Boronate Complexes

Stereospecific 1,2-Migrations of Boronate Complexes Induced by Electrophiles

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The stereospecific 1,2-migration of boronate complexes is one of the most representative reactions in boron chemistry. This process has been used extensively to develop powerful methods for asymmetric synthesis, with applications spanning from pharmaceuticals to natural products. Typically, 1,2-migration of boronate complexes is driven by displacement of an α-leaving group, oxidation of an α-boryl radical, or electrophilic activation of an alkenyl boronate complex. The aim of this article is to summarize the recent advances in the rapidly expanding field of electrophile-induced stereospecific 1,2-migration of groups from boron to sp² and sp³ carbon centers. It will be shown that three different conceptual approaches can be utilized to enable the 1,2-migration of boronate complexes: stereospecific Zweifel-type reactions, catalytic conjunctive coupling reactions, and transition metal-free sp²–sp³ couplings. A discussion of the reaction scope, mechanistic insights, and synthetic applications of the work described is also presented.

1. Introduction

Chiral boronic acids and related derivatives are valuable building blocks in modern synthesis as they can be easily prepared with high levels of enantioselectivity.[1] Crucial to the synthetic utility of organoboron compounds is their ability to be transformed stereospecifically into a range of functional groups.[2] In general terms, these transformations are initiated by the addition of a nucleophile to the boron atom, resulting in boronate complex formation, followed by a stereospecific 1,2-migration of a metal migrating group to the adjacent carbon centre.[3] An example of such a process is the homologation of boronic esters with carbonoids (Scheme 1a), which has seen wide application in asymmetric synthesis. In this context, Matteson’s substrate-controlled homologation[4] and Aggarwal’s reagent-controlled lithiation-borylation[5] methodologies are particularly noteworthy. Recently, the fields of radical chemistry with stereospecific 1,2-migration has been shown that radicals next to boronates can be generated by the addition of carbon-centred radicals to alkenyl boronates[6] or by α-C(sp²)–H abstraction.[7] These α-boryl radical anions can then undergo single-electron oxidation followed by 1,2-migration to afford the desired products. This active field has been recently reviewed so will not be discussed further.[8]

Stereospecific 1,2-migrations of alkenyl or aryl boronates can be induced by reactions with suitable electrophiles (Scheme 1c). Although significant and substantial work in this field has been reported, systematic review articles are rare.[9] Therefore, the aim of this Minireview is to provide an overview of recent developments in electrophile-induced stereospecific 1,2-migration of boronate complexes, including Zweifel-type reactions, conjunctive cross-couplings, and transition metal-free sp²–sp³ couplings. The scope of this review also extends to boronate complexes containing strained σ-bonds, which exhibit similar reactivity to α-bonds.

2. Stereospecific 1,2-Migration of Alkenyl Boronates Induced by Electrophiles

2.1. Zweifel-type Coupling Reactions

In 1967, Zweifel first reported the stereoselective synthesis of alkenes using organoboron intermediates (Scheme 2a).[10] The reaction was initiated by hydroboration of alkyne 1 with dicyclobutylborane, resulting in the formation of alkenyl borane 2a, which was then reacted with iodine in the presence of sodium hydroxide, leading to Z-alkene 5. The reaction proceeds via cyclic iodonium ion intermediate 3, followed by a stereospecific 1,2-migration affording β-iodoboronic acid 4. This species then undergoes anti elimination in the presence of base, which results in an overall inversion of alkene geometry from 2 to 5. Furthermore, it was later proved that the migrating moiety underwent 1,2-migration with complete retention of configuration by employing diastereomerically pure borane 6 as a substrate in the reaction (Scheme 2b).[11] Considering the stereochemical features of this process, a syn elimination (giving the E-alkene) should be possible if the interaction between the β-halogen and boron of the β-haloboronic intermediate could be enhanced. Indeed, Zweifel demonstrated that syn elimination was favoured if a strong electron-withdrawing group (CN) was introduced on boron, which allowed coordination of the bromide to boron in intermediate 10 and resulted in the formation of E-olefins 11 (Scheme 2c).[12]

The vinyl group is an important functional group, commonly found in natural products and functional materials.[13] In this context, the Zweifel olefination provides an excellent method to convert a boronic ester into a vinyl group by employing vinyl lithium or the corresponding Grignard reagent.[14] In 2009, Aggarwal applied this concept to the total synthesis of (+)-faranal (Scheme 3).[15] Enantioenriched boronic ester 12 was reacted with vinyl lithium and then treated with iodine and sodium methoxide, which provided alkene intermediate 13. Without isolation of 13, in situ hydroboration and oxidation gave alcohol 14 in 69% yield and with excellent stereoselectivity.

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diasteroselectivity. Finally, \((-\text{faranal})\) was obtained by oxidation of 14 with pyridinium chlorochromate (PCC). Additionally, this strategy was also successfully used by Morken to introduce an isopropenyl group in the total synthesis of debromohamigeran E (Scheme 4).\(^{[16]}\) Alkene 16 was formed in high yield on a gram-scale by Zweifel olefination of boronic ester 15 with isopropenyllithium.

Enantioenriched tertiary boronic esters 17 have also been subjected to the same Zweifel olefination conditions to form vinyl-substituted quaternary stereogenic centers 18 with complete enantiospecificity (Scheme 5a).\(^{[17]}\) It is noteworthy that allylsilanes 20 could also be obtained in high enantioselectivity using this protocol (Scheme 5b).\(^{[18]}\) However, the preparation of vinyllithium typically relies on in situ lithium–tin exchange of tetravinyltin, or lithium–bromide exchange of vinyl bromide, which reduces its practicality. Therefore, vinyl Grignard reagents, which are easier to handle and commercially available, have also been explored in the Zweifel olefination (Scheme 5c).\(^{[19]}\)

Whilst this method shows synthetic utility, it is not suitable for sterically hindered tertiary boronic esters, which makes the higher reactivity of vinyllithium more attractive. This is illustrated in a five-step synthesis of \((-\text{grandisol})\), where

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**Scheme 1.** Strategies for stereospecific 1,2-migrations of boronate complexes. Cb = N,N-diisopropylcarbamoyl. R\(_M\) = Migrating group.
a Zweifel olefination was used to convert tertiary boronic ester 24 into terminal alkene 25 (Scheme 5d). Subsequent hydroboration/oxidation and Cope elimination provided the natural product in good yield and high diastereoselectivity.

In the past decade, the scope of the Zweifel olefination reaction has been greatly expanded. For example, α-heteroatom-substituted alkenyl metals 27 have been successfully coupled with secondary boronic esters (Scheme 6a), which provides great opportunities for application in synthesis as the vinyl ether products 29 can be easily converted into ketones by hydrolysis under mild conditions. This methodology was used to convert boronic ester 30 into enol ethers 31 and 32 in the synthesis of the reported and revised structures of baulamycins A and B, respectively (Scheme 6b).

The enantiospecific alkynylation of secondary and tertiary boronic esters is an extension to the established Zweifel olefination. In situ α-lithiation of vinyl bromides or carbamates in the presence of the boronic ester provided boronate complexes 33 that underwent iodine-induced olefination to give alkynyl bromides or carbamates 34 (Scheme 7a).
Subsequent base-induced 1,2-elimination afforded the alkylnlated products. In this reaction, various terminal and silyl-protected alkynes can be obtained with high enantioselectivity, and a broad range of functional groups (alkenes, azide, alkyne, and ester groups) are tolerated. Furthermore, it was used in the total synthesis of tatanan A, where complex boronic ester—constructed using iterative reagent-controlled homologation—was employed in an enantiospecific Zweifel-type alkynylation to afford alkyne (Scheme 7b).

It should be noted that alkynyl anions cannot be used directly in Zweifel-type alkynylation since they react reversibly with boronic esters. However, they can used in reactions with boranes or borinic esters.

Intramolecular Zweifel olefination has also been achieved, which provides access to methylene cycloalkanes (Scheme 8). Alkenyl bromide-containing boronic ester—obtained with high stereoselectivity from by lithiation-borylation—was treated with BuLi to form an alkynyl lithium intermediate through lithium-halogen exchange. This species cyclised to give an intermediate cyclic boronate complex. Subsequent treatment with iodine and methanol under Zweifel olefination conditions afforded ring contracted methylene cyclopentane in 97% yield with 100% enantiospecificity, which was then transformed into the natural product. This high level of stereocontrol is often unachievable with metal-catalyzed Suzuki–Miyaura cross-couplings, which has resulted in the Zweifel olefination being commonly employed in the synthesis of complex natural products and pharmaceutical intermediates.

2.2 Sulfur and Selenium-Based Electrophiles

In 2017, Aggarwal reported a modified Zweifel-type olefination proceeding through a novel syn elimination process (Scheme 9). This was achieved by employing PhSeCl as the electrophile for the selenation of alkenyl boronates, which led to β-selenoboronic esters through the stereospecific 1,2-migration ring-opening of seleniranium intermediates. It was found that m-CPBA was able to chemoselectively oxidise the selenide to give selenoxide intermediate, which underwent syn elimination to provide boronic esters into structurally diverse alkenes with excellent control of alkene geometry. Importantly, by proceeding through a stereospecific 1,2-migration mechanism, the chiral information of the boronic ester substrate is fully translated to the alkene product.
alkenes 44 in high stereoselectivity. DFT calculations showed that the oxygen atom of selenoxide 47 interacts strongly with the boron atom, therefore resulting in a syn elimination pathway. This selenium-mediated olefination showed broad substrate scope in terms of both the boronic esters and the alkenyl lithium reagents (di- and trisubstituted), leading to synthetically useful alkene products 44 with high selectivity for retention of olefin geometry.

In 2018, Denmark reported an alternative chalcogenation-induced 1,2-migration of alkenyl boronates (Scheme 10).[28] Through the use of a chiral Lewis base catalyst in combination with N-(phenylthio)saccharin (51) as a source of electrophilic sulfur, an enantioselective sulfonylation was achieved. This provided access to a broad array of enantioenriched anti β-sulfenoboronic esters 50 with two contiguous stereogenic centers with complete diastereoselectivity. Chiral sulfonylating reagent 52, formed from the nucleophilic addition of chiral selenophosphoramidate catalyst (S)-L1 to 51, is a cationic donor-acceptor species with a highly electrophilic sulfur atom. Reaction of 52 with alkenyl boronate 48 generates the enantioenriched thiiranium ion 49, which undergoes 1,2-migration to generate anti-products 50 with high enantioselectivity.

2.3. Transition Metal-Catalyzed Conjunctive Cross-Couplings

It is known that π-acidic late transition metal complexes in high oxidation states, such as PdII and NiII, are highly electrophilic and able to strongly coordinate to π-bonds. In 2015, Morken reported that such species could interact with the electron-rich π-bond of alkenyl boronate complexes, triggering a 1,2-migration of an alkyl or aryl group on boron (Scheme 11).[29] Key to the success of this reaction was the use of aryl triflates rather than aryl halides, which generated a more reactive cationic PdII intermediate, and the use of the Mandyphos ligand L2 to reduce the propensity for β-hydride elimination of intermediate alkylpalladium(II) intermediates. Furthermore, using a chiral phosphine ligand gave the conjunctive coupling products in good yield and high enantioselectivity. The choice of diol ligand on boron played an important role in determining the enantioselectivity. Interestingly, the optimum diol ligand was found to be dependent on the triflate electrophile, with neopentyl glycol
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**Scheme 11.** Enantioselective conjunctive cross-coupling enabled by palladium-induced 1,2-migration. [a] Using the pinacol-derived boronate complex. R_0 = Migrating group.

Ligands proving optimal for aryl triflates, whereas pinacol ligands provided significantly improved selectivity in reactions of alkenyl triflates. Mechanistically, it was postulated that oxidative addition of Pd⁰ species to an aryl/alkenyl triflate generates the electrophilic PdII intermediate (Scheme 12). This complexes with alkenyl boronate to form complex 55, which triggers 1,2-migration to generate alkyl palladium(II) intermediate 58. This is followed by reductive elimination, giving the boronic ester 59 and regenerating the Pd⁰ catalyst. The large bite-angle of ligand L_1 limited the undesired β-hydride elimination of 58.

Morken has built on this discovery with a number of important developments (Scheme 13). Firstly, the reaction has been extended to Grignard reagents instead of organolithiums and to halide electrophiles in place of triflates (Scheme 13a). It was found that the conjunctive cross-coupling was inhibited by halide ions, which had previously limited the use of aryl halide electrophiles. However, this limitation was overcome by using a combination of NaOTf and DMSO as additives, which allowed the formation of cross-coupled products 61 with high yields and enantioselectivities. The effect of these additives was two-fold: (i) the NaOTf resulted in precipitation of the sodium halide salt, thus avoiding the detrimental coordination of halide ions to palladium and creating the more electrophilic PdII complex; and (ii) the combination of NaOTf and DMSO greatly increased the stability of the alkenyl boronate complexes 60 generated from the vinyl Grignard reagent. Conjunctive cross-couplings between alkenyl boronic esters 62, vinyl-lithium, and aryl/alkenyl triflate were next explored (Scheme 13b). These reactions proceed through bis-alkenylboronate complexes 63, with the PdII intermediate showing a preference for reaction with the less substituted alkene, and allow access to chiral allyl/boronic esters 64. Extension of this approach to boronate complexes derived from α-substituted alkenyl boronic esters 65 allowed access to highly desirable tertiary boronic esters 66 with good enantioselectivity (Scheme 13c). β-Substituted alkenyl boronic esters 67 were also successfully employed, but required alterations to the boron ligand design to prevent undesired Suzuki-Miyaura-type reactivity, which was found to dominate with pinacol and neopentyl glycol boronic ester substrates (Scheme 13d). A more sterically demanding boronic substituent (mac), derived from acenaphthoquinone, was required to minimize Suzuki-Miyaura coupling and direct the approach of the palladium(II) complex to the more congested β-carbon, thus enabling access to the conjunctive cross-coupling products 68 with excellent stereoselectivities. Furthermore, this approach was applied to β-silyl alkenyl boronate complexes 69 for the efficient construction of anti-1,2-borosilanes (Scheme 13e). Finally, using propargylic carbonates 72 in place of aryl triflates furnished fully substituted β-boryl allenes with high enantioselectivity (Scheme 13e). It was found that a methanol additive resulted in formation of a dimethoxyboronate intermediate through boron ligand exchange, which significantly enhanced both the yield and enantioselectivity of the reaction.

Morken has since extended this conjunctive cross-coupling to include enyne-derived boronate complexes 74, which give α-hydroxy allenes 75 after oxidative work-up (Scheme 14). Interestingly, enyne boronates derived from Z-allenes provided α-boryl allenes with high diastereoselectivity, whereas E-allene substrates gave low diastereoselectivity. This was rationalized based on the steric interactions between the migrating group and the palladium complex: in the case of the Z-allene, complex syn-76 has these moieties in close proximity so they orientate to minimize steric interactions, making anti-76 the reactive conformer; whereas in the E substrate, there is little interaction between the migrating group and the palladium complex in either conformers anti-77 or syn-77, resulting in poor diastereorecontrol. For reactions with alkyl migrating groups, substitution of the pinacol ligand on boron for an acenaphthoquinone-derived boronic substituent (hac⁺) was essential for achieving high stereoselectivity, which was attributed to enhanced catalyst-substrate steric interactions.

Electrophilic palladium complexes have also been used to trigger a 1,2-migration in indole-derived boronate complexes. Following Ishikura’s studies on palladium-catalyzed allylation of 2-indolyboronates derived from trialkylboranes, Ready...
showed that these reactions could be extended to boronic esters and rendered asymmetric using Pd(BINAP) catalysts (Scheme 15). The indole-derived boronate complexes reacted with Pd(α-allyl) complexes, to form indolin-2-yl boronic esters with high levels of diastereo-, regio-, and enantioselectivity. The boronic esters products were oxidized with basic hydrogen peroxide to provide the corresponding indoles. Alternately, protodeborylation of benzylic boronic ester products with TBAF trihydrate gave 2,3-disubstituted indolines. Various aryl and alkyl migrating groups could be employed in this asymmetric three-component coupling, which provided indoline products with three contiguous stereogenic centers. The scope of the reaction was subsequently extended to 3-alkyl-substituted indoles by using a Pd/phosphoramidite catalyst system, which enabled the enantioselective formation of indolin-2-yl boronic esters with adjacent quaternary stereocenters.

Morken has also demonstrated that nickel(II) complexes interact with alkyl boronates in a similar manner to palladium(II) complexes. When investigating a one-pot 9-BBN hydroboration/enantioselective conjunctive cross-coupling reaction between alkenes and aryl iodides, they found that the Pd/Mandyphos catalyst system that was optimal for pinacol boronate substrates only provided racemic products when applied to the 9-BBN-derived boronates (Scheme 16). However, a nickel catalyst in combination with the diamine ligand gave the products in high enantioselectivity. Detailed mechanistic studies indicated that the reaction involves initial oxidative addition of the aryl iodide to Ni(0) to give a Ni(II) species, which binds the alkene (forming 85) to induce 1,2-migration with stereospecific addition of the migrating group and Ni(II) across the alkene. Morken subsequently extended the scope of these nickel-catalyzed conjunctive cross-couplings to other electrophiles, including alkyl halides and acid chlorides.

Scheme 13. Catalytic conjunctive cross-coupling reactions enabled by palladium-induced 1,2-migration. $R_\alpha =$ Migrating group.
3. Stereospecific sp²–sp³ Coupling of Chiral Boronic Esters with Aromatic Compounds

In 2014, Aggarwal disclosed an efficient and general method for stereospecific sp²–sp³ couplings of electron-rich (hetero)aromatics with chiral secondary and tertiary boronic esters (Scheme 17a). The reaction occurs by initial reaction of an aryllithium with boronic ester 18 to form aryl boronate complex 86, followed by treatment with an electrophilic halogenating agent to provide the arylated product 87 in high yield and with complete stereospecificity. This process could be used to introduce various electron-rich aromatic groups, including 5-membered ring heteroaromatics and 6-membered ring aromatics with meta-electron-donating groups, and was applicable to a broad range of secondary and tertiary boronic esters with different steric demands. In most cases, NBS was the optimal electrophile, with NIS being employed in cases where further halogenation of the electron-rich aromatic ring occurred. Mechanistically, the addition of NBS to the aromatic ring of boronate complex 86 generates cation 88. This triggers a stereospecific 1,2-migration, forming δ-halo allylic boronic ester intermediate 89, and subsequent elimination/rearomatization leads to the arylated product 87.

Subsequent DFT calculations on the reaction between furyl boronate complex 86 and NBS provided evidence for simultaneous electrophilic bromination and 1,2-migration steps, without formation of the postulated cationic intermediate 88. In later studies, it was found that the coupling of 6-membered ring aromatics was dramatically affected by solvent choice (Scheme 17b). Solvent exchange from THF to MeOH led to improved yields of coupled products 87, which was due to a reduction of the amount of undesired S_{2,2} bromination of the C–B bond of 86. Interestingly, switching to less nucleophilic alcohol solvents promoted an alternative arylation pathway to provide Bpin-incorporated coupling products 93 with complete stereospecificity. Using an iPrOH-MeCN mixed solvent system resulted in an inefficient nucleophile-promoted Bpin elimination of dearomatized intermediate 91, therefore 91 underwent a 1,2-Wagner–Meerwein shift of the Bpin moiety to form carbocation 92, which relieved steric encumbrance and allowed subsequent rearomatization by deprotonation to afford 93.

Aggarwal has since expanded this concept of electrophilic-induced arylation of boronic esters to allow coupling of a range of substituted aromatic rings. For example, phenyl-
acetylene products 95 and 96 could be accessed by coupling between \( p \)-lithiated phenylacetylenes (generated by halogen-lithium exchange of the corresponding bromide 94) and a range of chiral boronic esters 18 (Scheme 18). Treatment of the intermediate TMS-phenylacetylene-derived boronate complex with NBS results in bromination of the alkyne motif, which triggered a stereospecific 1,2-migration leading to dearamatized bromoallene intermediate 97. Using unhindered neopentyl glycol boronic esters and MeOH as solvent, subsequent nucleophile-promoted elimination and rearomatization of 97a occurred, resulting in the formation of coupled product 95. In contrast, the use of the more hindered pinacol boronic esters and \( \text{iPrOH} \) as the solvent prevented nucleophile-promoted elimination, therefore 1,2-Wagner–Meerwein shift of the Bpin moiety occurred instead. This led to carbocation 98, which, after loss of a proton, furnished the ortho Bpin-incorporated product 96.

Ortho- and para-substituted phenols provide a different opportunity for triggering 1,2-migration of aryl boronate complexes (Scheme 19). In the coupling of \( para \)-lithiated phenolates 99 with boronic esters, following formation of boronate complex 100, 1,2-migration occurred upon the activation of the phenolate with Martin/C29s sulfurane (Ph\(_2\)S-[OC(CF\(_3\))\(_2\),Ph]) or triphenylbismuth difluoride (Ph\(_3\)BiF\(_2\)), forming boronate complexes 102 and 103, respectively (Scheme 19a). Elimination of Bpin from cyclohexadienone 104 then provides the coupled products 101. This method was less effective for ortho-substituted phenols due to increased steric hindrance, which prevented effective phenolate activation. Interestingly, this limitation was overcome by performing the coupling with lithiated N-phenoxy benzotriazole 105, where the pre-incorporated benzotriazole acts as a leaving group (see intermediate 106) so circumvents the challenging ortho-phenolate activation (Scheme 19b). 1,2-Migration successfully occurred at ambient temperature to allow access to ortho-substituted phenol products 107 with complete stereospecificity.

A similar strategy was used by Aggarwal to access aniline products 110 through N-acylation of boronate complexes generated from lithiated \( para \)- and ortho-phenyl hydrazines 108 (Scheme 20a). Acylation of the \( para \)-hydrazinyl boronate complex with trifluoroacetic anhydride (TFAA) formed acyl ammonium 109, with subsequent concurrent 1,2-migration and N–N bond cleavage. After Bpin elimation/rearomatization and further reaction of the resulting amino group with TFAA, the trifluoroacetamide products 110 were isolated in good yield and with complete stereospecificity. For the corresponding ortho-hydrazinyl boronate complexes, changing the N-activator from TFAA to the less reactive 2,2,2-trichloro-1,1-dimethylethyl chloroformate (Me\(_2\)Troc-Cl) was required to obtain the ortho-aniline products in good yield.

By taking advantage of this N-acylation approach, Aggarwal showed that boronate complexes 111 derived from ortho-benzylamines can also undergo electrophile induced 1,2-migration (Scheme 20b). Treatment of boronate complex 111 with Me\(_3\)Troc-Cl generated N-acylated intermediate 112, which triggers a 1,2-migration/anti-S\(_2\)' reaction to form dearamatized intermediate 113. This step is surprisingly fast and complete within 5 minutes at \(-78^\circ\text{C}\). A subsequent
suprafacial Lewis acid mediated 1,3-borotropic shift of 113 gave enantioenriched ortho-substituted benzylic boronic esters 114 in high yields and stereospecificities. Furthermore, through the use of enantioenriched secondary benzylic amine substrates, it was shown that the anti-S_N2' and 1,3-borotropic shift processes also proceeded with high stereospecificity, which allowed doubly stereospecific reactions to occur when enantioenriched boronic esters were also employed (see product 114c). Further work highlighted the synthetic utility of the intermediate enantioenriched dearomatized tertiary boronic esters 113, which were utilized in rearomatizing allylic Suzuki–Miyaura cross-coupling reactions to provide complex enantioenriched 1,1-diarylmethane products 116 with three readily addressable points of diversification (Scheme 20c). [49]

In an alternative N-acylation-induced 1,2-migration of aryl boronate complexes, Aggarwal developed a general protocol for the stereospecific coupling of chiral secondary and tertiary boronic esters with electron-deficient N-heteroaromatics (Scheme 21a). [50] After formation of chiral boronate complexes 119 from lithiated 6-membered ring N-heterocycles 117 (including pyridines, quinolines and isoquinolines), 1,2-migration was triggered by N-acylation with 2,2,2-trichloroethyl chloroformate (Troc-Cl), leading to dearomatized tertiary boronic ester 121 via the intermediate N-acyl pyridinium 120. A one-pot oxidation/hydrolysis/elimination sequence finally furnished the coupled heteroaromatic products 118 with complete stereospecificity. A modified approach was reported by Ready, in which the pyridyl boronate complexes 119 were generated by adding organometallic reagents to 4-pyridyl boronic ester 18e (Scheme 21b). [51] It was shown that, in addition to organolithium reagents, organozinc and Grignard reagents could also be employed in this heteroarylation reaction.

4. Electrophile-Induced 1,2-Migration of Strained Boronates

It is shown above that electrophilic metal complexes, including Pd II and Ni II, can coordinate with the $\pi$-bonds of alkynyl boronate complexes to trigger 1,2-migration and achieve carbometallation of alkenes (Scheme 11). Although such metal species readily react with C=C $\pi$-bonds, they generally do not react with C=C $\sigma$-bonds. However, Aggarwal has recently reported that cationic palladium(II) complexes can activate $\sigma$-bonds of highly strained boronate complexes to promote 1,2-migration and achieve $\sigma$-bond carbopalladations (Scheme 22). [52] To achieve such a process, bicyclo[1.1.0]butyl boronate complexes 124 were prepared from sulfoxide 122 by sulfoxide-lithium exchange and in situ borylation of the resulting bicyclo[1.1.0]butyl lithium (123). The high ring strain of the bicyclo[1.1.0]butyl (≈ 66 kcal mol$^{-1}$) weakens the

*Scheme 18. Coupling boronic esters with phenylacetylenes via alkyne activation.*

*Scheme 19. Coupling boronic esters with ortho- and para-phenols.*
central α-bond, and the release of this strain provides significant driving force to allow efficient reaction of 124 with a Pd II catalyst. This enabled a distal cross-coupling of boronic esters and aryl triflates to provide 1,1,3-trisubstituted cyclobutanes 125 in high yields and with complete stereospecificity and diasterecontrol. The proposed mechanism involves initial oxidative addition of the aryl triflate to the Pd 0 catalyst 126 to form the cationic Pd II complex 127. Reaction of 127 with boronate complex 124 occurs at the more nucleophilic β-carbon to provide the cyclobutyl palladium intermediate 128. As 1,2-migration requires an anti-periplanar alignment of the migrating group (R M) and the breaking C–C bond, this makes the endo face of the reactive conformer more sterically hindered, thus the bulky metal complex approaches from the more exposed exo face. This forms intermediate 129 with complete diastereocontrol for syn-carbopalladation, which, after stereospecific reductive elimination provides 125 in excellent diastereoselectivity. This interesting strain release-driven 1,2-migration of bicyclo[1.1.0]butyl boronate complexes opens up new directions for stereospecific transformations involving 1,2-migration to sp3-hybridized carbons.

5. Summary and Outlook

Organoboron compounds are indispensable in synthetic chemistry, providing a powerful platform for myriad transformations. The stereospecific 1,2-migration of boronate complexes is one of the most important processes in this area. This can be triggered by a suitable α-leaving group, oxidation of α-boryl radicals, or electrophilic activation. As described above, electrophilic activation of boronate complexes can take many different forms and provide access to a diverse array of products from readily available chiral...
boronic ester. In the case of the Zweifel olefination, reaction of alkynyl boronate complexes with iodine transforms boronic esters into alkenes with high selectivity for inversion of alkene geometry, providing a valuable methodology that has been exploited extensively in total synthesis. This concept has more recently been extended chalcogenation of alkynyl boronate complexes, including selenation, which provides a unique opportunity to switch the stereoselectivity of the Zweifel olefination from inversion to retention. Furthermore, the principles behind the Zweifel olefination have inspired so many new methodologies with broad-ranging applications in asymmetric synthesis. While the field of electrophile-induced 1,2-migration of boronate complexes is over 50 years old, it remains an exciting area that is continually expanding. It is remarkable that the seminal olefination work by Zweifel in 1967 has inspired so many new methodologies with broad-ranging applications in synthetic chemistry.

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Conflict of interest

The authors declare no conflict of interest.

[1] a) S. G. Aiken, J. M. Bateman, V. K. Aggarwal, Science of Synthesis—Advances in Organoboron Chemistry towards Organic Synthesis (Ed.: E. Fernández), 2019, pp. 393–458; b) B. S. L. Collins, C. M. Wilson, E. L. Myers, V. K. Aggarwal, Angew. Chem. Int. Ed. 2017, 56, 11700–11753; Angew. Chem. 2017, 129, 11860–11894; c) “Structure, Properties, and Preparation of Boronic Acid Derivatives”: D. G. Hall in Boronic Acids (Ed.: D. G. Hall), 2nd ed., Wiley-VCH, Weinheim, 2011, pp. 1–135.
[2] a) C. Sandford, V. K. Aggarwal, Chem. Commun. 2017, 53, 5481–5494; b) J. W. B. Fyfe, A. J. B. Watson, J. Am. Chem. Soc. 2017, 3, 31–55; c) P. Kaur, G. L. Khaitik, S. K. Nayak, Curr. Org. Synth. 2017, 14, 665–682; d) E. R. Burkhardt, K. Matos, Chem. Rev. 2006, 106, 2617–2650.
[3] a) S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, Chem. Rev. 2009, 9, 24–39; b) V. K. Aggarwal, G. Y. Fang, X. Ginesta, D. M. Howells, M. Zaja, Pure Appl. Chem. 2006, 78, 215–229; c) D. S. Matteson, Chem. Rev. 1989, 89, 1535–1551.
[4] a) D. S. Matteson, J. Org. Chem. 2013, 78, 10009–10023; b) D. S. Matteson, Acc. Chem. Res. 1988, 21, 294–300; c) D. S. Matteson, K. M. Sadhu, J. Am. Chem. Soc. 1983, 105, 2077–2078; d) D. S. Matteson, R. Ray, J. Am. Chem. Soc. 1980, 102, 7590–7591.
[5] a) D. Leonori, V. K. Aggarwal, Acc. Chem. Res. 2014, 47, 3174–3183; b) J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, Angew. Chem. Int. Ed. 2007, 46, 7491–7494; Angew. Chem. 2007, 119, 7635–7638.
[6] a) M. Silvi, C. Sandford, V. K. Aggarwal, J. Am. Chem. Soc. 2017, 139, 5736–5739; b) M. Kischkekwitz, K. Okamoto, C. Muck-Lichtenfeld, A. Studer, Science 2017, 355, 936–938.
[7] D. Wang, C. Mück-Lichtenfeld, A. Studer, J. Am. Chem. Soc. 2019, 141, 14126–14130.
[8] a) M. Kischkekwitz, F. W. Friese, A. Studer, Adv. Synth. Catal. 2020, 362, 2077–2087; b) G. J. Lovingin, J. P. Morken, Eur. J. Org. Chem. 2020, 2362–2368.
[9] S. Namirembe, J. P. Morken, Chem. Soc. Rev. 2019, 48, 3464–3474.
[10] G. Zweifel, H. Arzoumanian, C. C. Whitney, J. Am. Chem. Soc. 1967, 89, 3652–3653.
[11] G. Zweifel, R. P. Fisher, J. T. Snow, C. C. Whitney, J. Am. Chem. Soc. 1971, 93, 6309–6311.
[12] G. Zweifel, R. P. Fisher, J. T. Snow, C. C. Whitney, J. Am. Chem. Soc. 1972, 94, 6560–6561.
[13] Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, Chem. Rev. 2017, 117, 9333–9403.
[14] R. J. Armstrong, V. K. Aggarwal, Synthesis 2017, 49, 3323–3336.
[15] G. Dutheuil, M. P. Webster, P. A. Worthington, V. K. Aggarwal, Angew. Chem. Int. Ed. 2009, 48, 6317–6319; Angew. Chem. 2009, 121, 6435–6437.
Electrophile-induced stereospecific 1,2-migration of boronate complexes has been successfully applied in many asymmetric reactions. Typically, the electrophilic species provides the activation required for the boronate complex to undergo the desired migration of a group from boron to the adjacent sp² or sp³-hybridized carbon. Such activating species range from stoichiometric classical electrophiles to transition metal complexes present in catalytic quantities.