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C–H borylation: a tool for molecular diversification

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Iridium-catalyzed C–H activation and borylation has become as a powerful synthetic tool in the past few decades because of the widespread applicability and versatility of organoboron compounds. This reaction is currently receiving extensive research interest in both academia and pharmaceutical industries because of its ability to attain a high degree of molecular complexity from simple building blocks. This review aims to highlight the implementation of C–H activation and borylation strategies in tandem one-pot transformations for the synthesis of complex natural products, for the late-stage modifications of bio-active molecules and pharmaceuticals, and for the functionalization of aromatic polycyclic systems used in materials chemistry.

1. Introduction

In the last few decades, transition metal-catalyzed C–H bond functionalization[1–7] reactions have emerged as a powerful synthetic route for manufacturing complex molecules and pharmaceuticals. The C–H bond functionalization process has demonstrated the potential to shorten reaction paths, improve the economic feasibility, and reduce the related environmental burden.[8] Traditional C–H bond functionalization reactions are associated with the selective insertion of a transition metal into the inert carbon–hydrogen (C–H) bond[9] of an arenes (hetero) without any additional stoichiometric reagent needed for activation. The generated organometallic species (arenes (hetero) carbon–metal complex) undergoes subsequent reactions and, as a result, the C–M bond is converted into C–X, C–O, C–N, C–B, and C–C bonds with excellent site-selectivity.[10] Previously, these transformations generated organometallic species that were prepared from aryl(hetero) halides themselves, and each of these halides needed to be made by functionalizing the aryl(hetero) ring *via* a process that requires stoichiometric quantities of hazardous reagents and harsh cryogenic conditions.[11,12] Hence, it is obvious that the C–H

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Saikat Guria

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Mirja Md Mahamudul Hassan

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functionalization approach has enormous power to modernize the field of organic chemistry bypassing traditional difficult and lengthy synthetic strategies with ease.

Among the many important C–H bond functionalization reactions[13] that are known (*e.g.*, arylations, alkylations, oxidations, halogenations, *etc.*), C–H bond borylation[14–21] has evolved as one of the best strategies because the generated organoboron species serve as high-valued synthons for a variety of molecular architectures.[22] In 1993, Marder and coworkers[23] noticed toluene borylated mass in GC-MS results during the synthesis of an iridium tris-(catechol boryl) complex. This is considered to be the first example of arene C–H activation and borylation. However, the catalytic C–H borylation of arenes was first reported[24] by Smith and coworkers in 1999 using an iridium-complex containing a Cp* and phosphine ligand. Later on, in 2002, Hartwig *et al.* disclosed a ground-breaking discovery[25,26] of catalytic C–H borylation using an Ir(I) cyclooctadiene precatalyst and the 4,4′-di-*tert*-butylbipyridine (dtbpy) ligand. This catalytic system is known as the Ishiyama–Miyaura–Hartwig (IMH) protocol. Notably, it is capable of installing the boron functionality under mild reaction conditions with a turnover number of around 8000 and tolerates a broad range of functional groups. Subsequently, significant developments have been made in the mechanistic understanding, reaction conditions, expansion of the scope of the substrates and precatalysts, and in the design of novel ligand scaffolds.[14] For example, Hartwig and coworkers in 2019 realized that phenanthroline-based systems are often superior to the classic IMH catalyst due to their greater binding stability and catalyst lifetime.[27] Detailed mechanistic studies revealed[28] that an iridium-catalyzed C–H borylation reaction occurred through the formation of an iridium tris(boryl) complex. Kinetic studies suggested that C–H activation is the rate-determining step where an Ir(III) to Ir(V) catalytic cycle operated with a primary KIE of 3.8 (Fig. 1).

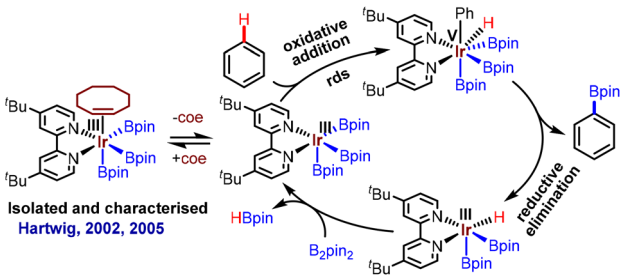

Fig. 1 Ir-catalyzed C–H borylation mechanism through an Ir(III)-Ir(V) catalytic cycle.

In the realm of synthetic organic chemistry, the strategy of C–H borylation flourished tremendously when this chemistry was implemented in the synthesis of bioactive natural products, not only in the laboratory but also in industry.[22] Pioneering groups like those of Gaunt (synthesis of rhazinicine: 2008),[29] Sarpong (synthesis of (+)-complanadine A: 2010),[30] and Baran (synthesis of verruculogen and fumitremorgin A: 2015)[31] used C–H functionalization and borylation techniques as the key steps towards the total synthesis of complex natural products.[32] Considering all these examples, undoubtedly, it may be stated that nowadays this strategy has evolved to be one of the mainstream techniques used to synthesize natural products, pharmaceutical ingredients, and organic materials.

In this review article, we intend to discuss, in detail, those examples where C–H activation and a borylation strategy are used as one of the vital steps to prepare natural products, and bioactive drug molecules, as well as discussing important tandem transformations.[33–35] We also covered all examples of the late-stage C–H borylation of biologically important molecules reported to date by many pioneering groups. Along with that, we aimed to highlight the application of C–H borylation to functionalize polycyclic systems used in material chemistry.

Buddhadeb Chattopadhyay

Buddhadeb was born and raised in Insura-Hooghly, West Bengal. He completed his PhD in 2009 with Professor K. C. Majumdar. Buddhadeb spent around six years as a postdoctoral research associate in the USA. In November 2016, he joined as an Assistant Professor and was promoted to Associate Professor in November 2019. His research interests include metal-catalysed C–H borylation chemistry and metalloradical activation chemistry. He is the recipient of the Thieme Chemistry Journal Award (2017), SERB-STAR Award (2019), and SERB-TETRA Award (2022), and has recently been elected as a fellow of The National Academy of Sciences (NASI), India, FNASc for the year 2023.

2. Applications

2.1. Tandem transformations

Boron functionality in a molecule can be used for further transformations in a variety of ways through known cross-coupling reactions. Various reports have appeared for these transformations of boronic acid and boronate ester counterparts.[33–35]

The importance of C–H borylation chemistry has been elevated by tandem transformations (*in situ* sequential one-pot transformations) of borylated arenes, generated from native arenes, to other important functional groups (Fig. 2A).[14] C–H borylation is a one-step solution for the derivatization of a molecule as this can bypass the extra steps of activating group installation and the use of hazardous cryogenic procedures.[36–38] On the other hand, C–H borylation is a highly regioselective reaction and can be tuned to *ortho-meta* to *para* functionalization by selective catalyst or ligand choice, rather

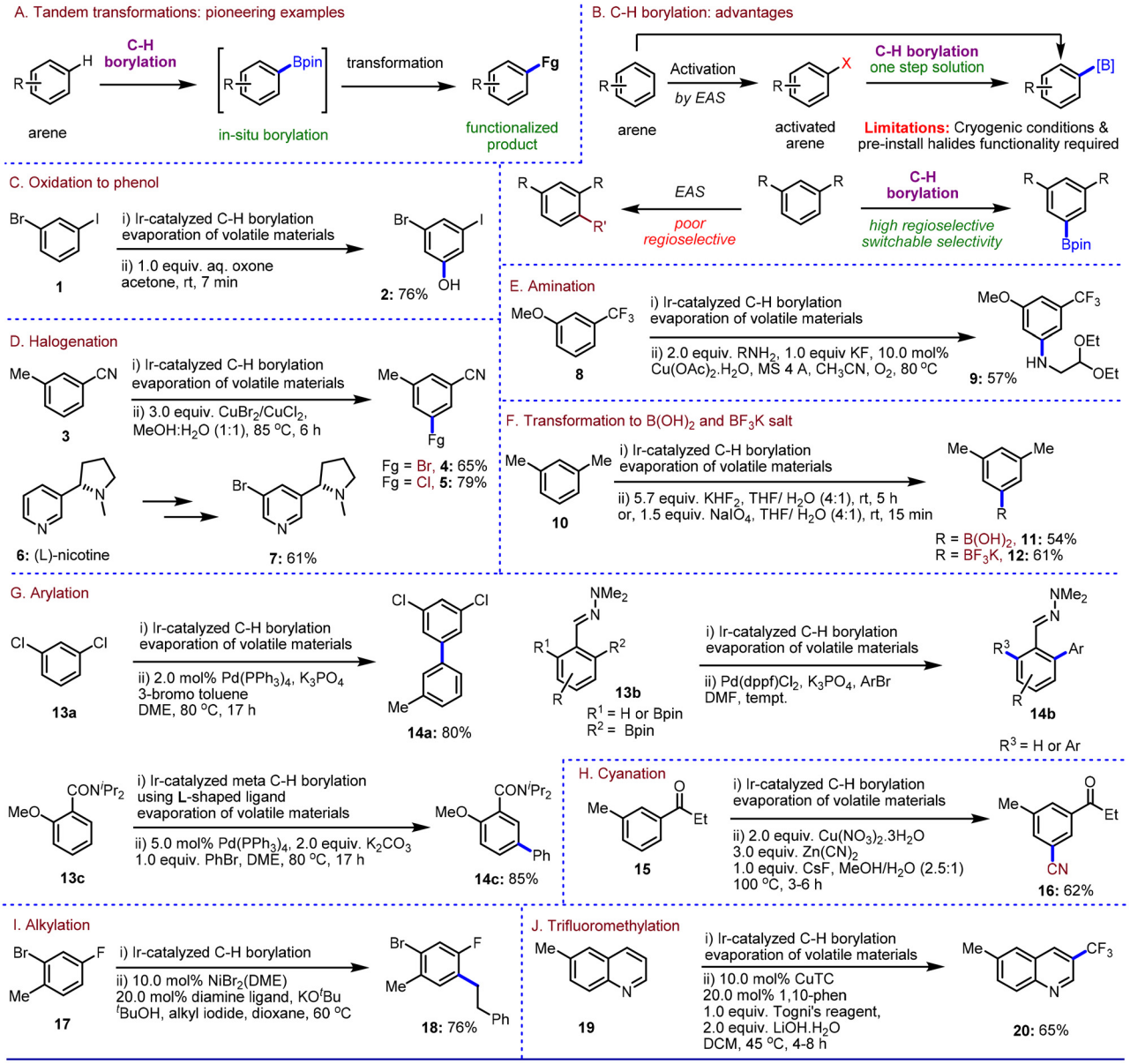

Fig. 2 Pioneering examples of tandem transformations.

than by installing functional groups using an electrophilic aromatic substitution (EAS) reaction (Fig. 2B).[19] The most remarkable approach to 3,5-disubstituted phenol (**2**) synthesis was demonstrated by the Smith group *via* an iridium-catalyzed C–H borylation followed by oxidation with aqueous oxone, resulting in molecules that are difficult to synthesize in another way (Fig. 2C).[39] Regioselective halogenation is a challenging task because electrophilic substitution depends on the electronics of the substituents present on the arene ring. However, these difficulties were overcome by the Hartwig group by demonstrating C–H borylation *via* iridium catalysis to halogenate at specific sites of a 1,3-disubstituted arene (**3**) and nicotine (**6**) with good isolated yields (Fig. 2D).[40] Amines are important functional groups in drug molecules and can be synthesized through C–H borylation followed by a Chan–Lam cross-coupling reaction. Hartwig *et al.* developed[41] a tandem Chan–Lam amination with a boronate ester resulting in a considerable isolated yield (57%) of the aminated product (**9**) (Fig. 2E). A more active and bench stable boronic acid (**11**) and a potassium trifluoroborate salt (**12**) could be synthesized in good isolated yields from an arene through C–H borylation followed by treatment with $NaIO_4$ and KHF_2, respectively (Fig. 2F).[42] The Suzuki cross-coupling reaction is an important technique to make C–C bonds for natural product and drug synthesis.[43] Several developments have appeared for the Suzuki cross-coupling reaction from the *in situ* generation of borylated species. The Smith group in 2002 first reported a tandem Pd-catalyzed Suzuki coupling reaction through an iridium-catalyzed C–H

borylation reaction with an 80% isolated yield of the product **14a** (Fig. 2G).[44] In 2012, Lassaletta and coworkers reported an elegant method for the directed *ortho* borylation (or *ortho*, *ortho'*-directed diborylation) of aromatic *N*,*N*-dialkylhydrazones followed by one-pot sequential Suzuki–Miyaura cross-coupling with different aryl bromides to prepare substituted aryl benzaldehyde derivatives **14b** (Fig. 2G) successfully in good yields.[45,46] Our group, in 2018, developed *meta*-selective C–H borylation reactions[47] of amides using the L-shaped ligand[48] we developed, and in that work it was shown that remote *meta* selective arylation could be performed using *meta* borylation of **13c** to give the desired product in an 85% isolated yield (Fig. 2G). Nitriles are a functional group that is widely found in many biologically active compounds[49] and can be synthesized by the transformation of boron functional groups. The Hartwig group demonstrated[50] a copper-catalyzed one-pot regioselective cyanation reaction of 1,3-disubstituted arenes through an iridium-catalyzed C–H borylation strategy with good isolated yield (Fig. 2H). Among various other functionalizations, alkylation[51] and trifluoromethylation[52] have been achieved *via* tandem transformations of a native arene using C–H borylation reactions (Fig. 2I & J). Several other reports[14] have been published on a regioselective version of this transformation, taking this C–H borylation reaction to new heights of molecular diversification.

2.2. Application in the total syntheses of natural products

In the literature, to date, many reports have appeared where complex molecular architecture is synthesized and where C–H bond activation and borylation have been utilized as one of the key steps to make the path simpler and more atom economic.[53,54] Nowadays, this strategy is making a huge impact on the construction of molecules in modern synthetic organic chemistry, ranging from laboratory methods to industrial deployment.[55] Applying this strategy, many researchers have successfully achieved step-economic syntheses of their targeted complex organic molecules. In this subsection, we are keen to discuss all the literature examples of total synthesis where C–H borylation was used as one of the crucial steps.

In 2010, Sarpong and coworkers demonstrated the total synthesis of complanadine A (**26**)[30] utilizing Ir-catalyzed *meta*-C–H borylation as one of the key steps (Fig. 3). Complanadine A (**26**) is a dimer of the well-known phlegmarine-derived alkaloid lycodine. The synthetic challenge lies with the fact that it is an unsymmetrical dimer and therefore selectively merging the two halves is necessary.[56] This difficulty was overcome using an iridium-catalyzed sterically controlled C–H borylation reaction. The synthesis of complanadine A (**26**) commenced with the convergent coupling of the enamide **21** and amine **22** followed by functional group operations to generate compound **24** and set the platform for the key reaction. In the event, treatment of **24** with Ir-catalyst, ligand 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), and B_2pin_2 as a borylating agent in THF provided compound **25** with a 75% yield.

The observed site selectivity is consistent with Hartwig's report[25] that pyridine functionalization is mainly under steric

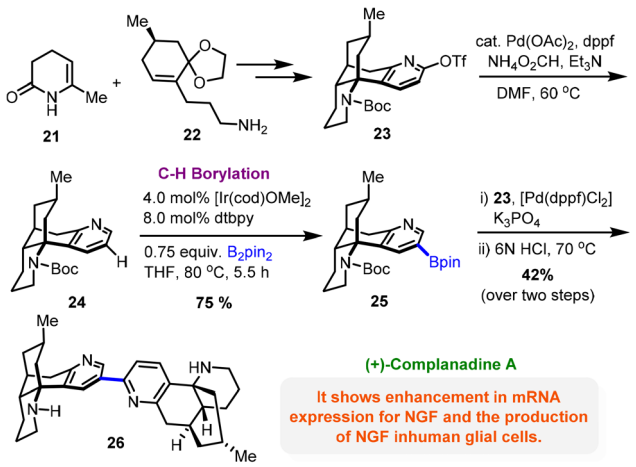

Fig. 3 Total synthesis of complanadine A.

control. Then, Pd-catalyzed Suzuki cross-coupling followed by deprotection of the Boc protecting group gave the target molecule complanadine A with a 42% overall yield (**26**).

In 2021, the authors further utilized their previously synthesized borylated intermediate (**25**) for the total synthesis[57] of two other lycodine-type lycopodium alkaloids, lycoplatyrine A (**28**) and lycopladine F (**29**). In that work, they performed the sequential borylation-bromination of *N*-Boc lycodine (**24**) with a 74% overall yield to obtain 2-bromolycodine (**27**), from which the target molecules were synthesized after a few more synthetic transformations (Fig. 4).

In 2011, Hartwig *et al.* prepared for the first time an important intermediate in the enantioselective total synthesis of (–)-taiwaniaquinol B (**36**) and its congener (–)-taiwaniaquinone H (**35**) (Fig. 5).[58] Structurally, both these natural products are from a family of unusual diterpenoids possessing a [6,5,6]-abeo-abietane skeleton and containing a benzylic quaternary stereogenic center.[59–62] The key step for this synthesis was the iridium-catalyzed C–H borylation of 2-isopropyl 1,3-dimethoxy benzene (**30**) using 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as a ligand. This procedure resulted in (**31**), which then was converted in one pot to its bromo derivative (**32**) in a 75% isolated yield. On the contrary, this was difficult to achieve using elec-

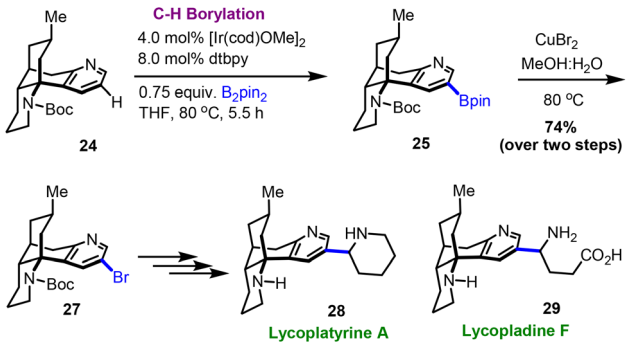

Fig. 4 Total synthesis of lycoplatyrine A and lycopladine F.

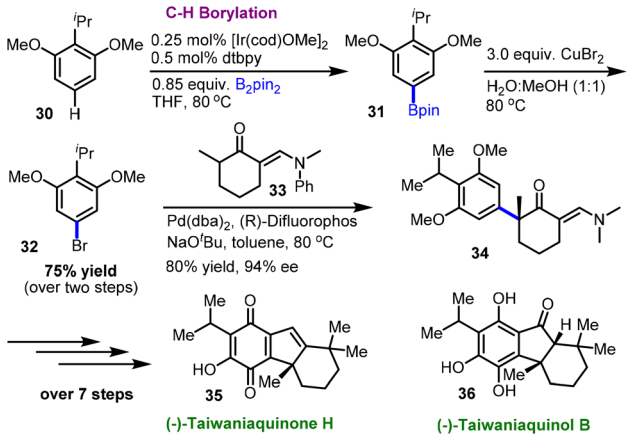

Fig. 5 Total synthesis of (–)-taiwaniaquinone H and (–)-taiwaniaquinol B.

trophilic aromatic substitution *via* bromination of (**30**) as it was difficult to avoid *ortho* bromination with respect to the methoxy substituent.[63] Thus, the transformation from (**30**) to (**32**) using C–H borylation is a highly regioselective one-pot sequential process. Intermediate (**32**) was then employed for the synthesis of (**34**), which is an important intermediate for the synthesis of **35** and **36**, under palladium-catalyzed conditions *via* α-arylation with (**33**).

Brimble and coworkers in 2012 reported[64] the first total synthesis of the HRV 3C protease inhibitor[65] (±)-Thysanone by applying a sterically controlled C–H borylation reaction (Fig. 6). The target molecule is a resorcinol-derived component of the natural product. To install the C7 hydroxyl group, a C–H borylation strategy was employed.

The authors started their synthesis from naphthopyran (**37**) and achieved a regioselective borylated product (**38**) which, after a one-pot oxidation, afforded the compound (**39**) with a 72% overall yield. The desired product (±)-thysanone (**40**) was obtained after 5 more synthetic transformations.

Considering the ubiquitous nature of indole frameworks in natural products, Jia's group reported[66] in 2014 the synthesis of (–)-goniomitine, a new type of the well-known aspidosperma family of indole natural products (Fig. 7). It has become a popular synthetic target by many research groups due to its

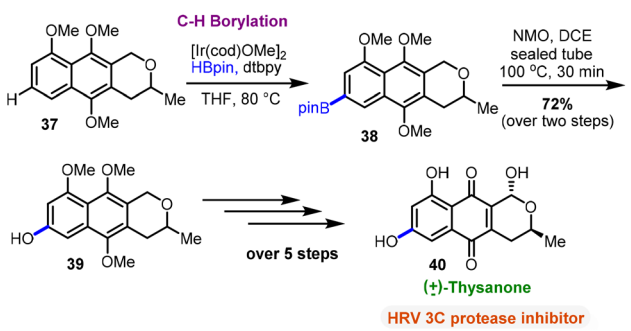

Fig. 6 Total synthesis of (±)-thysanone.

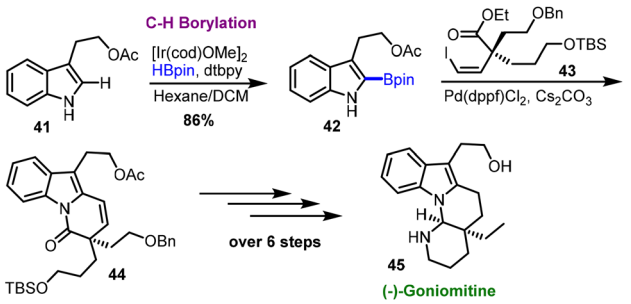

Fig. 7 Total synthesis of (–)-goniomitine.

unique structure and potential biological activities.[67–69] To synthesize the target molecule, an iridium catalyzed C–H borylation step was taken as the primary step and borylation of (**41**) resulted in the C2-borylated (**39**) in an 86% yield. A subsequent Pd-catalyzed Suzuki–Miyaura coupling with (**43**) generates compound (**44**), which is a potential intermediate for the desired (–)-goniomitine (**45**).

In addition to the above-mentioned C2 borylation of indole derivatives, the regioselective borylation of another *N*-protected indole derivative, tryptophan, was reported by the Baran group at the remote C6 position and applied for the synthesis of natural bioactive alkaloids, verruculogen and fumitremorgin A, for the first time (Fig. 8).[31] Apart from their exotic structures, these two compounds were first recognized due to their tremor-inducing activity[70–73] in mice whilst the fumitremorgins display potent activity against multi-drug resistant (MDR) cancer cell lines.[74,75] The modified chiral tryptophan derivative contains a Boc-L-Trp-OMe motif (**47**) with a bulky TIPS group on the indole nitrogen, preventing borylation at the C2 and C7 positions. Thus, under the developed conditions, regioselective borylation happens at the C6 position and afforded the borylated compound (**48**). This borylation strategy provides a general way to functionalize the C6 position of indole for the synthesis of indole-containing natural products and pharmaceuticals. Iridium-catalyzed C6 borylation followed by copper-catalyzed methoxylation resulted in (**49**) in a one-pot process with a 65% yield and an isomeric ratio of C6 : C5 = 8 : 1. Most importantly, the developed strategy was employed for the gram-scale synthesis of (**49**). After multiple functional group operations, the desired target molecules, verruculogen (**50**) and fumitremorgin A (**51**), were obtained.

Utilizing the same strategy for the C6 borylation of indole derivatives, in 2019 the same group demonstrated[76] another total synthesis of natural products, teleocidin B-1 and B-3, where C–H borylation was used as a key step (Fig. 9). The synthesis commenced from 4-bromoindole (**52**) along with compound (**53**) and after 6 steps they reached TIPS-protected indole derivative (**54**) which underwent C6 borylation under Ir-catalyzed conditions in the presence of a TMP ligand with a B_2pin_2 boron source, thus producing (**55**). After the borylation, a one-pot functional group conversion provided the product (**56**). The desired target molecules (–)-teleocidin B-3 (**57**) and (–)-teleocidin B-1 (**58**) were obtained from (**56**) over 2 steps.

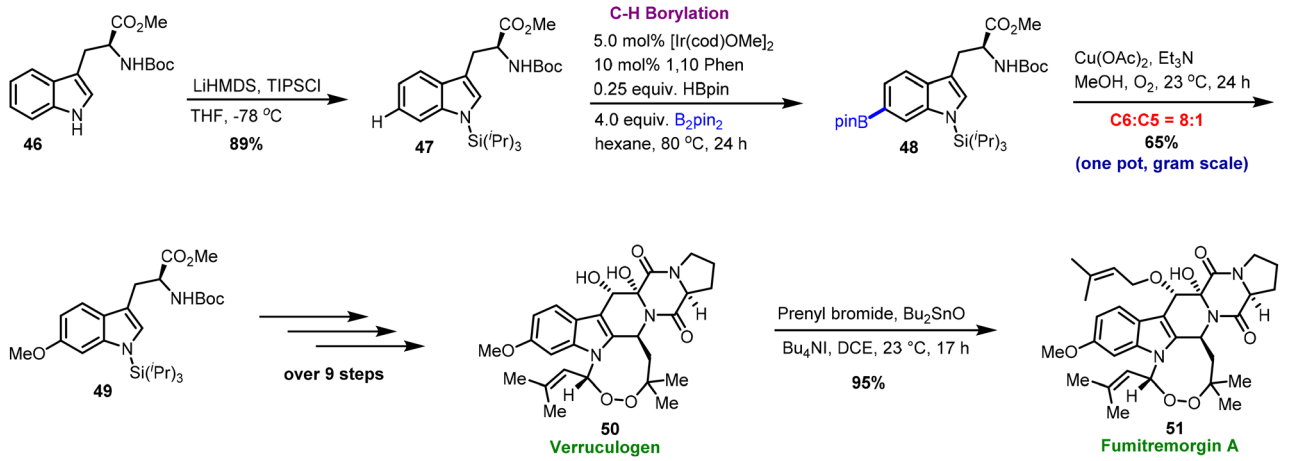

Fig. 8 Total synthesis of verruculogen and fumitremorgin A.

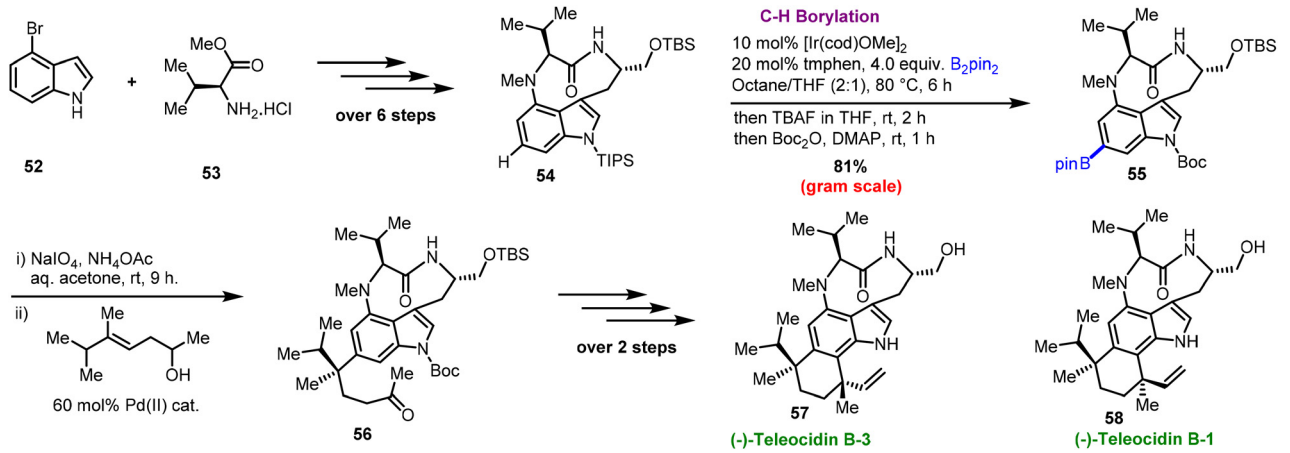

Fig. 9 Total synthesis of (–)-teleocidin B-3 and (–)-teleocidin B-31.

A significant application of iridium-catalyzed C–H borylation was reported by Sperry and coworkers where a short synthesis of two indolequinone natural products was described (Fig. 10).[77] Indolequinone pharmacophores are generally found in bioactive natural alkaloids, such as the archetypal quinone bioreductive anticancer agent mitomycin C[78,79] which is a natural product in clinical practice since the 1970s. Towards the synthesis of natural indolequinone, instead of choosing a fragment-based strategy, the author decided to procure a late-stage C–H functionalization approach. They began the synthesis from commercially available methoxyindoles (**59**) and were subjected to ruthenium-catalyzed *N*-hydrosilylation to block the competitive reaction site at the C2 position.[80] Then, iridium-catalyzed borylation of the *N*-hydrosilylindoles using the dtbpy ligand, as developed by Hartwig and co-workers,[81] delivered exclusively the C7 borylated product (**60**).[81] Then, the subsequent oxidation of the boronate ester afforded (**61**), an oxidation then provided the desired products 5-methoxyindole-4,7-quinone (**62**) or 6-methoxyindole-4,7-quinone (**63**), respectively.

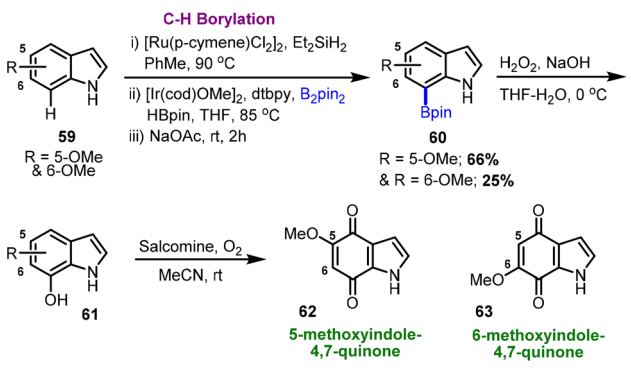

Fig. 10 Synthesis of indolequinones.

In 2015, the same group described another total synthesis of a symmetrical bisindole, named scalaridine A, which is isolated from the marine sponge *Scalarispongia* sp. (Fig. 11).[82] For that purpose, they performed iridium-catalyzed C3 borylation of *N*-Boc-5-methoxyindole (**64**) using the 3,4,7,8-tetramethyl-

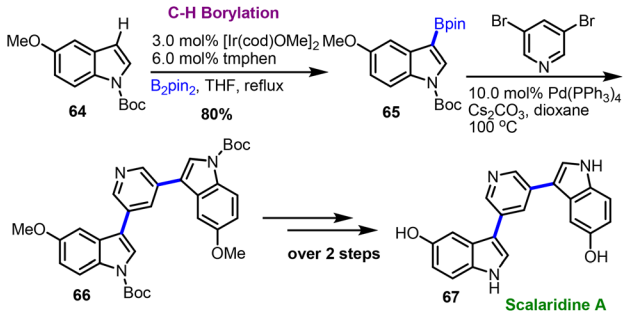

Fig. 11 Total synthesis of scalaridine A.

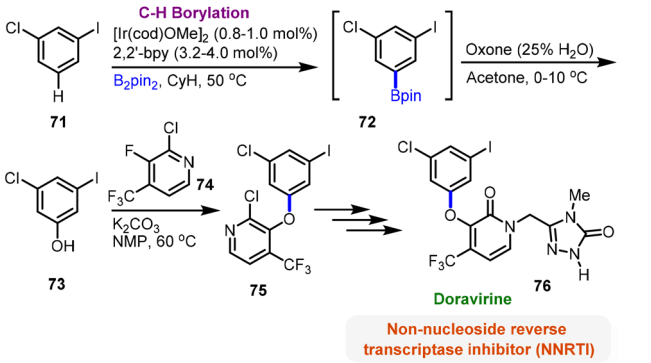

Fig. 13 Total synthesis of doravirine.

1,10-phenanthroline (Me_4Phen) ligand developed by Hartwig *et al.*[83] for heteroarene borylation. The borylated product (**65**) was obtained in an 80% yield. Then, from (**65**), a double Suzuki–Miyaura cross-coupling followed by functional group manipulation delivered the desired scalaridine A (**67**).

Hartwig's group in 2010 demonstrated the C7 borylation of indole[81] using hydrosilyl chelation and this strategy was utilized by Banwell and coworkers[84] for the convergent total synthesis of amaryllidaceae alkaloids (**70**) lycoranine A, lycoranine B, and 2-methoxypratosine (Fig. 12). The C7-borylated indole derivative (**69**) was subjected to a Suzuki–Miyaura cross-coupling reaction, which afforded the desired product (**70**).

The Smith and Maleczka groups in 2003 reported a remarkable method[39] to access 1,3-disubstituted phenols using a C–H activation and borylation followed by oxidation. Later, the Merck process group in 2016 developed a robust, scalable synthesis of Doravirine (**76**), a potential second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) (Fig. 13).[85] They began with 1-chloro-3-iodobenzene (**71**) and carried out a large-scale (75 kg) iridium-catalyzed C–H activation/borylation in the presence of a 2,2′-bipyridine ligand to obtain the borylated product (**72**). After oxidation of the borylated 1-chloro-3-iodobenzene, they ended up with 1-chloro-3-iodophenol (**73**), which is an important intermediate for the synthesis of target molecule (**76**).

A similar type of sterically controlled C–H borylation strategy was applied for the regioselective borylation of β-aryl-aminopropionic acid derivatives by the Nortcliffe group to access 3,5-functionalised protected β-aryl-aminopropionic acid boronates. These boronates serve as diverse building blocks in medicinal chemistry.[86]

Implementing this approach, they synthesized the 3-bromo-5-*tert*-butyl intermediate (**79**) from (**77**) as part of the synthesis of integrin antagonist **80** (Fig. 14). To access this intermediate, an Ir-catalyzed borylation using the 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) ligand was followed by a Cu-catalyzed bromination reaction. Then, multiple functional group operations furnished the desired product (**80**).

Chrysomycin A is a rare C-aryl glycoside that has potent anti-TB activity and has shown promising antimicrobial activity with a minimum inhibitory concentration (MIC) of 0.4 μg mL^{-1} against MDR-TB strains.[87] In 2020, Yu, Lei, and co-workers reported a 10-step gram-scale total synthesis of chrysomycin A in which a sterically controlled regioselective C–H borylation is used as one of the crucial steps (Fig. 15).[88]

To first achieve the site-selectivity in C–H borylation, they made the naphthalene ring asymmetric and installed a removable bromine group. Then, they performed iridium-catalyzed C–H borylation in the presence of the dtbpy ligand using HBpin as the boron source and got the product (**83**). Even at a 20 g scale, they achieved a 76% yield (87% yield brsm). From (**83**), 8 steps were required to obtain the target molecule chrysomycin A (**84**). This approach is also useful to synthesize other C-aryl glycosides like gilvocarcin V, polycarcin V, and 33 other derivatives (**85**).

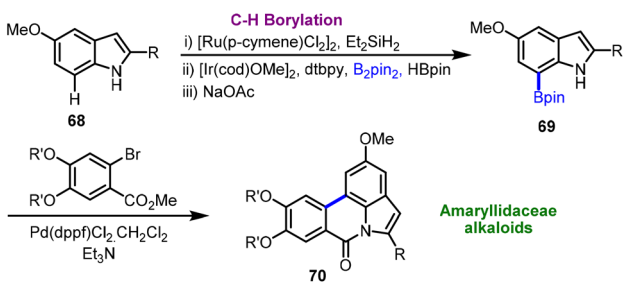

Fig. 12 Total synthesis of amaryllidaceae alkaloids.

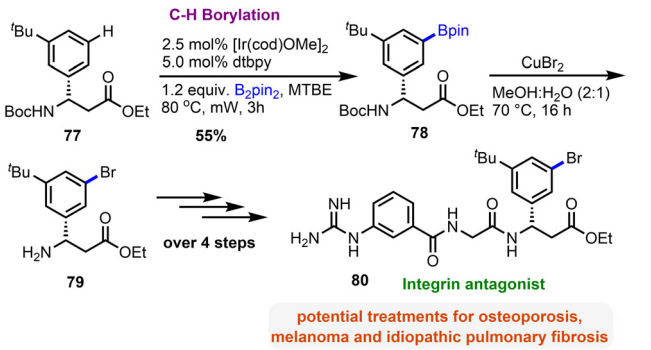

Fig. 14 Total synthesis of integrin antagonist.

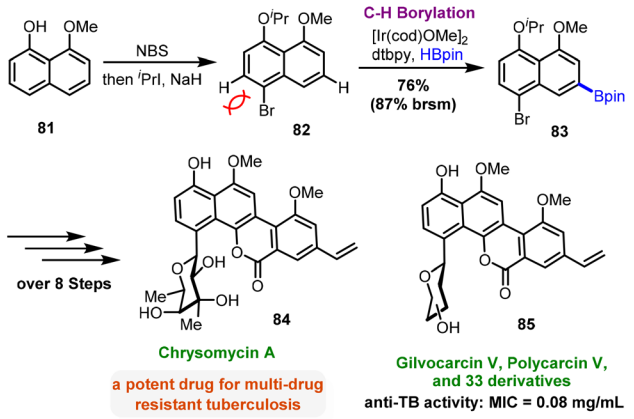

Fig. 15 Total synthesis of chrysomycin A.

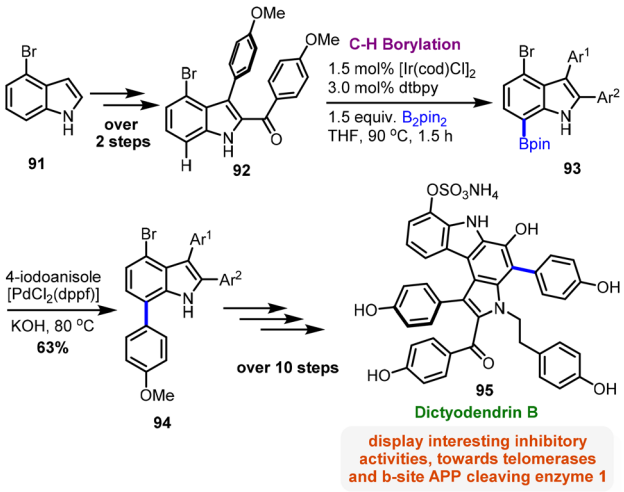

Fig. 17 Total synthesis of dictyodendrin B.

In 2008, Gaunt and coworkers demonstrated[29] the versatility of a metal-catalyzed C–H functionalization reaction to make a complex molecular architecture *via* an 11-step total synthesis of Rhazinicine (**90**) from commercially available materials (Fig. 16). To fulfill their goal towards the synthesis of the target molecule, the authors started with an iridium-catalyzed C3 borylation of an *N*-Boc pyrrole derivative (**86**) using the dtbpy ligand to afford compound (**87**). From this borylated pyrrole, in the same pot, a Suzuki cross-coupling with **85** gave the product (**89**) in a 78% overall yield. To obtain the target rhazinicine (**90**), additional steps were required.

In 2015, they utilized the same strategy[29] of sequential C–H functionalization for the synthesis of marine alkaloid dictyodendrin B and yet again C–H borylation was utilized as one of the crucial functionalizations (Fig. 17).[89] Here, C7 borylation of an indole derivative (**92**) was implemented using a catalytic amount of $[Ir(cod)Cl]_2$ along with dtbpy to obtain the product (**93**). Subsequently, a Suzuki cross-coupling gave the product (**94**) in a one-pot manner with a 63% yield. The target product Dictyodendrin B (**95**) was obtained after 10 more sequential steps.

In the first enantioselective total synthesis[90] of the potent monoamine oxidase inhibitor (−)-incarviatone A (**101**), Lei and coworkers applied a sterically directed iridium-catalyzed C–H borylation of compound (**98**) to reach one of the significant intermediates (**99**). A same pot transformation of the borylated product into its bromo derivative delivered compound (**100**) from which the target molecule (−)-incarviatone A (**101**) was obtained after several functional group operations (Fig. 18).

The use of chemo catalytic and biocatalytic C–H functionalization approaches to synthesize complex molecular scaffolds was showcased by Renata *et al.* in 2018 where the total synthesis of a nonribosomal tetrapeptide, tambromycin (**105**), was described (Fig. 19).[91] In one of these two approaches, an iridium-catalyzed C–H borylation plays a significant role in accessing one of the important key intermediates. The authors utilized Baran's N-TIPS indole C6 borylation strategy[31] to get the borylated product (**103**) from starting material (**102**). Then, the borylated product was transformed into its chloro derivative (**104**) *in situ* with a 53% overall yield. Finally, the target molecule (**105**) was obtained after some multistep reactions.

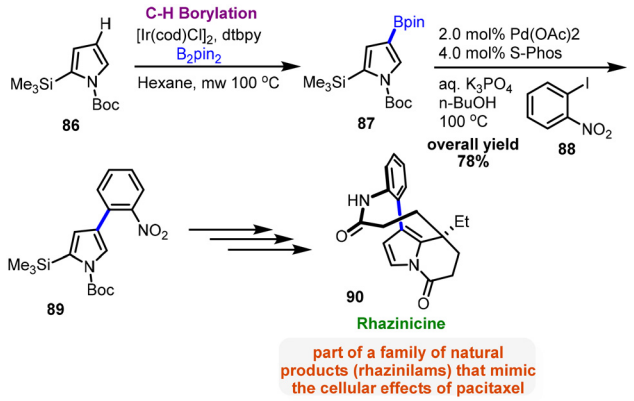

Fig. 16 Total synthesis of rhazinicine.

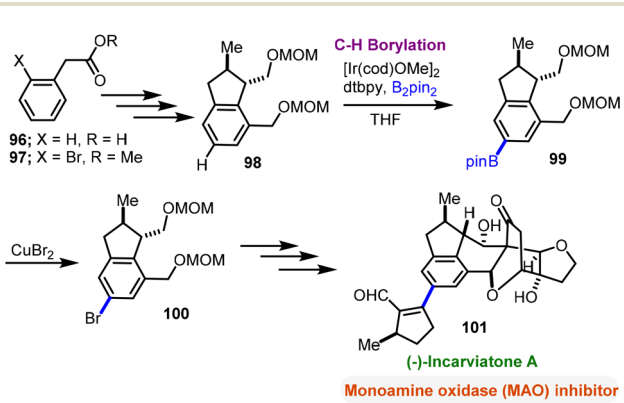

Fig. 18 Total synthesis of (−)-incarviatone A.

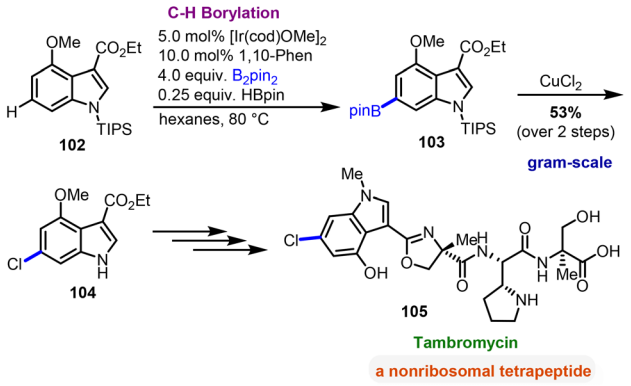

Fig. 19 Total synthesis of tambromycin.

Kanai and Shibasaki *et al.* revealed[92] an application of iridium-catalyzed C–H borylation by carrying out a total synthesis of SM-130686, a highly potent and orally active nonpeptidic growth hormone secretagogue (GHS) (Fig. 20). They synthesized an important borylated intermediate (**108**) from (**107**) using an Ir-catalyst and the dtbpy ligand where regioselectivity was controlled by steric crowding. Then, the boron functionality was transformed into a hydroxyl group to obtain compound (**109**) and an 11-step synthetic operation provided the desired product, SM-130686 (**110**).

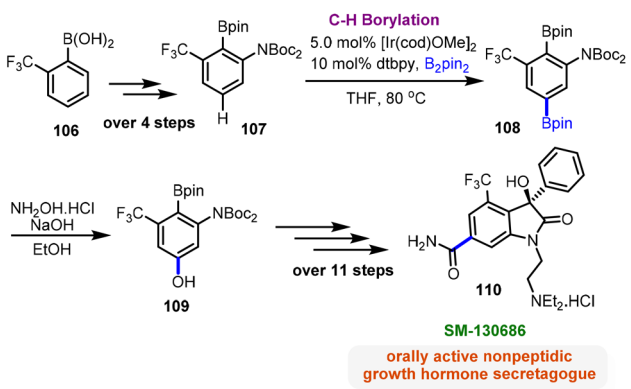

Fig. 20 Total synthesis of SM-130686.

In 2021, Dai and coworkers described[93] a convergent total synthesis of (±)-Hamigeran M which involved five C–H functionalization reactions and proceeded over 11 steps (Fig. 21). To achieve this total synthesis, along with the other C–H functionalization reactions, C–H borylation plays a major role. The synthesis began with an iridium-catalyzed *ortho* borylation of 4-methyl phenol (**111**), as developed by the Smith group,[94] on a gram-scale which afforded the borylated product (**112**) in a 65% yield. Then, after 7 steps, they reached compound (**114**) which underwent another directed C–H borylation at its oxazole derivative using Swamura's[95] $[Rh(cod)OH]_2$ protocol in combination with a silica-SMAP ligand to afford the desired boronate (**115**) using B_2pin_2 as the boron source. Under these reaction conditions, it was observed that the *in situ*-generated HBpin reduces the seven-membered ketone. To suppress this reduction, 1-octene was used to consume the boron hydride species. Thus, *in situ* oxidation of the boronate product (**115**) generated product (**116**) with a 50% overall yield. The desired target molecule hamigeran M (**117**) was obtained after the bromination of (**116**).

Recently, Nicolaou and coworkers reported[96] the total synthesis of one of the most complex natural tropolonoids, gukulenin B, *via* sequential C–H functionalization (Fig. 22). The target molecule consists of two monomers, and to synthesize the right-hand monomeric unit δ-borylation of the tropolone derivative was executed using an Ir-catalyst in the presence of the dtbpy ligand to afford the boronate (**120**) in an 83% yield. Subsequent oxidation of the –Bpin group to –OH, followed by

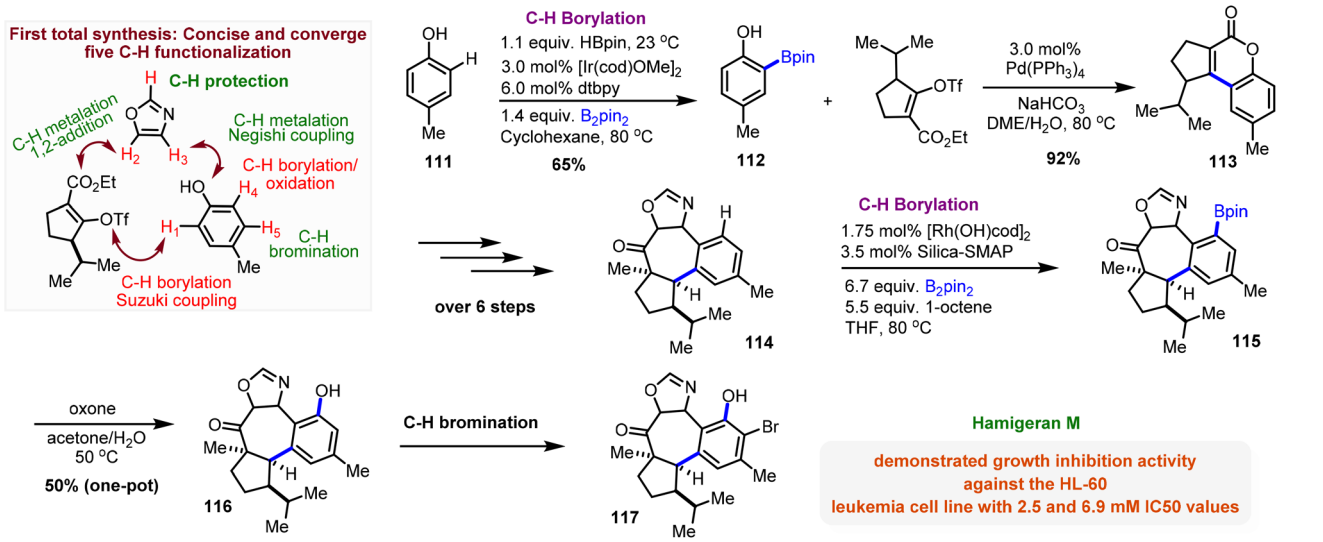

Fig. 21 Total synthesis of hamigeran M.

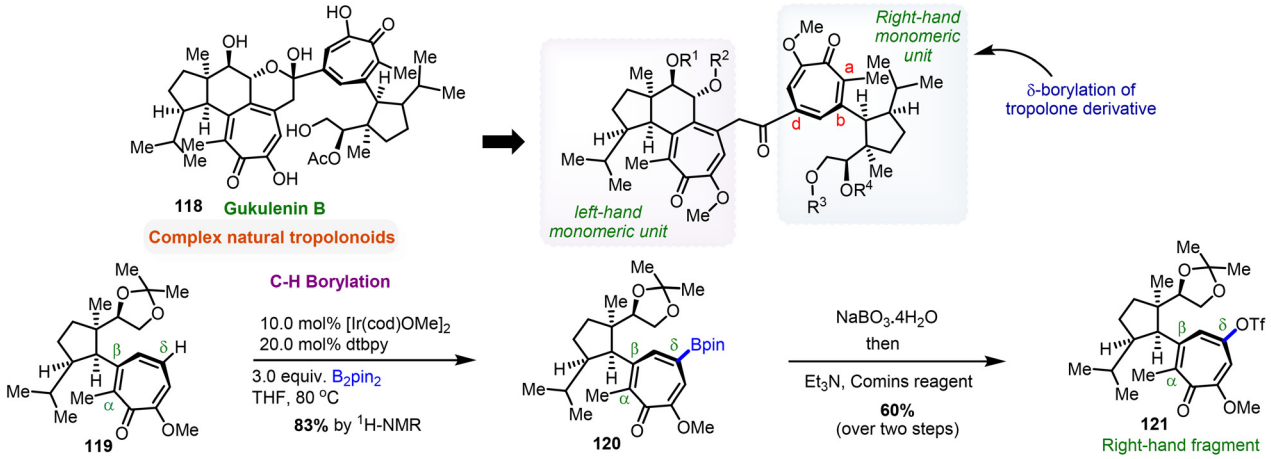

Fig. 22 Total synthesis of gukulenin B.

base-mediated triflate formation, provides the desired α,β,δ-trisubstituted tropolone fragment (**121**) in a 60% overall yield (Fig. 22).

Koert and coworkers reported[97] the total syntheses of Pestaphthalide A (**125**) and B (**126**), where C–H borylation followed by alkenylation was the crucial step (Fig. 23). In this total synthesis, they performed a sterically directed C–H borylation using the Ir-dtbpy system on (**122**) to achieve a 93% yield of the borylated product (**123**). Next, a Pd-catalyzed alkenylation and further treatment resulted in the target products (**125**) and (**126**).

In 2011, Movassaghi *et al.* reported[98] the concise and enantioselective total syntheses of (−)-trigonoliimine A and B by utilizing an iridium-catalyzed C–H borylation as one of the key steps. Their synthetic strategy commenced with the C2-borylation of the 6-methoxytryptamine derivative (**127**) to get the 2-borylindole product (**128**). To reduce the undesired borylation of the phthalimide substructure, they performed the reaction at 23 °C in DCM in the presence of an iridium pre-catalyst and the dtbpy ligand resulting in a 67% yield.

The Suzuki–Miyuara cross-coupling of boronate (**128**) and 2-iodo-tryptamine (**129**) in the presence of a Pd-catalyst provides bisindole (**130**), from which (−)-trigonoliimine A (**131**) and (−)-trigonoliimine B (**132**) can be synthesized after further treatment (Fig. 24).

In 2015, the same group utilized the same C2-borylation approach[97] of a tryptamine derivative to prepare compound (**132**), which when followed by a Pd-catalyzed coupling provided a 2,5′-bisindole precursor (**134**) which delivered bisindole alkaloid (**135**) after further functional group manipulation (Fig. 25).[99]

In 2019, the same group reported[100] the first total synthesis of (+)-kopsifoline E (**141**) and (−)-kopsifoline A (**142**) *via* the C17 late-stage functionalization of an intermediate, (**138**). To install a methoxy group at the C17 position of this vinylogous urethane (**138**), they implemented an iridium-catalyzed C–H borylation using $[Ir(cod)OMe]_2$ in the presence of the tmphen ligand along with stoichiometric amounts of HBpin and B_2pin_2 in THF at 23 °C obtaining a 49% yield.

The use of either only B_2pin_2 or only HBpin under otherwise identical conditions led to either no reaction or a diminished yield of the product, whilst raising the reaction tempera-

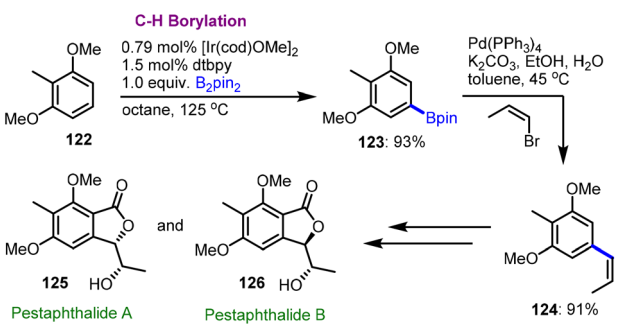

Fig. 23 Total synthesis of pestaphthalide A and B.

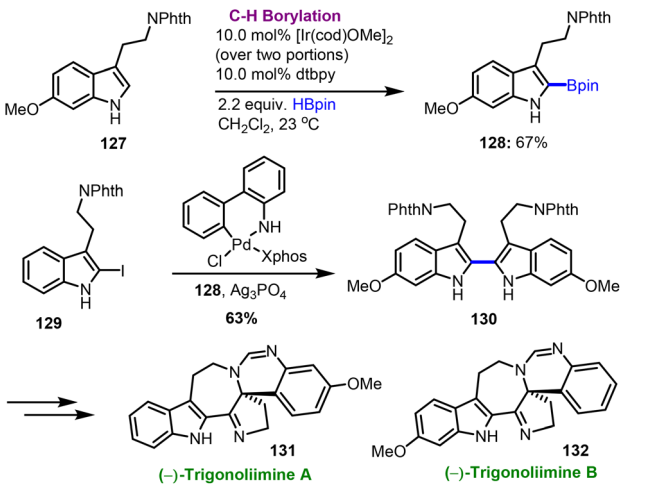

Fig. 24 Total synthesis of (−)-trigonoliimine A and B.

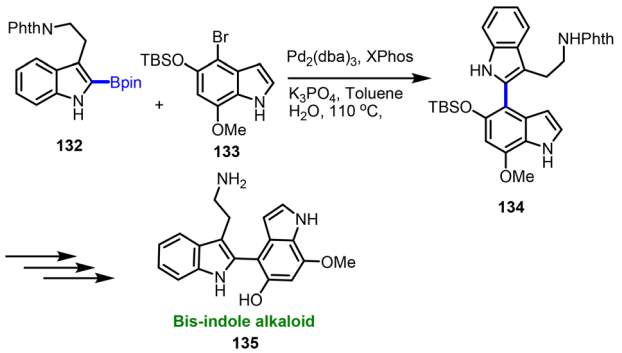

Fig. 25 Total synthesis of a bisindole alkaloid.

ture to 60 °C resulted in significant decomposition of compound (**139**). From boronate species (**140**), methoxylation followed by functional group manipulation delivered the desired products (**141**) and (**142**) (Fig. 26).

Boger and coworkers in 2020 disclosed[101] a next-generation total synthesis of vancomycin aglycon (**143**) in 19 steps with a 3.7% overall yield (Fig. 27). For the successful synthesis of the A ring, in the first step, an iridium catalyzed 3,5-diborylation (*meta-meta* di) of compound (**144**) was applied using 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) as the ligand on a 20 g scale. Conversion to the desired di-*meta*-borylated intermediate (**145**) was estimated to be >66% by crude NMR. Then, methoxylation in one pot from (**145**) generated the key intermediate (**146**) which was effectively used for further synthesis.

Iridium catalyzed C–H borylation using the tmphen ligand was used by Pfizer[102] to produce the borylated nicotine intermediate (**148**) on a 19 kg scale with high regioselectivity (Fig. 28). Their main aim was to obtain the monotosylate salt of the nicotine analog (**150·TsOH**). In this synthesis, they used $[Ir(cod)Cl]_2$ rather than $[Ir(cod)OMe]_2$ as a pre-catalyst. Optimization of the ligand helped to reduce the Ir-catalyst

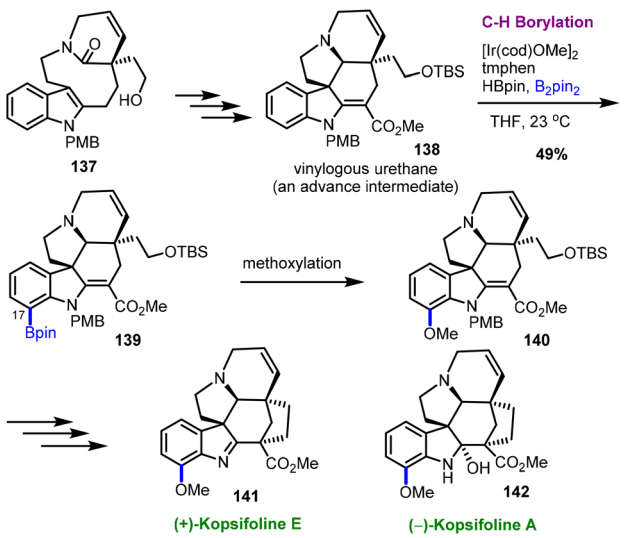

Fig. 26 Total synthesis of (+)-kopsifoline E and A.

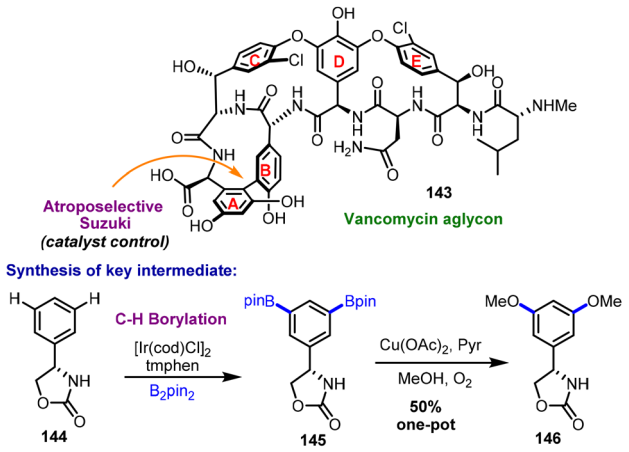

Fig. 27 Total synthesis of vancomycin aglycon.

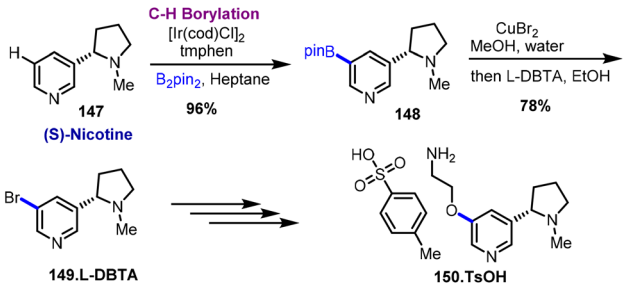

Fig. 28 Nicotine-derived synthesis of **150·TsOH**.

loading from 6 mol% to 2 mol%. This new route offers the preparation of nicotine analog (**150·TsOH**) *via* an Ir-catalyzed borylation that delivered the desired product with high purity and all impurities controlled to a level below 0.1%.

C–H borylation was again demonstrated in the synthesis of key intermediate (**152**) by AstraZeneca in 2019 to supply their phase IIA trial of the $A_{2A}R$ agonist, AZD4635 (Fig. 29).[103,104] For that purpose, they loaded just 0.25 mol% of iridium catalyst in the presence of the dtbpy ligand on a 6 kg scale and achieved a 76% yield.

Napthaylisoquinoline alkaloids isolated from lianas of the tropical plant families ancistrocladacae and dioncophyllacae represent a large and still growing class of structurally and bioactively interesting natural biaryl products. These compounds have axial chirality and exhibit different biological properties as well as being active against the pancreatic cancer

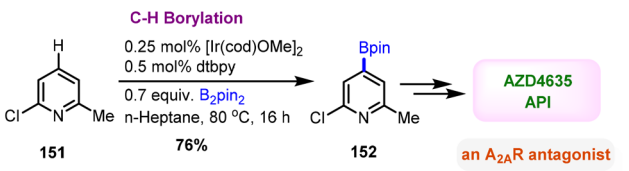

Fig. 29 Synthesis of $A_{2A}R$ agonist AZD4635.

cell line.[105] Recently, Otterlo *et al.* reported[106] the total synthesis of ancistrolikokine J_3 where a C–H borylation followed by methylation is an important step. They borylated (**154**) under iridium-catalyzed conditions to achieve (**155**), which was then employed for methylation utilizing Hartwig's methylation protocols[107] to obtain (**156**). Next, a nickel-catalyzed atroposelective cross-coupling reaction delivered the target product (**157**) (Fig. 30).

Beta-carboline alkaloids are widely found in several biological scaffolds that exhibit diverse range of biological properties.[108] The Lei group,[109] in 2023, synthesized several beta-carboline bioactive alkaloids utilizing C–H borylation as the one of the important steps (Fig. 31). They performed iridium-catalyzed borylation of (**158**) to obtain (**159**). After that, methoxylation and hydroxylation of that boronate ester resulted in (**160**) and (**161**), respectively, and further treatment gave several bioactive alkaloids, picrasidine S (**167**), T (**168**), R (**166**), and I (**165**), and dehydrocrenatidine (**164**) in good yields.

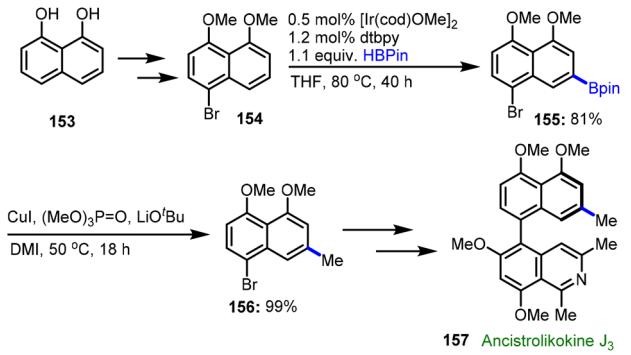

Fig. 30 Synthesis of ancistrolikokine J_3.

2.3. Application in the late-stage borylation

Although many complex bioactive and pharmaceutically valuable organic molecules are available from natural sources, their laboratory synthesis is still crucial, as well as challenging. Undoubtedly, functionalization to access the various derivatives of these natural products and pharmaceuticals offers an opportunity for the rapid construction of libraries of drug candidates with diverse functionality.[110–112] However, the selective introduction of functional groups into complex structures for late-stage modification *via* C–H functionalization is a new approach to accessing drug-like molecules with improved structure–activity relationships (SAR) and enhanced biological activities.[113] In this context, C–H activation and borylation have gained much attention for their high reactivity and excellent site selectivity. In this part of the discussion, we accommodate all these literature reports where late-stage C–H borylation of many pharmaceutically and medicinally important molecules have been showcased to demonstrate the practical synthetic utility of this method.

In 2015, Itami and coworkers accomplished[114] a highly *para*-selective C–H borylation of benzene moieties substituted with quaternary carbon substituents using an iridium catalyst bearing a bulky diphosphine ligand, Xyl-MeO-BIPHEP (**L1**) (Fig. 32). The regioselectivity is primarily controlled by the steric repulsion between substrate and catalyst. Along with various other mono-substituted arenes, they demonstrated the utility of the developed method for the late-stage C–H borylation of pharmaceutically important molecules like caramiphen (**169**), which is an anticholinergic drug used in the treatment of Parkinson's disease. Under the developed conditions, 83% of the *para*-borylated product (**170**) was afforded in a 61% yield. Next, a useful synthetic transformation of this intermediate delivered numerous important derivatives (**171–174**) of caramiphen in moderate to good yields.

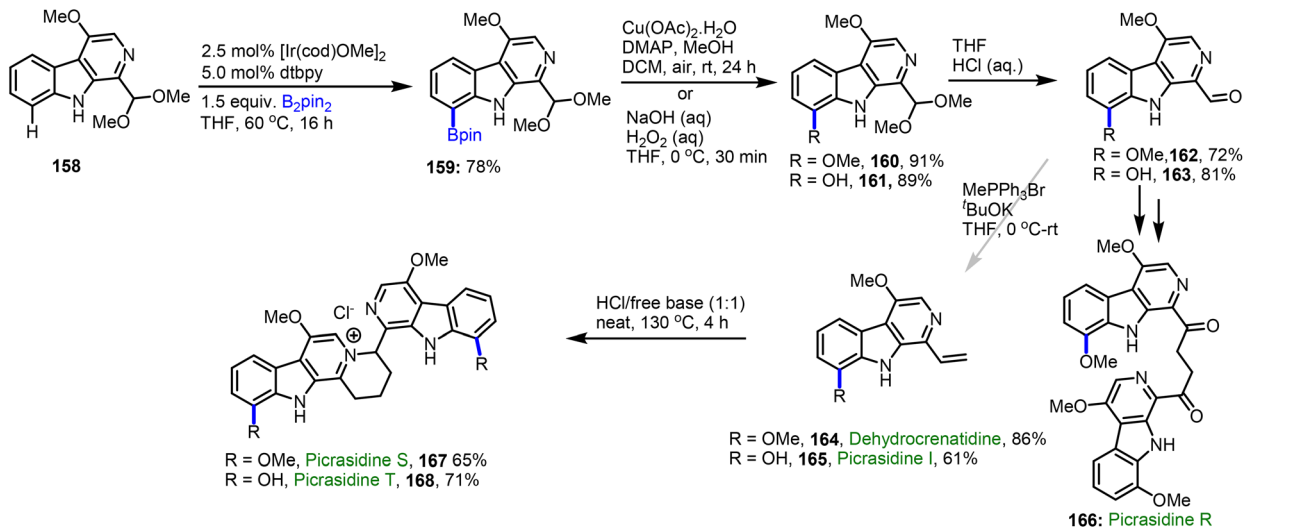

Fig. 31 Synthesis of picrasidine S, T, I, R, and dehydrocrenatidine.

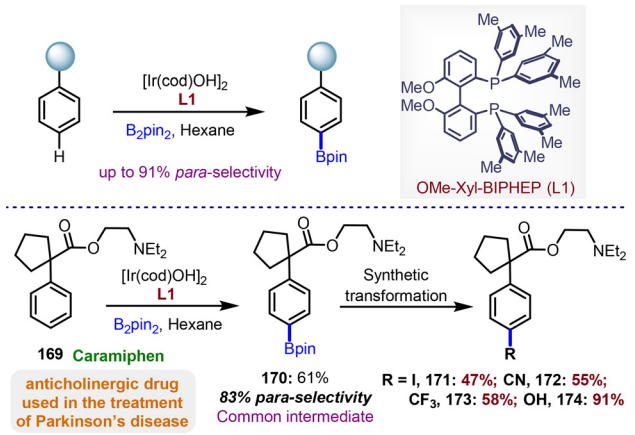

Fig. 32 Late-stage *para* borylation of caramiphen.

In 2020, the same group further showcased their methodology using the same catalytic system with a slight modification of the ligand for the highly C3-selective C–H borylation of Strychnine (**175**) accompanied by an olefin isomerization (Fig. 33).[115] In the presence of an iridium-catalyst and the Xyl-BIPHEP (**L2**) ligand, 73% olefin-isomerized C3-borylated Strychnine (**176**) was obtained in a 65% isolated yield.

From this common borylated intermediate (**176**), 15 useful Strychnine derivatives could be accessed. Moreover, using the same method they reported a highly *para*-selective borylation of the pharmaceutically important molecule Nifedipine (**182**), a widely used calcium channel antagonist.

In 2014, Steel, Marder, and Sawamura *et al.* developed[116] a heterogeneous Ir-catalyst based on a silica-supported cage-type monophosphane ligand SMAP, which catalyzes the site-selective C–H borylation of quinoline derivatives at the C8 position. They also demonstrated that this technique was useful for synthesizing a corticotropin-releasing factor1 (CRF1) receptor antagonist (**187**) *via* a late-stage C–H borylation strategy (Fig. 34). Starting with commercially available 3-methoxyaniline (**184**), several functional group operations generate 4-dipropylamino-7-methoxyquinalidine (**185**), which acts as a substrate for the Ir-catalyzed C–H borylation reaction. Then, using 1.0 equiv. of B_2pin_2 and the Silica–SMAP–Ir catalyst system, they produced the desired C8-borylation product (**186**) with good site selectivity. Finally, in the same pot, a Pd-catalyzed cross-coupling with 4-bromochlorobenzene gave the desired CRF1 receptor antagonist (**187**) in a 57% yield.

In 2016, a powerful application of non-covalent ion pair-directed *meta*-selective C–H activation and borylation of aromatic quaternary ammonium salts was disclosed by the Phipps group[117] using their developed anionic bipyridine ligand (**L3**) (Fig. 35). A huge range of substrates were well tolerated under the reaction conditions with very high regioselectivity, which demonstrated the viability of ion-pair interaction to control the *meta* selectivity. Using this hypothesis, they demonstrated the *meta*-selective diborylation of the anti-

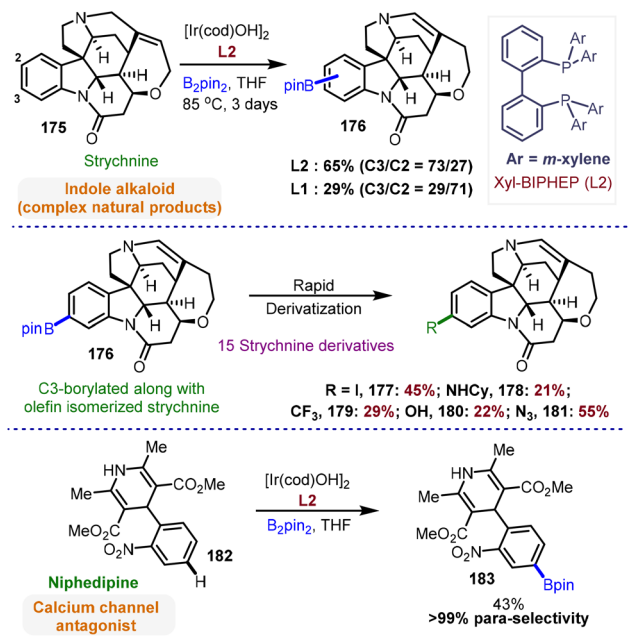

Fig. 33 Late-stage *para* borylation of strychnine.

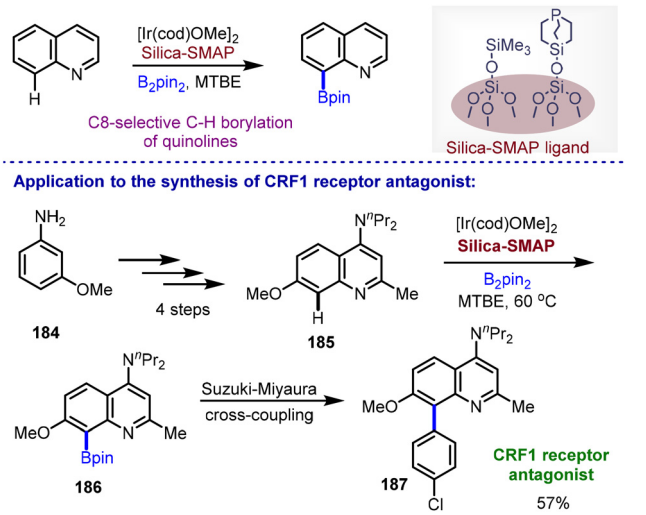

Fig. 34 Late-stage borylation of a CRF1 receptor antagonist.

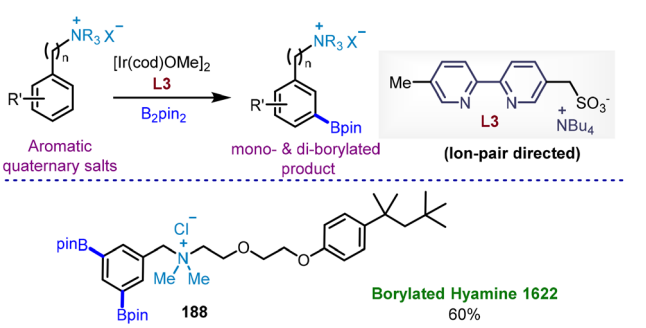

Fig. 35 Late-stage *meta*-*meta* di borylation of Hyamine 1622.

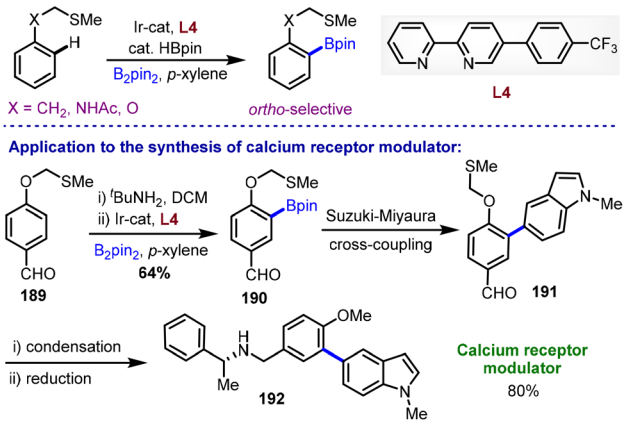

Fig. 36 Synthesis of calcium receptor modulator.

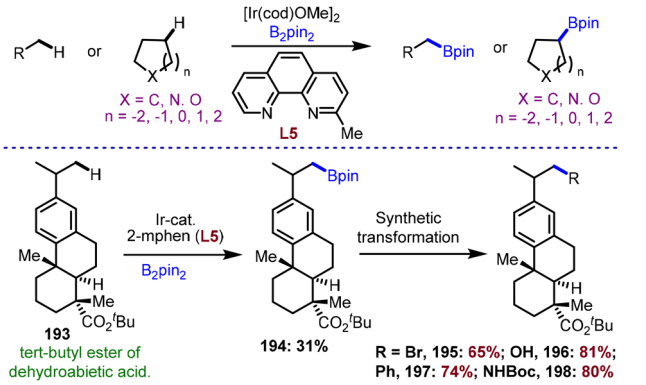

Fig. 37 Late-stage aliphatic borylation.

microbial surfactant benzthionium chloride (Hyamine 1622) (**188**) with a 60% yield.

Kuninobu *et al.* reported[118] the *ortho*-selective C–H borylation of phenols and anilines containing a methylthiomethyl group on the hydroxy and amino groups catalyzed by iridium and a bipyridine-type ligand (**L4**) (Fig. 36). It was observed that the introduction of an electron-withdrawing substituent to the bipyridine ligand dramatically alters the regioselectivity from the *meta* and *para* positions to the *ortho* position of aromatic substrates. Utilizing this concept, they synthesized a calcium receptor modulator (**192**) in a high isolated yield. The authors commenced the synthesis by protecting the –CHO group of the starting material with an imine followed by selective *ortho*-borylation, which afforded (**190**) in a 64% yield. After the borylation, Suzuki–Miyaura cross-coupling and functional group manipulations delivered the desired calcium receptor modulator (**192**) with an 80% yield.

The borylation of strong aliphatic C–H bonds of organic molecules is always a challenging task due to their high bond strength and the large excess of substrates that is required. Hartwig and coworkers, in 2020, solved this problem and reported[119] an iridium catalyst ligated by a 2-methylphenanthroline ligand (**L5**) for the borylation of undirected primary C–H bonds. When primary C–H bonds are absent or blocked, borylation occurs on strong secondary C–H bonds where the substrate was used as a limiting reagent (Fig. 37). Additionally, they showed the synthetic utility of the borylated product and the borylation of medicinally relevant synthetic structures containing many C–H bonds and functional groups. For example, dehydroabietic acid (**193**), which contains a carboxylate group along with many aryl and alkyl C–H bonds, was selectively borylated at the methyl C–H bond of the isopropyl group over the aryl C–H bonds. The generated borylated product (**194**) acts as a base for many other useful synthetic transformations and delivers a series of products (**195–198**).

In 2021, our group discovered[120] a remarkably efficient iridium catalyst (**CB1**) for the C–H borylation of aromatic, heteroaromatic, and aliphatic systems. The designed ligand acted as a bidentate mono-anionic ligand that coordinated in an N, C-manner with the iridium. A catalytic reaction occurred with the formation of an iridium bis(boryl) complex. This newly developed catalyst showed very high *ortho*-selectivity and excellent reactivity for a diverse class of substrates along with being active in the late-stage borylation of bioactive molecules (Fig. 38). The biomolecules such as Sertraline (antidepressant, **199**), and the cannabinoid core (psychoactive drug, **200**), although containing multiple sites for borylation, were selectively borylated and exclusively yielded one isomer with good yields. Paroxetine (**201**), a marketed drug used as an antidepressant, was selectively borylated at the C(sp^3)–H bond without affecting the many other C–H bond sites, including the reactive arene C–H bonds.

Subsequently, we reported[121] another strategy for the *ortho*-borylation of arenes and pharmaceuticals in the presence of an iridium catalyst under ligand-free conditions. The reaction proceeds *via* a unique mechanistic pathway by the formation of active catalytic species (**202**), as evidenced by experiments and detailed DFT calculations. Also, kinetic studies showed that a secondary KIE was observed with the rate-determining C–H activation step. Diverse classes of arenes such as 2-phenoxypyridines, 2-anilinopyridines, benzylamines, aminophenylethane derivatives, and other important scaffolds could be converted to *ortho* borylated products smoothly with high regioselectivity (Fig. 39).

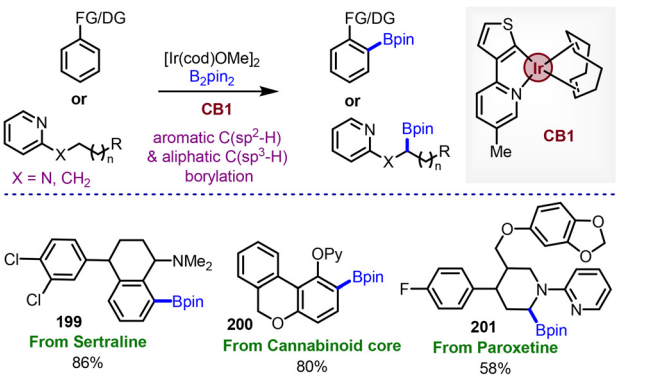

Fig. 38 Late-stage proximal borylation.

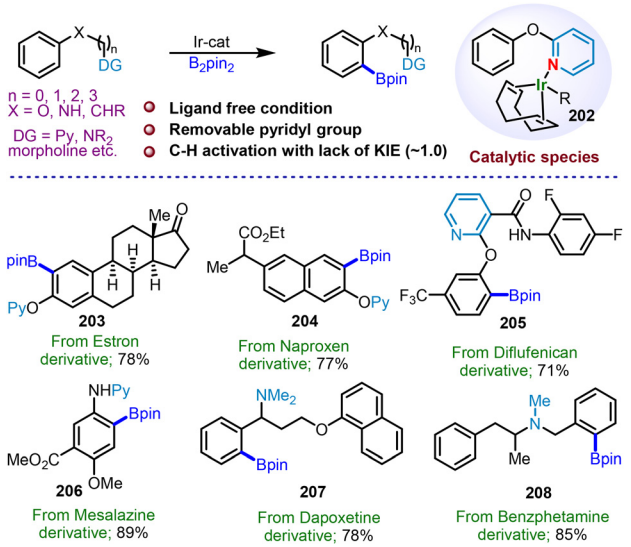

Fig. 39 Late-stage directed ligand-free *ortho* borylation.

Several late-stage borylations of bioactive molecules and drugs were achieved using this developed strategy. For example, the late-stage borylation of drug and drug-like molecules (**203–208**) such as estrone, naproxen, diflufenican, mesalazine, dapoxetine, benzphetamine, *etc*. containing OPy, NHPy, and other directing groups occurred in excellent yields. These generated synthons could be useful as potential building blocks for further structural diversifications.

A highly *para*-selective C–H bond activation and borylation of aromatic amides was developed by our group[122] using a newly designed ligand framework (defa; 1st generation, **L6**) where unprecedented substrate–ligand distortion between the twisted aromatic amides and ligand controlled the regioselectivity (Fig. 40). Numerous aromatic molecules and heteroaromatic bis-Boc protected amides could be borylated with high *para*-selectivity. Notably, amides derived from α-tocopherol (**209**) and deoxyarbutin (**210**) also gave the product with >90% *para*-selectivity under the developed reaction conditions in good to excellent yields.

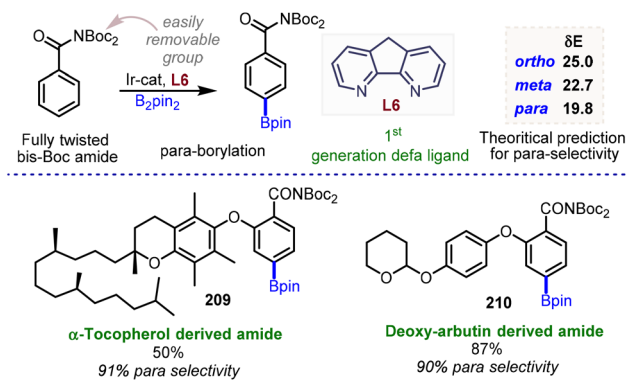

Fig. 40 Late-stage *para* borylation of bis (Boc) amide derivatives.

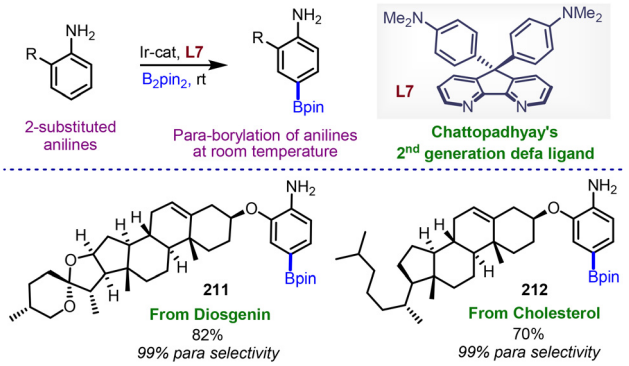

Fig. 41 Late-stage *para* borylation of aniline derivatives.

Concurrently, we reported[123] another *para*-borylation of *ortho*-substituted anilines using the 2nd generation defa ligand (**L7**) (Fig. 41). Several control experiments concluded that the origin of the high *para* selectivity solely depends on the steric crowding created by the *ortho* substitution of the aniline substrates and the *in situ*-generated *N*-Bpin species.

Anilines containing several sensitive functional groups at the *ortho* position were well tolerated and the borylated product was obtained with excellent selectivity. Under the developed reaction conditions, the late-stage borylation of anilines derived from diosgenin (**211**) and cholesterol (**212**) was performed with 99% *para*-selectivity.

In 2021, Ilies and coworkers developed[124] a method for the *ortho*-selective borylation of fluoroarenes under iridium-catalyzed conditions with the terpyridine-type ligand (**L8**). In the presence of many functional groups such as bromide, chloride, ester, ketone, amine, *etc*., high *ortho*-selectivity was observed with respect to the fluorine. Complex drug molecules, such as haloperidol (**213**), could generate the highly selectively *ortho* borylated product (**214**) under the reaction conditions with 50% product conversion. The borylated Haloperidol underwent a Suzuki–Miyaura cross-coupling in one pot with an aromatic bromide to obtain the corresponding haloperidol derivative (**215**) in a 32% yield as a single isomer (Fig. 42).

In continuation, the authors came up with a novel strategy[125] based on remote *meta*-selective borylation of a range of mono-substituted substrates using spiro bidentate bipyridine type ligand (**L9**) under iridium-catalyzed conditions (Fig. 43). The regioselectivity is solely controlled by the ligand bulky substituents which create a barrier to avoid *para* borylation.

meta-borylated derivatives of drug molecules like caramiphen (an anticholinergic drug used for the treatment of Parkinson's disease, **216**), pirfenidone (an *N*-phenylpyridinone derivative used for the treatment of idiopathic pulmonary fibrosis, **217**), and Methylphenidate (a stimulant drug used mostly for the treatment of attention deficit hyperactivity disorder, **218**) could be delivered with high regioselectivity under these reaction conditions, although the conversions were lower.

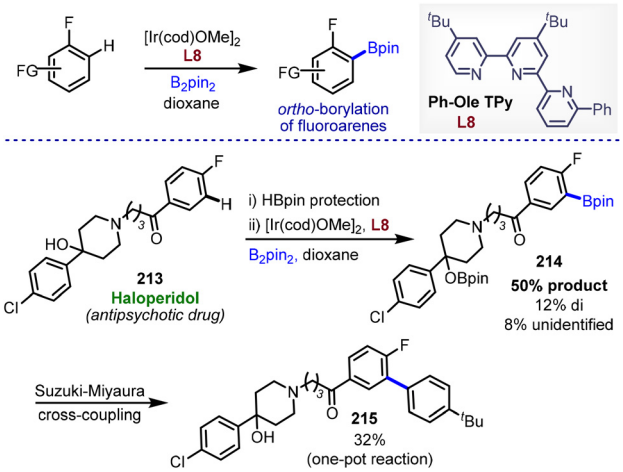

Fig. 42 Late-stage *ortho* borylation of haloperidol.

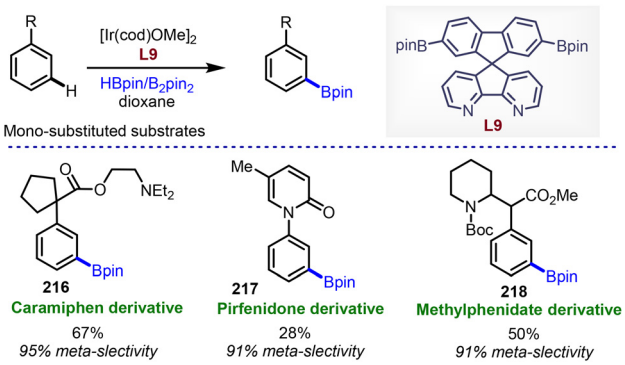

Fig. 43 Late-stage *meta* borylation of mono-substituted bioactive molecules.

Phenols are a very important bioactive core of many important pharma or household products. So, late-stage functionalization of phenol-bearing molecules is highly important for the discovery of better and more effective biological properties. In this context, we have developed **PY-PYRI: L10**, a tautomerized ligand system for the *meta*-selective C–H borylation of phenols as well as the C6 borylation of indole derivatives bearing tri-isopropyl silyl steering group (Fig. 44).[126] The inspiration for the innovative ligand design came from an intriguing O–Si secondary interaction. After a detailed computational study, it was found that an unprecedented Bpin shift occurs during the transformation of the iridium bis(boryl) complex to the iridium tris(boryl) complex. A combined dispersion of OBpin and the *tert*-butyl group of the ligand makes a suitable pocket for the phenol bearing tri-isopropyl silane group which controls the regioselectivity for these *meta*-selective borylation reactions.

We have found that our developed systems were very effective for the *meta* borylation of phenols, irrespective of the substitution patterns or the electronic properties of the substituents on the arene ring. Several important bioactive phenol

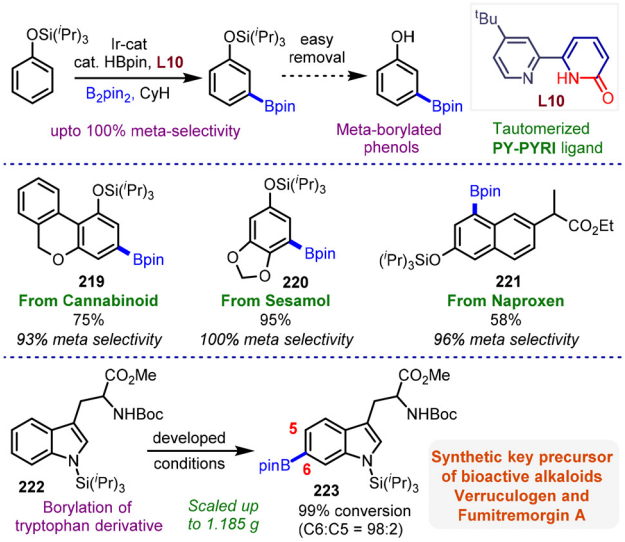

Fig. 44 Late-stage *meta* borylation of phenol and indole derivatives.

bearing molecules were *meta* borylated under the developed reaction conditions in high isolated yields and selectivities. It was found that silyl protected tryptophan derivative **222**, a synthetic precursor of the bioactive alkaloids verruculogen and fumitremorgin A,[31] gave a very high level of C6 borylation under the developed reaction conditions.

Recently, the Mascarenas group reported[127] the *ortho* borylation of aromatic amides governed by unusual outer-sphere non-covalent interactions between the amide group of the substrate and the CF_3-substituted electron deficient pyridine ring of the bipyridine ligand (**L10**). As shown in Fig. 45, this novel concept is also applicable for the late-stage C–H borylation of various drug derivatives containing amide functionality, resulting in high *ortho*-selectivity and good to excellent yields.

The Ir-catalyzed enantioselective C–H borylation of the C(sp^3)–H bonds of various cyclic and acyclic substrates having a directing group was developed[128–131] by the Xu group using a class of chiral bidentate boryl ligands (CBLs). The unique design of the CBLs along with a specific directing group, such

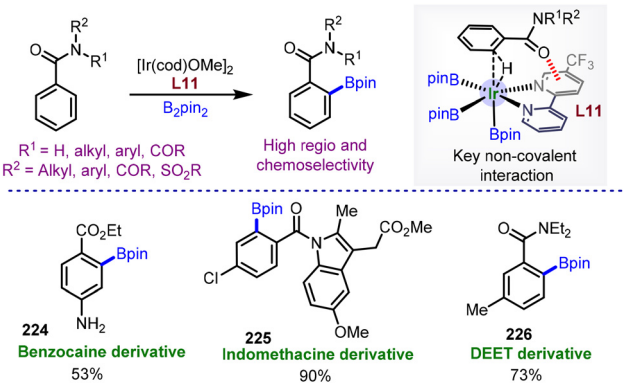

Fig. 45 Late-stage *ortho* borylation of bioactive amide derivatives.

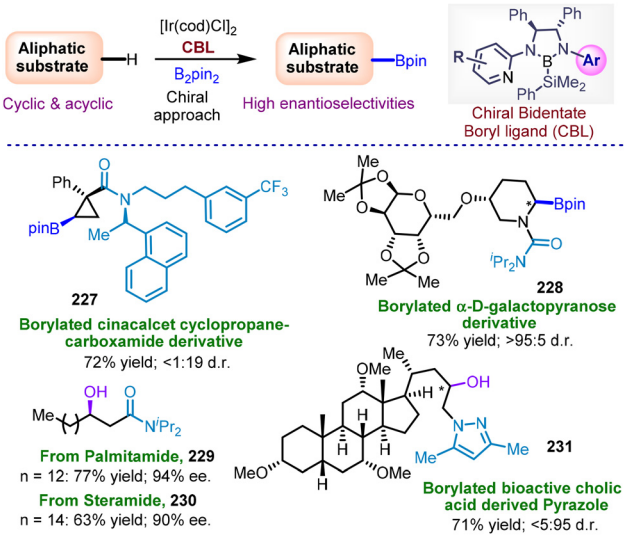

Fig. 46 Late-stage enantioselective aliphatic borylation.

as amides, pyrazoles, *etc*., attached to the substrates was responsible for the excellent regio- and enantioselectivities (Fig. 46). Their method was also equally applicable to the late-stage borylation of bioactive and pharmaceutically important molecules. For example, under their developed conditions, cinacalcet-derived cyclopropanecarboxamide (**227**), α-D-galactopyranose derived piperidine (**228**), amides derived from palmitic (**229**), stearic acids (**230**), and bioactive cholic acid derived pyrazoles (**231**) afforded very good amounts of enantioselective sp^3(C–H) borylated products.

Staurosporine (**232**) is among the most potent naturally occurring kinase inhibitors of the vast majority of the human kinome and has served as a major compound for numerous drug development efforts in several therapeutic areas.[132,133] In this report,[134] the authors have utilized C–H borylation chemistry to access analogues of Staurosporine which were previously unreachable to medicinal chemists. After the Boc protection of staurosporine, an iridium-catalyzed C–H borylation in the presence of the 1,10-phen ligand produced a borylated synthon which can be further functionalized for the preparation of many new analogs, undeniably opening the door to promote kinase activity by this class of molecule (Fig. 47).

2.4. Application of borylation in polycyclic systems

Polycyclic aromatic hydrocarbons (PAHS) containing highly conjugated pi-electronic clouds are beneficial chemical compounds that are used as semiconductors and functional materials for optoelectronics, catalysis, and sensing applications.[135–137] By virtue of their peripheral substitution, the structural, physical, and electrochemical properties of these polycyclic aromatic hydrocarbons can be tuned properly.[138,139] For example, the introduction of any electron-donating or -withdrawing group at their peripheral position alters the electronic properties, and the solubility also increases when long alkyl chain and bulky groups are introduced. Equally, polycyclic systems containing boron functionality have many applications in real-life functions. In this context, boron group insertion at the peripheral positions of polycyclic systems *via* C–H activation and borylation is one of the best approaches because of its high site selectivity. In this sub-section, we have tried to cover a few examples of C–H borylation for the functionalization of polycyclic aromatic systems which unquestionably demonstrate the importance of this chemistry.

Osuka, Shinokubo, and their co-workers, in 2007, unveiled[140] a regioselective C–H bond activation and borylation of the aromatic substituents of porphyrins using iridium catalysis. In this report, they demonstrated that when the peripheral aryl groups of porphyrin substrates had adjacent β-substituents, the regioselectivity of the reaction was mainly guided by steric interactions.

For example, compound (**237**) contains a peripheral benzene ring and an adjacent –Me group in the β-position,

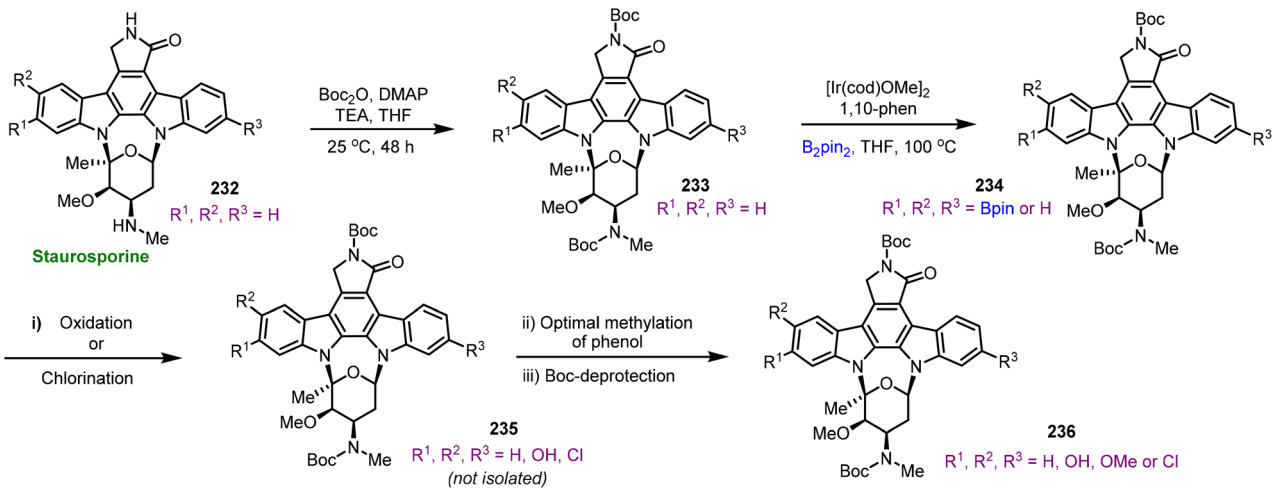

Fig. 47 Synthesis of staurosporine analogs.

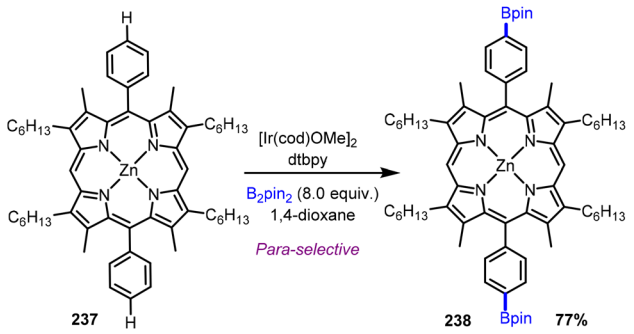

Fig. 48 Para selective borylation of Zn-porphyrin.

and under the reaction conditions in the presence of 8.0 equiv. B_2pin_2 the *para*-selective diborylated product (**238**) was delivered in a 77% yield (Fig. 48). Pyrene, perylene, and their derivatives are an important class of polycyclic aromatic hydrocarbons that act as fluorophores. They are widely used as fluorescent probes since they strongly emit fluorescence in live cells and have very low cytotoxicity with outstanding cell permeability. Moreover, these hydrocarbon-based organic electronics have been the subject of tremendous investigation and the synthesis of new derivatives is highly desirable. Realizing the significance, Marder *et al.* utilized a C–H borylation strategy and selectively functionalized pyrenes (**239**) and perylenes (**242**) with good to excellent yields.[141]

Under the developed reaction conditions *via* the combination of an Ir-catalyst and dtbpy, 2-pyrylboronic ester (**240**) was obtained as a major product when 1.1 equivalents of B_2pin_2 were used, whilst 2,7-diborylated pyrene (**241**) was obtained exclusively when 2.2 equivalents of B_2pin_2 were used. Under identical reaction conditions, using 4.4 equivalents of B_2pin_2, tetraborylated perylene (**203**) was obtained with an 83% yield. The authors also developed the direct borylation of a C–H bond at the 4-position of pyrene which is *ortho* to the ring junctions, even if the 2,7 positions of pyrene had been occupied by a bulky group.[142] Utilizing 2,7-diborylated pyrene (**241**) as a starting material under the developed conditions, 2,4,7-triborylated pyrene (**244**) was also afforded in a 62% yield (Fig. 49).

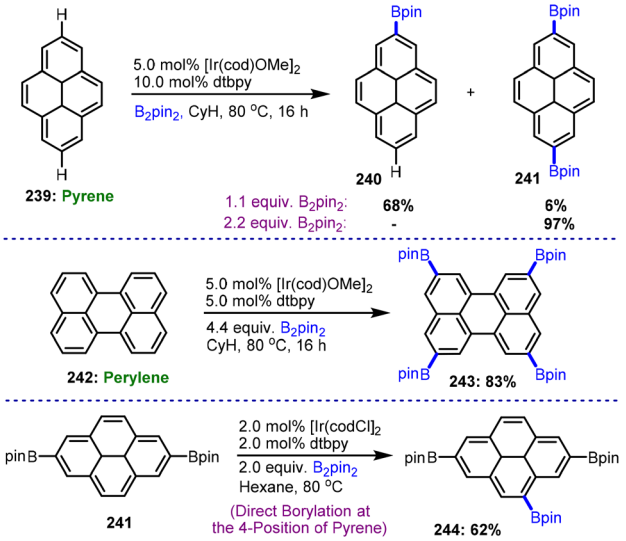

Fig. 49 C–H borylation of pyrene and perylene.

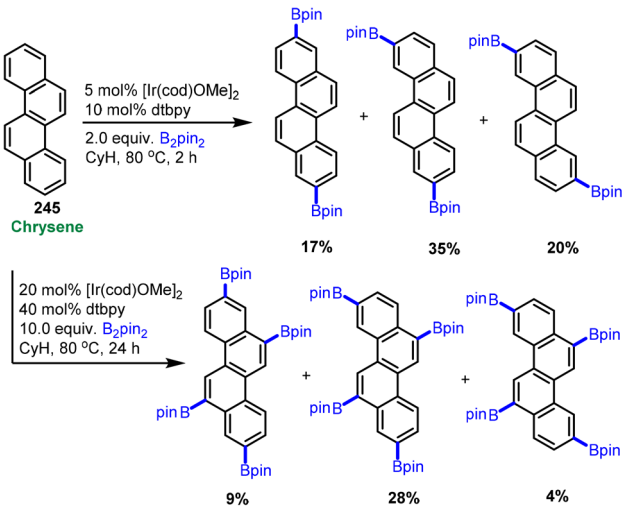

Fig. 50 C–H borylation of chrysene.

Phenacene is another versatile polycyclic aromatic hydrocarbon where the benzene units are fused in a zigzag form and it is found to be useful in electronic applications in emissive and semi- or superconducting materials. Among the variant congeners of phenacene, the diborylated phenacenes are of current interest due to their potential role as base arylene units in the synthesis of finite models for single-wall carbon nanotubes (SWNTs). Thus, understanding their importance, the Isobe group in 2012 reported[143] the iridium-catalyzed two-fold borylation of [4]phenacenes (chrysene, **245**) in the presence of the dtbpy ligand and borylation took place selectively at the edge sites. Using excess borylating reagent (10 equiv.), tetraborylated phenacenes were obtained with reasonable yields in a site-selective manner (Fig. 50). Although the reaction to synthesize the di-borylated product proceeds in good yields, it ends up with a mixture of isomeric products (2,8- : 2,9- : 5,9- = 1 : 2.1 : 1.2). To avoid a lengthy purification, in 2015, Quayle *et al.* developed a methodology to access the single regioisomer of a tetra-substituted chrysene derivative.[144]

They selected 4,10-dichlorochrysene (**246**) as a model substrate and performed an iridium-catalyzed regioselective C–H borylation to enable the orthogonal synthesis of "A_2B_2"-tetraborylated chrysenes, a molecule which shows a broadened UV-vis absorption spectrum when compared to the parent chrysene. The catalytic combination of $[Ir(cod)OMe]_2$/dtbpy and B_2pin_2 as a borylating agent delivered the compound (**247**) which serves as an important synthon to synthesize many tetra-substituted derivatives (Fig. 51).

The synthetic utility of this methodology lies in the fact that, due to the extensive conjugation of the core chrysene

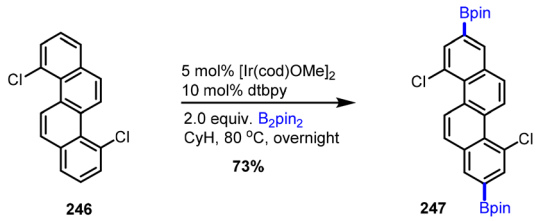

Fig. 51 C–H borylation of 4,10-dichlorochrysene.

unit, the band gap decreases and the HOMO levels become higher in energy, thus unlocking opportunities for utilization in organic electronic applications such as p-type semiconductors or as tunable emissive materials in OLED applications.

NDT3 is the most useful building block of a series of isomeric naphthodithiophenes (NDTs) for developing semiconducting polymers In 2012, Takimiya *et al.* demonstrated[145] the synthesis of NDT3-based polymers utilizing the selective borylation of naphtho[1,2-*b*;5,6-*b*′]dithiophene (NDT3, **248**). To achieve this, they first blocked the α-position of the thiophene core with a bulky substituent to prevent the borylation process at the active thienyl C–H bonds. Then, direct borylation of the α-functionalized NDT3 (2,7-dioctyl-NDT3, as the substrate) catalyzed by Ir complexes and B_2pin_2 delivered 2,7-dioctyl-5,10-bis[(pinacolato)boryl]-NDT3 (**249**) (75% isolated yield) with selective borylation at the 5- and 10-positions. The diborylated compound (**249**) is readily transformed into other functionalities that can act as new building blocks for the synthesis of NDT3-based polymers (Fig. 52).

An iridium-catalyzed C–H borylation strategy was used for the direct functionalization of hexa-*peri*-hexabenzocoronene (HBC), thus enabling the regioselective introduction of boryl groups to the *para*, *ortho*-, and *meta*-substituted HBCs in high yields.[146–148] The author showed that functionalization of the HBCs influenced their photophysical properties and enhanced the fluorescence quantum yields. Under the developed borylation conditions, HBC (**252**) was converted to the di-borylated HBC (**253**) product, which upon oxidation generates hydroxyl-substituted HBC (**254**). Hydroxyl-substituted HBC (**254**) could be further oxidized with PIFA to tetra oxo-substituted HBC (**255**) which is a π-extended quinone (Fig. 53).

In materials science, perylene tetracarboxylic acid bisimide (PBI) is an important class of dye. PBI has gained much attention for its widespread applications in organic optoelectronic materials due to its thermal, chemical, and photochemical stability. Understanding the importance of PBI, Shinokubo and coworkers reported[149] the direct C–H borylation of PBIs at the 2,5,8,11-positions inspired by the pioneering work developed by Miyaura, Ishiyama, and co-workers where iridium-catalyzed *ortho*-borylation of benzoate ester was demonstrated.[150,151] Under the developed conditions, borylation afforded PBIs (**257**) that were tetraborylated at the 2, 5, 8, and 11 positions in good yields with perfect regioselectivity. A subsequent oxidation provided tetrahydroxy PBI (**258**) in an excellent yield (Fig. 54).

The hydroxy group is involved in a hydrogen bonding interaction with the carbonyl group which stabilizes the HOMO level, and, as a result, substantially blue shifts the UV/vis absorption spectrum observed. In addition, these tetraborylated PBIs serve as excellent building blocks for further synthetic transformations.

In 2015, Ros and Pischel *et al.* reported[152] various aryl isoquinoline skeletons with strong fluorescence properties containing four-coordinate organoboron species (**261**). To synthesize these compounds, they first performed an iridium-catalyzed nitrogen-directed *ortho* borylation of aryl isoquinolines (**259**) using 2-pyridine carboxaldehyde *N*,*N*-dibenzylhydrazone as the ligand and B_2pin_2 as the boron source (Fig. 55).

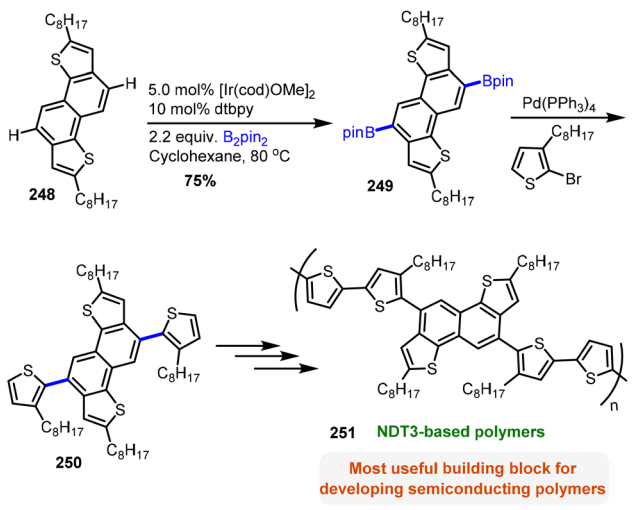

Fig. 52 Synthesis of NDT3-based polymers.

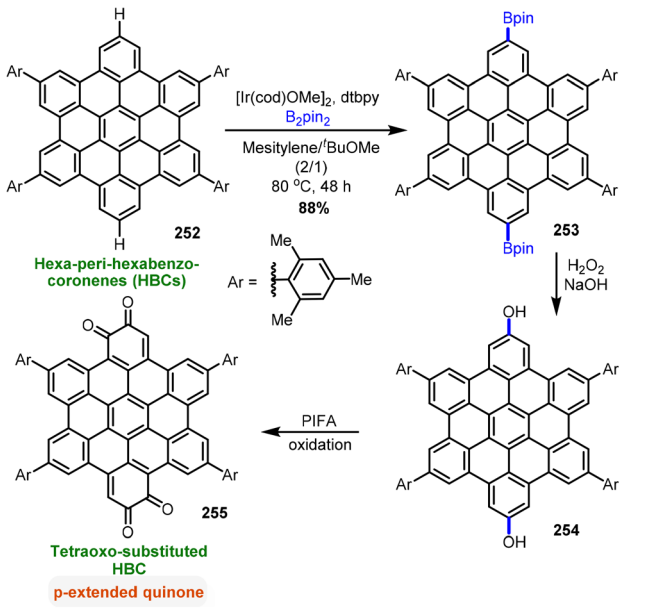

Fig. 53 C–H borylation of hexa-*peri*-hexabenzocoronene.

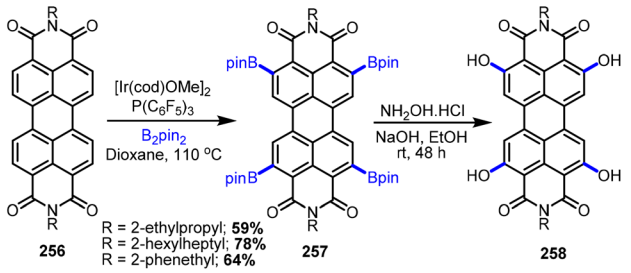

Fig. 54 C–H borylation of perylene tetracarboxylic acid bisimide (PBI).

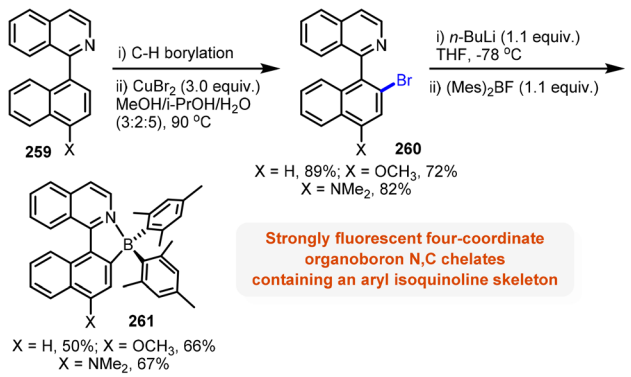

Fig. 55 Synthesis of tetra-coordinated organoboron species *via* C–H borylation.

After introduction of the boryl group, they subsequently transformed it into a bromide derivative (**260**) that is difficult to make by any other means. Hence, this route provides versatile access to bromide derivatives which can be easily converted to other target compounds *via* bromide–lithium exchange followed by trapping of the lithiated species with Mes_2BF. These dyes showed the versatile photophysical and structural properties needed to construct functional probes for diverse fluorescence-microscopy applications. Later, in 2022, the same group again reported[153] modified polycyclic aromatic hydrocarbon (PAH) fluorophore dyes derived from bis-borylated arylisoquinoline using the same C–H borylation-bromination strategy. These PAHs are an important class of compound that serve as fluorophores and $^1O_2$ photosensitizers.

3. Conclusions

C–H borylation is an emerging tool for constructing molecular architectures in a regioselective way with high productivity. Organoboron functional groups act as a base for the transformation of functional groups into a variety of other important functionality. The ease with which organoboron functional groups can be manipulated means that they are used in natural product syntheses, resulting in shorter routes. For the discovery of new drugs and drug leads, late-stage functionalization plays an important role in setting structure–activity relationships. It is also evident that C–H borylation now plays an important role in materials synthesis in a sophisticated way. Thus, further development and utilization of C–H borylation would be beneficial for drug discovery, late-stage functionalization, and natural product synthesis.

Author contributions

B. C. conceived the concept of the review. All authors (B. C., S. G., and M. M. M. H.) contributed to the discussion and writing the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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