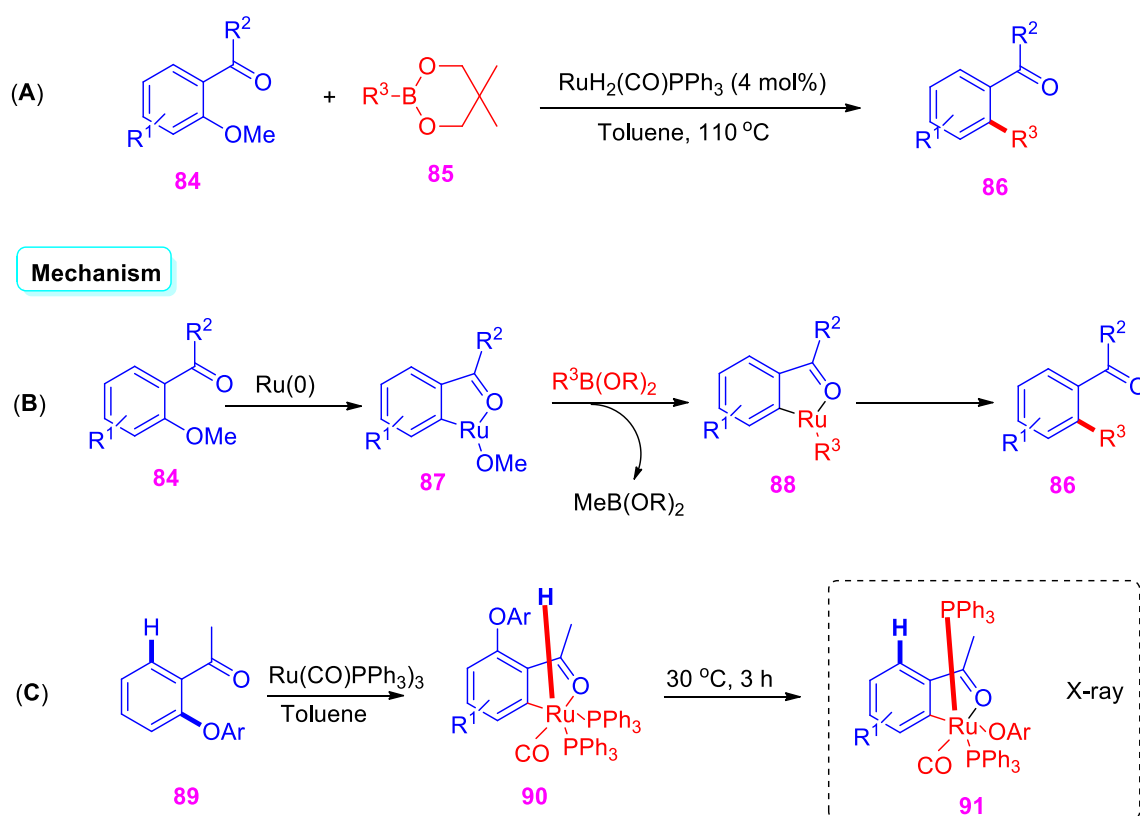
Scheme 16 Chelation-assisted Ru-catalyzed sp^3–sp^2 SMCs of C-OMe electrophiles **A** and mechanistic insight (**B**, **C**)

like that of B-alkyl SMC reactions. These reactions that are catalyzed by metals are already well-established techniques for organic synthesis. However, compared to other C–C coupling processes, cross-couplings are rarely documented. Additionally, using pseudohal-ides or R-X as coupling partners dominates this sector. Research on C–O-Alkyl electrophiles is still receiving a lot of interest. Undoubtedly, the advancement in the synthesis of stable carbon–boron reagents affects the growth of Suzuki–Miyaura type C–C cross-couplings. The focus on photocatalysis and dual has been mak-ing significant contributions in creating unique toolkits which produce active (energetically) adducts thus influ-encing complete areas under examination. This review has summarized four main reagent types for SMCs, highlighting the significance of synthetic schemes (Schemes 17, 18 and 19).
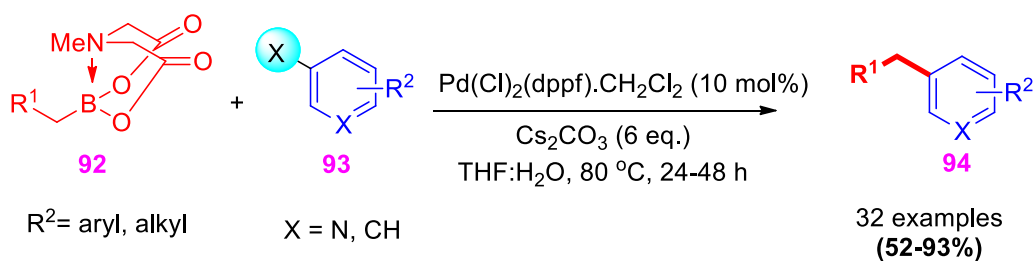
Scheme 17 sp3–sp2 SMCs using N-methylimodiacettic acid (MIDA) boronates
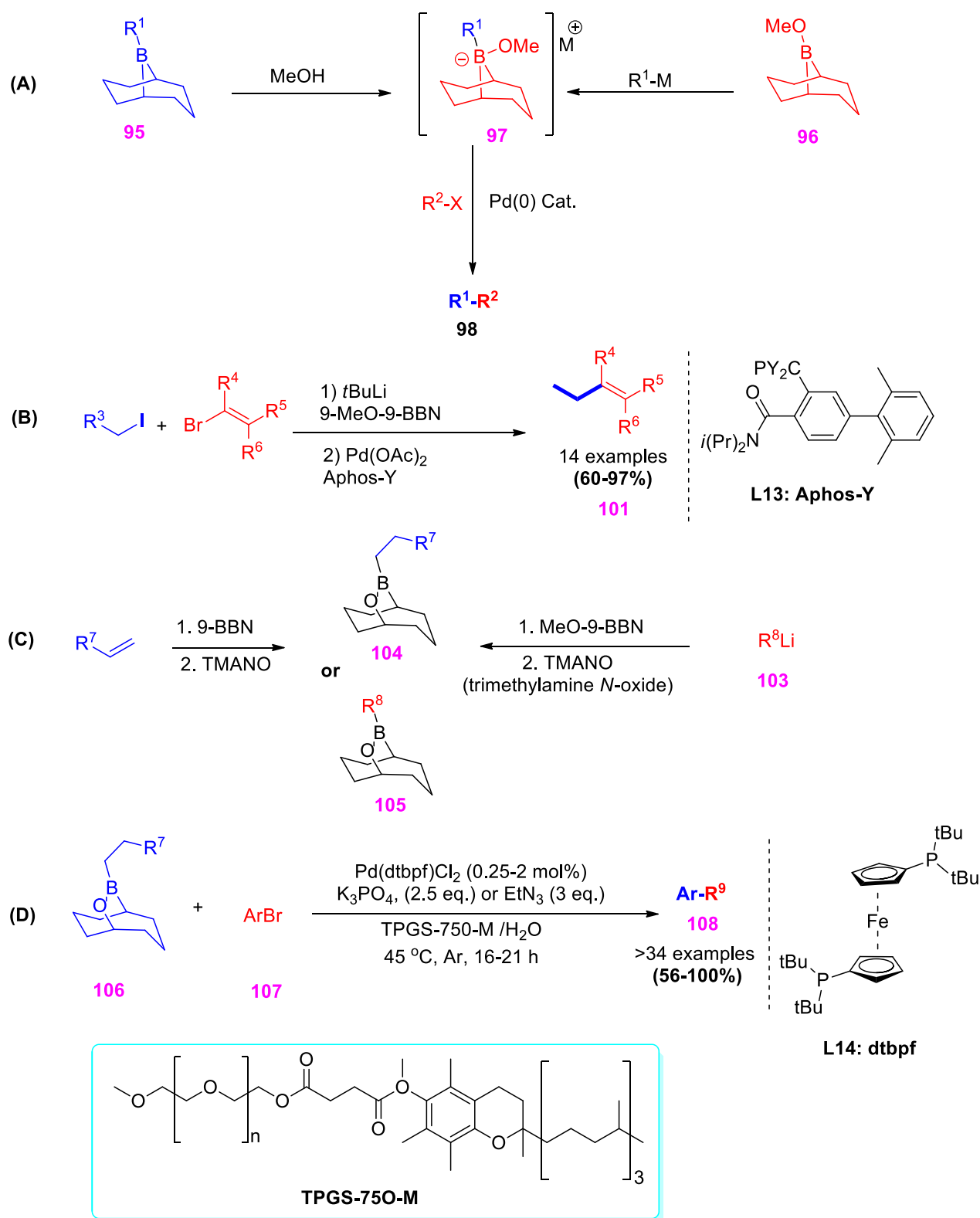
Scheme 18 B-alkyl SMCs using BBN variants (9-MeO-9BBN (**A**, **B**) and OBBD derivatives (**C**, **D**)
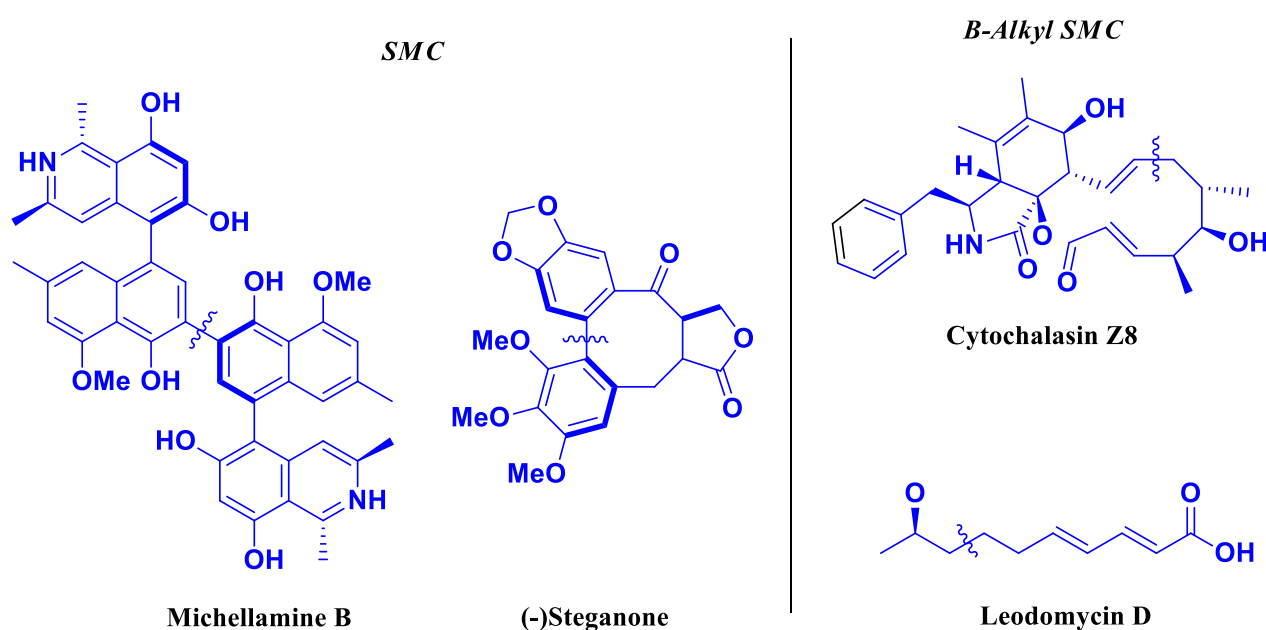
Scheme 19 Example of drugs and active molecules whose total synthesis involved SMC

Abbreviations

SMC	Suzuki–Miyaura couplings
9-BBN	9-Borabicyco[3.3.1]nonane
THF	Tetrahydrofuran
DMA	Dimethylacetamide
MIDA	Methyliminodiacetic acid
dtbbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
PG	Protecting group

Acknowledgements
Not applicable.

Author contributions
AA was involved in conceptualization, methodology, data curation and drafting the paper; IM was responsible for study, drafting the paper and critical revision; SC contributed to data curation, conceptualization and formal analysis; and all authors have read and approved the final manuscript.

Funding
This work was not supported by any funding agencies.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The authors declare no conflict of interest.

Competing interests
The authors declare that they have no competing interests.

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