Boron Directed Regioselective Aromatic *Ortho*-Functionalizations

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Boron Directed Regioselective Aromatic *Ortho*-Functionalizations

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To my parents,
For your endless love, sacrifices, and unwavering belief in me.

To my wife,
For your patience, encouragement, and being my constant source of strength.

To my sisters,
For your support, kindness, and always being there for me.

This work is dedicated to you,
With all my love and gratitude.

Abstract

Selectivity is crucial in modern organic synthesis, as it allows for precise molecular modifications while minimizing undesired side reactions. Controlling selectivity is essential for improving reaction yields, reducing purification steps, and enhancing overall synthetic efficiency. This is particularly important in synthetic methodologies, where precise control over regioselectivity is essential for constructing complex molecules efficiently and reliably.

In this work, we have developed a series of selective deborylative transformations that leverage the unique reactivity of dibromoboracycles to achieve regioselective C–halogen, C–aryl, and C–benzyl bond formations in 2–aryl–*N*–heteroarenes, aldehydes, *N*–aryl amides and ureas. By integrating nitrogen and carbonyl-directed borylation with subsequent functionalization, we have introduced efficient, metal-free, and scalable methodologies that address long-standing challenges in site-selective C–H functionalization.

Our oxidative halodeboronation strategy provides a direct and regioselective approach to *ortho*-halogenation, eliminating the need for transition-metal catalysts while ensuring high functional group tolerance. This protocol expands the synthetic utility of boron, enabling the precise installation of halogens in 2–aryl–*N*–heteroarenes and *N*–aryl amides under mild conditions.

Furthermore, we have demonstrated that dibromoboracycles can be directly employed in *ortho*-arylation and *ortho*-benzylation, bypassing the conventional BBr_2-to-BPin conversion. This unique approach facilitates the efficient synthesis of biaryl amides, diarylmethane amides, and dibenzoazepines, unlocking new avenues for selective C(sp^2)–C(sp^2) and C(sp^2)–C(sp^3) bond formation. Additionally, our method enables one-pot diagonal diarylation, allowing streamlined access to complex molecular architectures such as tetraarylbenzenediamines and *N*–doped fulminenes.

Finally, we introduce a scalable and chromatography-free synthesis of aryl-difluoroborane (Ar–BF_2) compounds, which exhibit enhanced stability and reactivity. These Ar–BF_2 species serve as highly versatile intermediates for late-stage functionalization, enabling diverse transformations, including radioiodination, halogenation, hydroxylation, azidation, and Suzuki-Miyaura cross-coupling. Their broad applicability highlights their potential as powerful tools in pharmaceutical synthesis and beyond.

Overall, this work represents a significant advancement in boron-mediated functionalization, establishing a unified platform for regioselective C–H activation and cross-coupling reactions. By harnessing the intrinsic reactivity of dibromoboracycles, we provide highly selective, operationally simple, and scalable strategies that eliminate unnecessary synthetic steps, paving the way for future developments in boron-directed transformations and late-stage functionalization.

Keywords: BBr_3-mediated borylation, late-stage functionalization, oxidative halodeboronation, regioselective functionalization, Suzuki-Miyaura cross-coupling.

Sammanfattning

Inom organisk kemi är selektivitet avgörande för att styra reaktioner så att exakt rätt produkt bildas. Utan selektivitet skulle kemiska synteser vara ineffektiva, skapa onödigt avfall och kräva komplicerade reningssteg. Särskilt inom läkemedelsutveckling och materialkemi är det viktigt att kunna kontrollera var och hur olika funktionella grupper introduceras i en molekyl.

I detta arbete har vi utvecklat nya och selektiva metoder för att modifiera aromatiska föreningar med hjälp av borbaserade reagens. Genom att utnyttja den unika reaktiviteten hos dibromboracykler har vi skapat strategier för att introducera halogener, aryl- och alkylgrupper på specifika positioner i en molekyl – något som tidigare varit en utmaning. Våra metoder är dessutom metallfria, vilket gör dem mer miljövänliga och enklare att tillämpa i stor skala.

En av våra innovationer är en oxidativ halodeboronering, där vi kan introducera halogener (som klor, brom eller jod) på en specifik plats i en molekyl utan att behöva använda dyra eller svårhanterliga metaller som katalysatorer. Detta är särskilt användbart för att skapa byggstenar till läkemedel och funktionella elektroniska material.

Vi har också visat att dibromboracykler kan användas direkt för att koppla ihop aromatiska system och skapa komplexa molekyler på ett effektivt sätt. Denna strategi möjliggör en selektiv syntes av biarylamider och andra strukturer med relevans för både farmakologi och materialvetenskap. Dessutom har vi utvecklat en ny metod för att skapa aryl-difluorboraner (Ar-BF_2), stabila och reaktiva föreningar som fungerar som mångsidiga byggstenar i kemiska synteser, inklusive viktiga reaktioner som Suzuki-Miyaura-kopplingar.

Genom att dra nytta av organiska borföreningars unika kemi har vi utvecklat effektiva, hållbara och skalbara metoder som kan tillämpas inom läkemedelsutveckling, materialdesign och andra viktiga områden.

Nyckelord: BBr_3-medierad aromatisk borylering, *ortho*-funktionalisering, regioselektiv, Suzuki-Miyaura-koppling.

Acknowledgments

The past four years have been a transformative journey, filled with challenges, growth, and countless lessons. This path was not an easy one, it demanded years of hard work, resilience, and unwavering determination. I still vividly remember the day of my Ph.D. interview, when harsh weather and technical issues threatened to derail my chances. Yet, it was Henrik who saw beyond those obstacles and recognized the vision and passion within me. For that, I will always be grateful.

I would like to extend my deepest gratitude to Henrik for his unwavering guidance and support throughout this journey. As the ancient Sanskrit verse says:

॥आचार्यात् पादमादत्ते आधत्ते पादं शिष्यः स्वमेधया। पादं सब्रह्मचारिभ्यः पादं कालक्रमेण च॥

This translates to: A student acquires one-quarter of knowledge from the teacher, one-quarter from their own intellect, one-quarter from peers, and the remaining quarter with time and experience. Your mentorship has been the foundation of my growth, and I am deeply thankful for the wisdom you have shared, which has shaped not only this work but also my perspective as a researcher and individual. I thoroughly enjoyed being your student, and if I could, I would gladly extend my PhD just to have more time under your guidance. Your passion for chemistry, your patience, and your ability to inspire have made this journey unforgettable.

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To my beloved wife, thank you for being my pillar of strength and my greatest source of support. Your love, patience, and encouragement have been my guiding light through every challenge and triumph. This journey would not have been possible without your support, and I am forever grateful for the sacrifices you’ve made and the joy you’ve brought into my life.

To my parents and sisters, thank you for your endless love, prayers, and belief in me. Your sacrifices and encouragement have shaped me into the person I am today, and I owe everything I have achieved to your unconditional support.

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List of Publications

This thesis is based on the following publications, which are referenced in the text using Roman numerals. Reprints of these works have been included with the kind permission of the respective publishers.

I. **Boron-Mediated Regioselective Aromatic C–H Functionalization via an Aryl BF_2 Complex.**
Shinde, G. H.; Sundén, H.
Chem. Eur. J. **2023***, 29,* e202203505.

II. **Regioselective *Ortho* Halogenation of *N*–Aryl Amides and Ureas via Oxidative Halodeboronation: Harnessing Boron Reactivity for Efficient C–Halogen Bond Installation.**
Shinde, G. H.; Ghotekar, G. S.; Amombo Noa, F. M.; Öhrström, L.; Norrby, P.-O.; and Sundén, H. *Chem. Sci.* **2023**, *14*, 13429–13436.

III. ***Ortho* Arylation of *N*–Aryl Amides and the Construction of Diagonal Tetraarylbenzenediamines and *N*–Doped Fulminenes via BBr_3-Derived Dibromoboracycles.**
Shinde, G. H.; Ghotekar, G. S.; and Sundén, H.
Chem. Eur. J. **2025**, *31*, e202403938.

IV. **Site Selective Boron Directed *Ortho* Benzylation of *N*–Aryl Amides: Access to Structurally Diversified Dibenzoazepines.**
Shinde, G. H.; Castlind, H.; Ghotekar, G. S.; Amombo Noa, F. M.; Öhrström, L.; and Sundén, H.
Org. Lett. **2025**, 27, 207–211.

V. **Introducing Aryl–Difluoroborane: A Versatile Building Block for Selective *Ortho*–Functionalization, Radioiodination, and Cross-Coupling Reactions.**
Shinde, G. H.; Babiker, J.; Prigent, A.; Foucras, G.; Amombo Noa, F. M.; Öhrström, L.; Cailly, T.*; Sundén, H*.
Manuscript. **2025**.

Contribution report

Paper I: I carried out the optimization studies, synthesized the substrate scope, and conducted all mechanistic investigations. I wrote the Supporting Information and co-wrote the manuscript with Henrik Sundén.

Paper II: I conceived the idea and designed the study in collaboration with Ghotekar. G. S. The experimental work was carried out by Ghotekar. G. S. and me. I wrote the Supporting Information and co-wrote the manuscript with Henrik Sundén.

Paper III: I designed the study and carried out the optimization studies. The experimental work was carried out by Ghotekar. G. S. and me. I also designed and conducted the application part of the project. Additionally, I wrote the Supporting Information and co-wrote the manuscript with Henrik Sundén.

Paper IV: I designed the study and supervised a bachelor's student, Hugo Castlind (H.C.), with whom I carried out the synthesis of products. Post-functionalization and dibenzylations were performed by me. Additionally, I wrote the Supporting Information and co-wrote the manuscript with Henrik Sundén.

Paper V: I designed the study and supervised a bachelor's student, Jonatan Babiker (B.J.), with whom I synthesized the Ar–BF_2 compounds. I conducted the post-functionalization of Ar–BF_2. I wrote the Supporting Information and co-wrote the manuscript with Henrik Sundén.

The contribution report is hereby approved by Prof. Henik Sundén, supervisor and corresponding author of all papers included in the thesis.

Henrik Sundén

Abbreviations

ACN	Acetonitrile
AcOH	Acetic acid
Chloramine T	*N*-Chloro-*p*-toluenesulfonamide sodium salt
DBU	1,8-Diazabicyclo[5.4.0]undec-7ene
DCE	Dichloroethane
DCM	Dichloromethane
DG	Directing group
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Equiv.	Equivalent
EDG	Electron donating group
EWG	Electron withdrawing group
FDA	Food and drug administration
GC	Gas chromatography
LCMS	Liquid chromatography-mass spectrometry
MS	Molecular sieves
MSA	Methanesulfonic acid
NBE	Norbornene
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NIS	*N*-Iodosuccinimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
pin	Pinacol
PPA	Polyphosphoric Acid
PTSA	*p*-Toluenesulfonic acid
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TBHP	tert-Butyl hydroperoxide
TCICA	Trichloroisocyanuric acid
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

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Chapter 1

Background

1. Boron: Element, Isotopes, and Historical Significance

Boron (B) is a metalloid element in Group 13 (IIIA) of the periodic table, with atomic number 5, atomic mass 10.811 g/mol, and a valence electron configuration of $2s^2\ 2p^1$. Although formally identified in 1808 by Sir Humphry Davy, Joseph Louis Gay-Lussac, and Louis Jacques Thénard (**Figure 1**),[1,2] boron compounds have been utilized for centuries. Ancient civilizations, including the Babylonians and Egyptians, employed boron-containing minerals such as borax ($Na_2[B_4O_5(OH)_4]\cdot 8H_2O$) in goldsmithing, mummification, and medicine.[3] By the eighth century, borax trade routes connected Medina and China, and by the 12th century, European goldsmiths had widely adopted its use.

In Sweden, Torbern Bergman[4a] studied the reaction between borax and sulfuric acid, identifying boracic acid (now known as boric acid) as the reaction product, thereby contributing to the early understanding of boron chemistry. Early attempts to isolate elemental boron yielded impure samples. The first successful production of high-purity boron is attributed to Ezekiel Weintraub (1909), who refined the process through electrolysis.[4b]

Figure 1. Discoverers of Boron: (a) Joseph Louis Gay-Lussac (1778–1850), (b) Louis Jacques Thénard (1777–1857), (c) Humphry Davy (1778–1829).

Boron's natural distribution is modest yet essential. It constitutes approximately 10 parts per million (ppm) of the Earth's crust.[3] It is found in hydrothermal and volcanic regions, with major deposits in Turkey and the United States. In seawater, boron averages 4.6 ppm and exists primarily as boric acid ($B(OH)_3$) or borate anions ($B(OH)_4^-$). Boron occurs in two naturally stable isotopes: ^{10}B and ^{11}B.[3] Boron exists in amorphous (brown-black powder) and crystalline forms (hard black material). Its chemical properties, characterized by hybrid

metal/nonmetal behavior, enable the formation of oxides (e.g., B_2O_3), salts (e.g., $B_2(SO_4)_3$ and acids (e.g., H_3BO_3).

1.2 Bonding Characteristics and the Evolution of Boron Chemistry

The chemical versatility of boron is deeply rooted in its bonding characteristics. Boron's electron-deficient sp^2-hybridized trigonal planar geometry (e.g., in boron trifluoride, BF_3) features a vacant *p*-orbital orthogonal to the plane. This configuration renders it a potent Lewis acid, readily forming sp^3-hybridized tetrahedral complexes such as BF_4 upon nucleophilic attack (**Figure 2**). This transition from trigonal planar to tetrahedral geometry dramatically alters the chemical properties of boron species. Electron-deficient, tricoordinated boron species are highly reactive, whereas tetrahedral complexes are chemically stable, finding applications in polymer stabilization and catalysis.

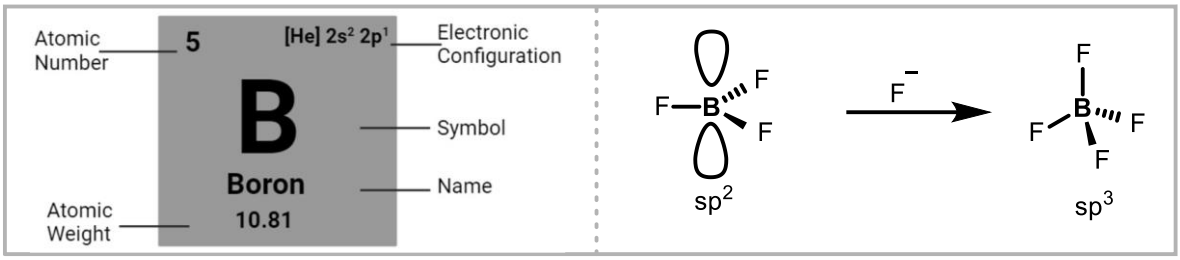


Figure 2. Boron and its molecular geometries in BF_3 (trigonal planar) and BF_4^- (tetrahedral).

The synthesis of diborane (B_2H_6) in the early 20th century marked a turning point in boron chemistry, paving the way for the development of polyhedral boron clusters and organoboron compounds. This groundbreaking work culminated in two Nobel Prizes: William Lipscomb in 1976[5,6] for elucidating the nature of chemical bonding in boranes, including B_2H_6 and boron clusters, and Herbert Brown in 1979[6,7] for pioneering research in boron chemistry, particularly in the use of boron-containing reagents for organic synthesis. The impact of boron continued with the 2010 Nobel Prize[6,8,9] for palladium-catalyzed cross-coupling reactions involving organoboron compounds, underscoring its role in modern synthetic methodologies. Today, boron remains a cornerstone of chemical innovation, with its compounds playing vital roles in advanced technologies and sustainable solutions.[10]

2. Organoboron

Organoboron compounds, defined by the presence of at least one carbon-to-boron bond, are pivotal in numerous areas of chemical science, including synthetic chemistry, materials science, and medicinal chemistry.[2, 11] Their structural diversity encompasses boranes, boronic acids, boronic esters, borinic acids, borinic esters, boronamides, borate anions, and other derivatives (**Figure 3**). Boronic acids and esters, among the most extensively studied organoboron compounds, are celebrated for their versatility in organic synthesis, particularly in transformations like the Brown hydroboration[7] and Suzuki-Miyaura (SM) cross-coupling reactions.[8-11] Boronic acids comprise two hydroxyl groups and one organic group attached to boron, while boronic esters have two alkoxy groups instead of hydroxyl groups. Moreover,

borate esters, synthesized from boric acid ($B(OH)_3$), and borate anions, including organotrifluoroborates[12] (RBF_3^-), contribute to various chemical processes. Other notable classes include boronamides, with two nitrogen atoms bonded to boron, and boron trihalides, whose strong Lewis acidity underpins their significance in numerous applications. In medicinal chemistry, organoboron species serve as bioisosteres for carboxylic acids[13], enabling modifications of physicochemical properties in drug candidates.[14,15]

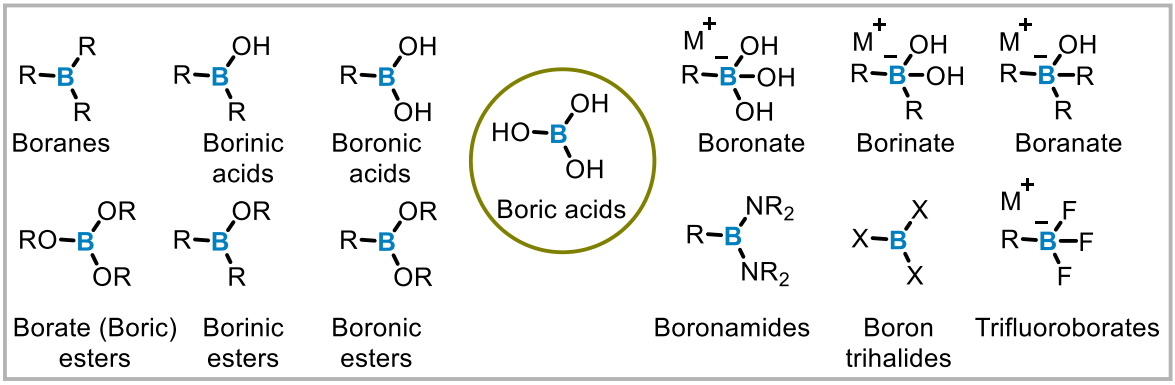


Figure 3. Examples of boron containing compounds.

2.1. Common Aryl-Boron Reagents: Stability, Reactivity, and Synthetic Versatility

Boronic acids and boronic esters, exemplified by phenylboronic acid (**1**) and its pinacol ester (**2**) (**Figure 4**), are important functionalities in modern organic synthesis, particularly as precursors in the SM reaction.[8,10] These compounds are notable for their stability under ambient conditions, although their reactivity depends on the nature of the organic substituent. For instance, aliphatic boronic acids and esters are prone to oxidation, whereas aryl and alkenyl derivatives exhibit greater stability.[3] Despite their utility, boronic acids pose challenges in chromatographic separation and extraction due to their high polarity and water solubility.[16]

Boronic esters are often preferred over boronic acids for their enhanced stability and ease of purification.[2, 16] While acyclic boronic esters are susceptible to hydrolysis, yielding boronic acids, bulky cyclic esters like pinacol boronic esters (Bpin) demonstrate increased robustness under various conditions.[2] Additionally, MIDA (*N*–methyliminodiacetic acid) boronate esters (**3**) have been designed to stabilize boronic acids by coordinating the boron atom (**Figure 4**). This coordination rehybridizes boron from sp^2 to sp^3, effectively eliminating the reactive empty *p*-orbital via a dative bond. These properties not only improve air stability but also enable MIDA esters to act as protecting groups, facilitating iterative cross-coupling strategies through their mild basic cleavage.[17]

Boron's strong affinity for fluorine leads to the formation trifluoroborates. Trifluoroborates (**4**),[12,18] with their tetracoordinated boron, share similar roles with MIDA boronate esters as stable protecting groups for boronic acids (**Figure 4**). One significant advantage of trifluoroborates is their efficient hydrolysis under mild conditions using silica gel and water,[19]

which enhances their practicality as intermediates in synthetic workflows. However, their limited solubility in apolar solvents can present challenges,[11] though this property is advantageous for purification via crystallization.

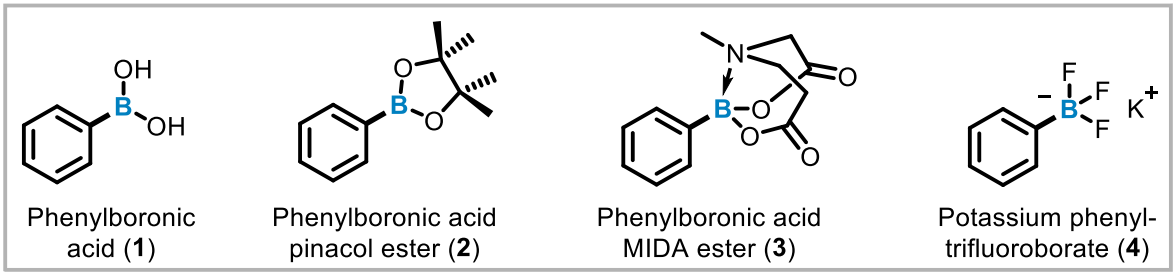


Figure 4. Structures of commonly used boron reagents.

The reactivity of boronic acids and esters is influenced by the electron-deficient nature of boron, rendering them susceptible to deboronation in the presence of aqueous acids, bases, nucleophiles, or oxidants.[20] Unlike carboxylic acids, boronic acids function as mild Lewis acids rather than Brønsted acids.[2,3] Their Lewis acidity is diminished relative to boranes due to the electron-donating interaction between oxygen lone pairs and the boron center. This fine balance of stability and reactivity underpins the integral role of boronic acids and esters in diverse chemical transformations.

2.2. Applications of Organoboron Compounds

The role of boron in modern chemistry is still growing, and organoboron compounds are now featuring as vital tools in a wide variety of fields. Advances in synthetic methodologies have enabled their use in the construction of C–C, C–O, C–N, and C–X bonds, making them pivotal reagents in pharmaceuticals, agrochemicals, and materials science (**Figure 5**).[2, 21] Their air and moisture stability, versatility, and compatibility with a wide range of functional groups make the organoboron compounds more appropriate, over traditional carbon nucleophiles[21] such as lithium and Grignard reagents.

One of the most notable features of boronic acids, boronate esters, and potassium organotrifluoroborates is that they can serve as carbon feedstocks for further functionalization. The boron-carbon (C–B) bond can be employed as a source of nucleophilic carbon to establish bonds with electrophiles upon appropriate conditions.[2, 21] Potassium organotrifluoroborates, for instance, are easily handled derivatives of boronic acids with enhanced nucleophilicity due to anionic activation.[12] This sort of nucleophilicity allows the direct use of C–B bonds in bond-forming reactions.

In catalytic cycles, organoboron compounds are frequently paired with high-oxidation-state transition metals (i.e., Pd, Ni) for facilitating elementary reaction steps.[2, 10, 11] The SM reaction,[8, 10, 22] Hayashi-Miyaura C–C coupling,[23] and Evans-Chan-Lam reactions[24] are hallmark examples in which boronic acids or esters are employed as key reagents. These reactions involve transient organometallic intermediates that undergo reductive elimination for the formation of new bonds, highlighting the application of boron compounds in catalytic transformations. Furthermore, under certain conditions, the C–B bond itself may directly

participate in bond-forming reactions without the need for transition metals, extending the scope of organoboron chemistry to transcend traditional catalytic cycles (**Figure 5**).[21, 25, 26] This direct reactivity highlights the versatility of organoboron reagents, making them highly effective for the construction of intricate molecular frameworks, as demonstrated by the *ipso*-functionalization studies discussed in **Chapters 2** and **3**.

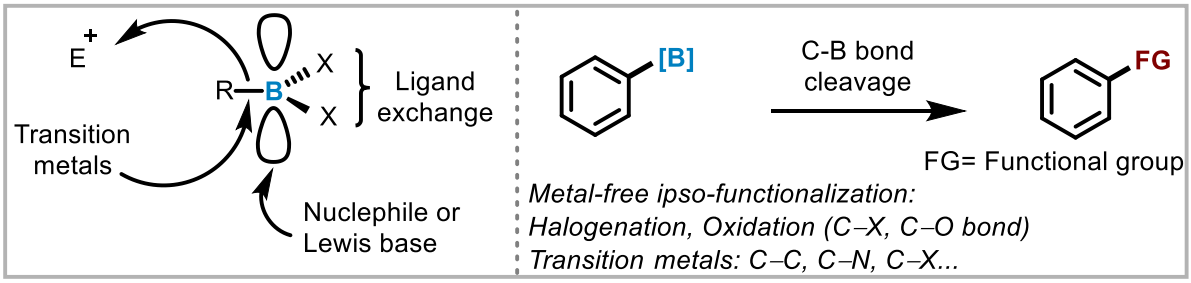


Figure 5. Activation modes and applications of organoboron compounds.

2.2.1. Boron-Containing Drugs

The approval of boron-containing drugs has marked a significant milestone in medicinal chemistry, demonstrating the versatility and therapeutic potential of boron-based compounds. Over the past 20 years, five FDA-approved drugs have entered the market, showcasing the utility of boron in diverse therapeutic areas (**Figure 6**).[14,15, 27]

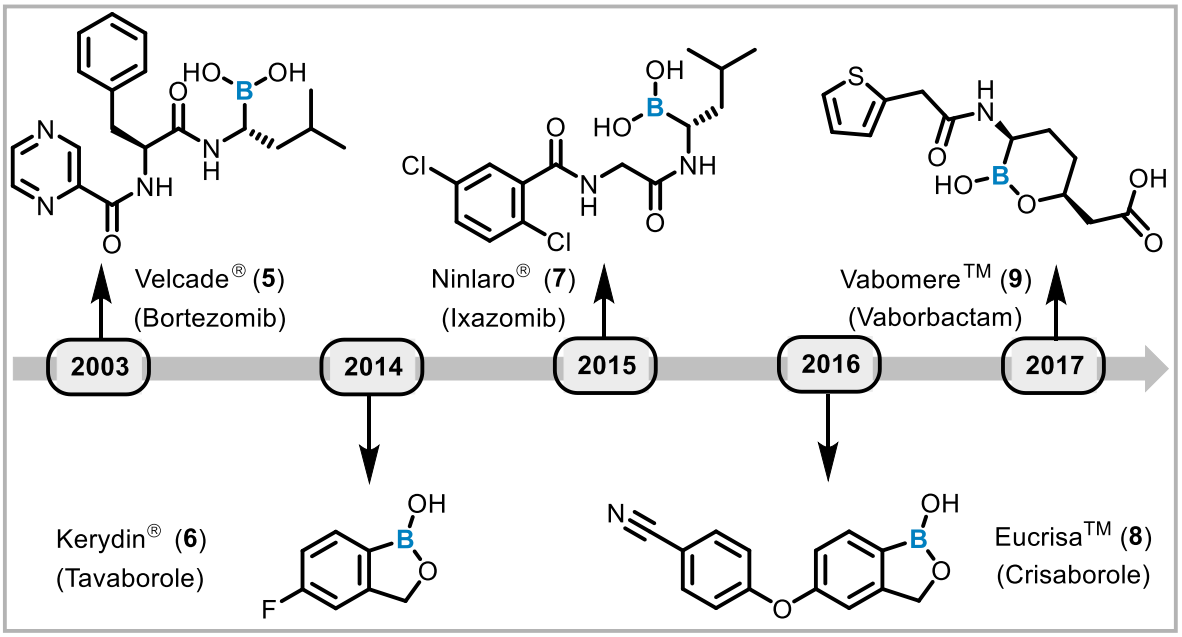


Figure 6. FDA-approved boron-containing drugs: Timeline and molecular structures.

Bortezomib (Velcade) (**5**) was the first boron-containing drug approved by the FDA in 2003 and the European Medicines Agency (EMA) in 2004 (**Figure 6**). This boronic acid-based proteasome inhibitor is used in the treatment of multiple myeloma and remains a landmark in the field. Tavaborole (Kerydin) (**6**), approved in 2014, is a borole-based topical antifungal treatment for onychomycosis. Following this success, Ixazomib (Ninlaro) (**7**), a boronic acid dipeptide with similar structure and mechanism of action to bortezomib, gained FDA approval

in 2015 and EMA approval in 2016. Its oral bioavailability provided an advantage in terms of patient compliance. This was followed by Crisaborole (Eucrisa) (**8**) in 2016, another borole compound used as a topical treatment for eczema. In 2017, Vaborbactam (Vabomere) (**9**) was approved as a cyclic boronic acid-based β-lactamase inhibitor. Used in combination with meropenem, it offers a novel approach to treating bacterial infections, including urinary and abdominal infections.[14,15, 27]

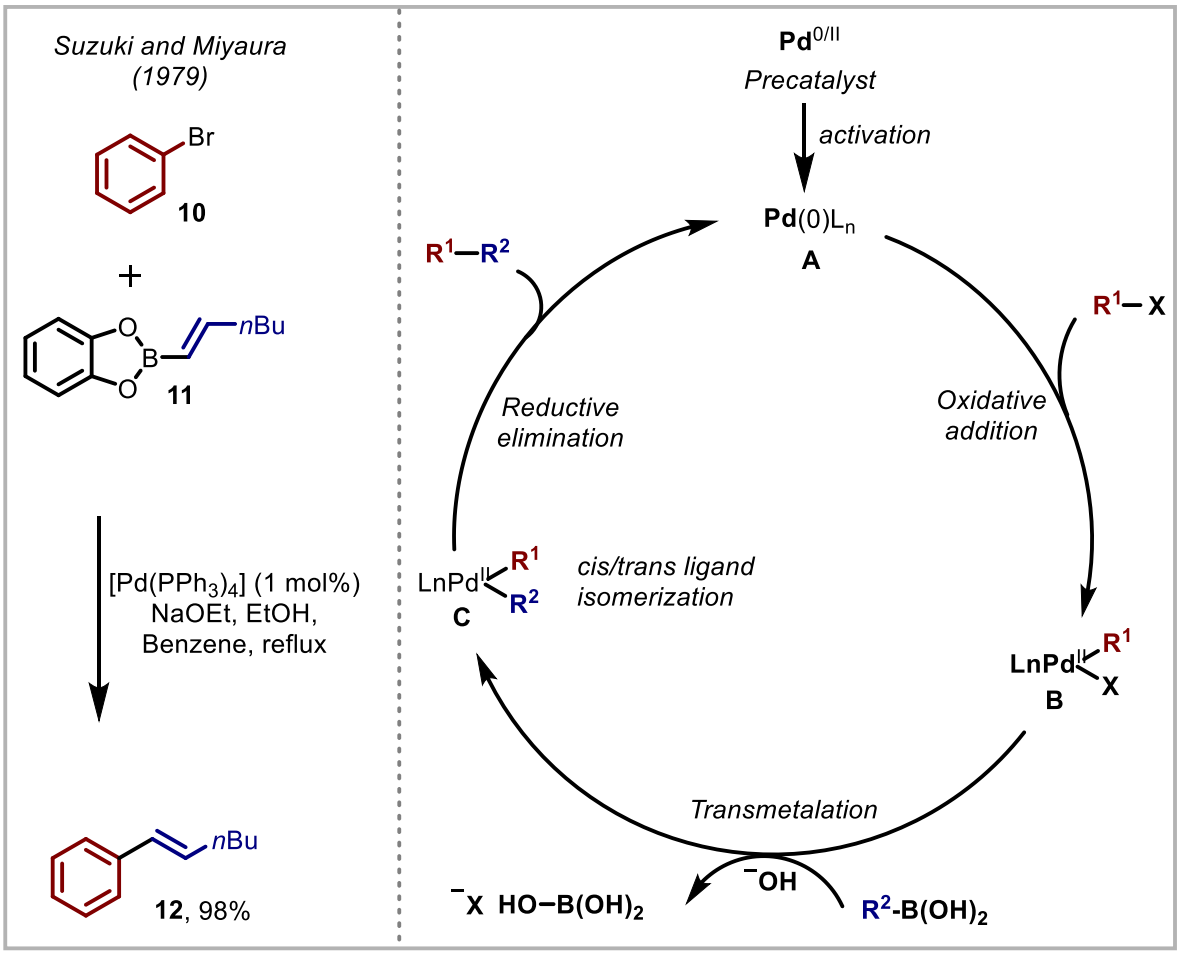
The success of these boron-containing drugs highlights their versatility and growing significance in drug discovery, with numerous boron-based compounds currently undergoing clinical trials as anticancer, antiviral, antibacterial, and anti-infective agents, reinforcing their role as a vital class of therapeutic molecules,[27] while **Chapter 5** introduces new boron species that are bench-stable and easy to prepare.

2.2.2. Transition-Metal Catalyzed C–C Bond Formation: Suzuki-Miyaura Coupling

The SM coupling reaction, a hallmark of modern organic synthesis, was developed by Akira Suzuki in 1979 following his postdoctoral work with H. C. Brown. Suzuki's innovative contribution was the palladium-catalyzed cross-coupling of 1–alkenylboranes with aryl halides, which harnessed boronic acids as nucleophilic partners in C–C bond formation (**Scheme 1**).[22b] While early evidence of boronic acid reactivity in cross-coupling was reported by Richard Heck[28] in 1975, it was Suzuki's demonstration of catalytic efficiency that transformed this reaction into a widely adopted methodology. This groundbreaking work contributed to the Nobel Prize in Chemistry awarded in 2010 to Heck, Suzuki, and Negishi for their collective advancements in palladium-catalyzed cross-coupling chemistry.[6,8,9,10a]

Over time, the reaction has evolved to accommodate more specialized conditions and reagents. Modifications of organoboron compounds, such as Genêt/Molander's potassium organotrifluoroborates[12] (BF_3K salts) and Burke's MIDA boronates,[29] have facilitated milder and more selective coupling reactions. These innovations have expanded the scope and efficiency of the SM reaction, making it a preferred method for constructing complex molecular frameworks.[17] In **Chapter 4**, we continue this exploration by developing SM coupling on new boron species, further advancing the field of organoboron reagents.

The SM reaction proceeds through a Pd(0)/Pd(II) catalytic cycle, involving three fundamental steps:[11] oxidative addition, transmetalation, and reductive elimination (**Scheme 1).** The cycle begins with the oxidative addition of the electrophilic aryl halide or pseudohalide to a coordinatively unsaturated Pd(0) catalyst. This step forms a Pd(II) complex with an aryl-Pd bond (**B**). In the subsequent transmetalation step (**C**), the nucleophilic organoboron species transfers its organic moiety to the Pd-center, facilitated by a base that activates the boronic acid. Finally, reductive elimination occurs (**D**), coupling the two organic fragments and regenerating the Pd(0) catalyst to complete the cycle.



Scheme 1. The Suzuki-Miyaura cross-coupling reaction and its generic mechanism.

This unparalleled versatility of the SM coupling has not only made it a cornerstone of academic research but also a pivotal tool in industrial-scale synthesis (**Figure 7**).[11] Its mild reaction conditions, functional group tolerance, and ease of scalability have enabled its widespread adoption in the pharmaceutical and agrochemical industries. For instance, boronic acids play a key role in the synthesis of BASF's multipurpose fungicide, Boscalid (**13**), which represents one of the largest-scale applications of this reaction, producing over 1000 tonnes annually. Similarly, Merck utilized this methodology for the construction of the biaryl motif in their antihypertensive drug, Losartan (**14**), highlighting the reaction's critical role in the development of life-saving drugs.

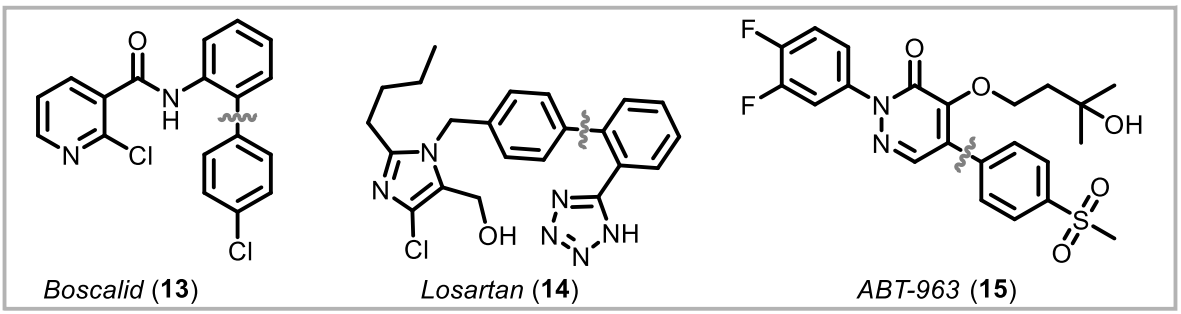
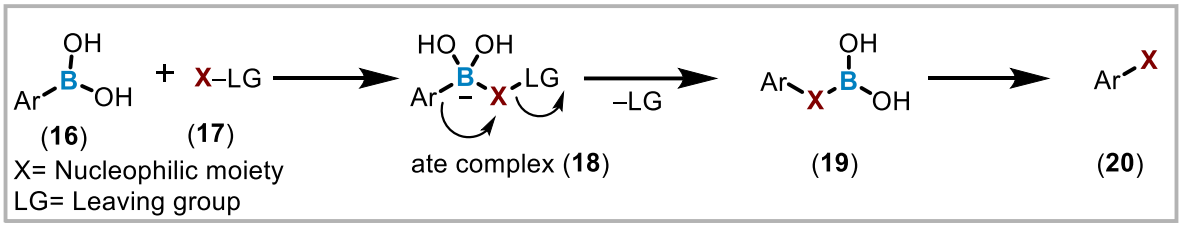


Figure 7. Industrial applications of Suzuki–Miyaura coupling in large-scale synthesis.[11]

2.2.3. Transition-Metal Free *Ipso*-Functionalization

Transition-metal-free *ipso*-functionalization has emerged as an efficient and sustainable approach for modifying organoboron reagents, eliminating the need for precious metal catalysts.[21,25,26] This methodology leverages the intrinsic reactivity of boron reagents to achieve selective transformations. The process involves the activation of the boron center through nucleophilic interaction, facilitating the substitution of the boronic group with various functional groups such as halides, hydroxyls, and amines.[25]

In organoboronic acids, the sp^2-hybridized boron atom features a vacant *p*-orbital, rendering it Lewis acidic (**Scheme 2**). When a nucleophile (X–LG, **17**) or Lewis base interacts with boron, it forms a tetravalent "ate" complex (**18**), causing the boron atom to rehybridize from sp^2 to sp^3. This rehybridization increases electron density on boron and induces steric strain in the complex. These factors facilitate the cleavage of the Ar–[B] bond, resulting in aryl migration to the adjacent acceptor atom (**19**).



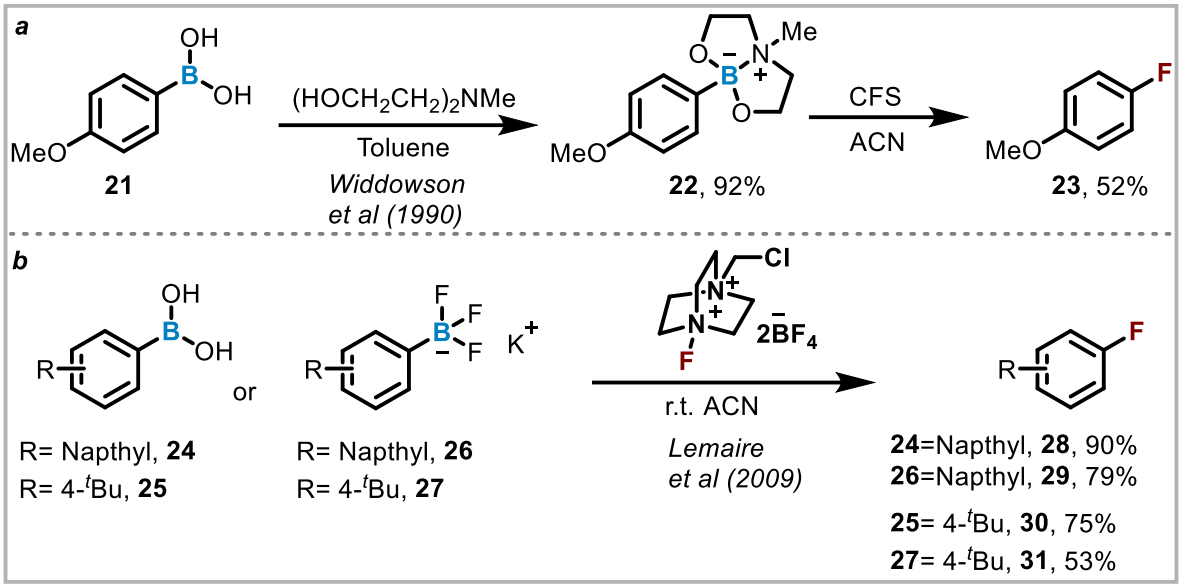
Scheme 2. General strategy for transition metal-free functionalization of organoboronic acid.[25]

2.2.3.1. Carbon–Halogen (F, Cl, Br, I) Bond Formation

Aryl halides are widely utilized as versatile synthetic intermediates for constructing carbon–carbon and carbon–heteroatom bonds.[(10)] The selective introduction of aryl–halogen bonds into complex polyfunctional molecules remains a significant and challenging area of research. Among various approaches, halodeboronation of arylboronic acids offers a practical method for synthesizing aryl halides.[(25, 30)] The transition-metal-free fluorodeboronation of arylboronic acids was pioneered by Widdowson and co-workers,[(31)] employing cesium fluoroxysulfate ($CsSO_4F$, abbreviated as CFS) as the fluorinating agent (**Scheme 3a**). Boronic acid (**21**) was first converted into diethanolamine ester (**22**), as this intermediate provided enhanced stability and improved yield (**22**). Subsequent treatment of the **22** with CFS produced aryl fluorides (**23**), albeit in low to moderate yields for electron rich and electron-deficient substrates. To minimize side reactions involving single-electron transfer, catalytic amount of 1,3–dinitrobenzene was added to the reaction. However, even with this modification, the yields were not significantly improved.[(31)]

Next, Lemaire and co-workers[(32)] developed a Selectfluor-mediated method for the *ipso*–fluorination of arylboronic acids (**24-25**) and trifluoroborates (**26-27**), achieving moderate to good yields at room temperature (**Scheme 3b**, **28-31**). However, the method showed significant limitations, including incompatibility with electron-deficient substrates and protodeboronation was observed as a competing side reaction, further highlighting the

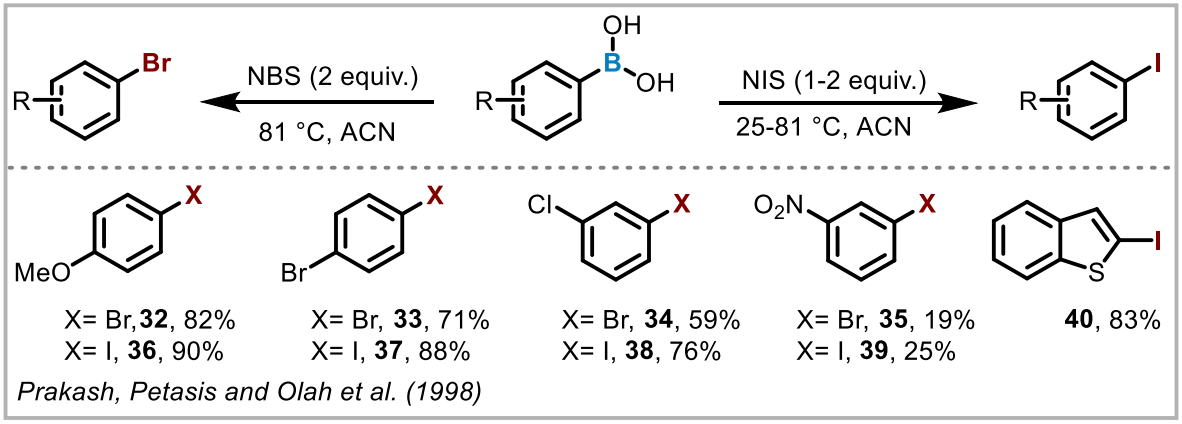
challenges in developing a broadly applicable, transition-metal-free fluorination approach for arylboronic acids.



Scheme 3. Fluorination of arylboronic acids and trifluoroborates with CFS and Selectfluor.

Prakash, Petasis, and Olah reported the mild *ipso*-bromination and iodination of arylboronic acids using *N*–halosuccinimides (NBS and NIS), offering a practical and efficient approach to halogenated arenes (**Scheme 4**).[33] In the presence of NIS, a broad range of arylboronic acids, including those with electron-donating groups and halogens, were successfully converted into iodoarenes with moderate to good yields (**Scheme 4**, **32-35**). Sulfur-containing heterocycles (**40**) were also well-tolerated, yielding the corresponding iodoarenes.

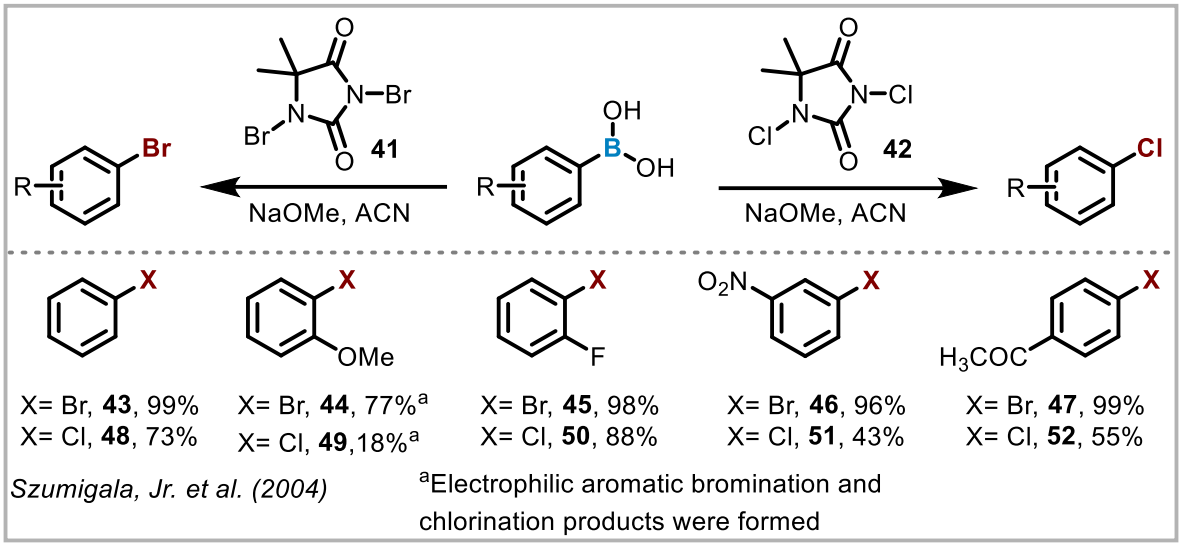
Similarly, bromination of arylboronic acids using NBS provided bromoarenes under mild conditions (**Scheme 4**, **36-39**).[33] However, substrates with strong electron-withdrawing nitro group, exhibited lower yields for both bromination and iodination, highlighting a limitation of the method.



Scheme 4. *Ipso*-bromination and iodination of arylboronic acids using NBS and NIS.

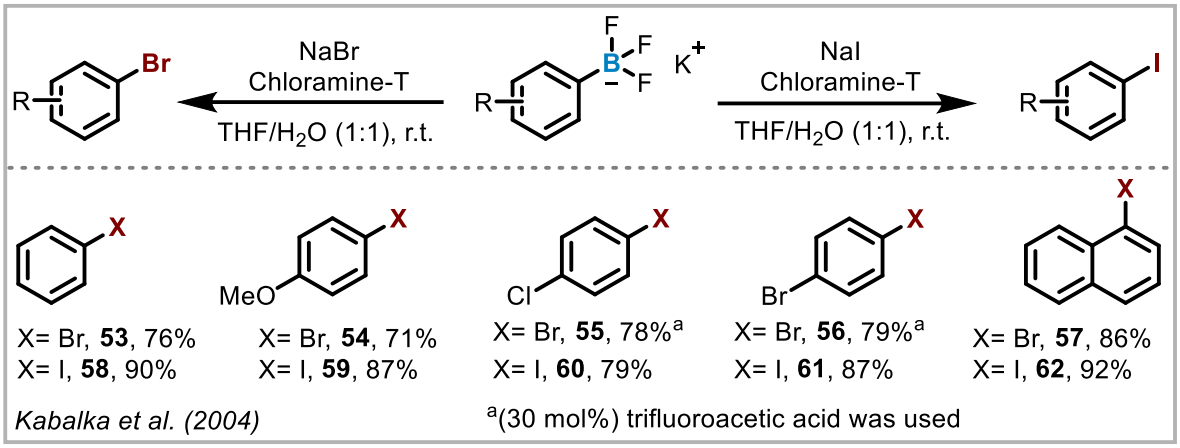
An efficient method for the *ipso*-halogenation of arylboronic acids, providing access to bromoarenes and chloroarenes, was later developed. Using 1,3–dibromo–5,5–dimethylhydantoin (DBDMH) (**41**) as the brominating reagent and catalytic sodium methoxide,

arylboronic acids were converted into bromoarenes with excellent yields (**Scheme 5**).[34] Notably, nitro-substituted boronic acids, which typically underperform in similar reactions, achieved an impressive 96% yield under these conditions. This approach was extended to the chlorination of arylboronic acids using 1,3–chloro–5,5–dimethylhydantoin (DCDMH) (**42**) (**Scheme 4**).[34] However, yields for chlorinated products were generally lower and more variable. Substrates with strong electron-donating groups, such as methoxy, resulted in a mixture of products due to competing electrophilic aromatic substitution.



Scheme 5. *Ipso*-bromination and chlorination of arylboronic acids using DBDMH and DCDMH.

Building on the advancements in *ipso*-halogenation, Kabalka and Mereddy extended the approach to aryltrifluoroborates, enabling their transformation into aryl bromides and iodides (**Scheme 6**).[35] The halogenating agent was generated *in-situ* by combining chloramine–T with sodium iodide for iodination or sodium bromide for bromination. Under these conditions, a variety of aryltrifluoroborates, including substrates with electron-rich, halogenated, electron-withdrawing groups and extended aromatics, were converted to iodoarenes at room temperature with good yields (**Scheme 6**, **53-57**).[35] Similarly, bromination conditions proved effective for aryl–, heteroaryl–, alkenyl–, and alkynyltrifluoroborates, yielding the corresponding bromides with high efficiency. Notably, bromination of substrates bearing chloro (**55**) and bromo (**56**) groups required catalytic trifluoroacetic acid for the reaction to proceed to completion.



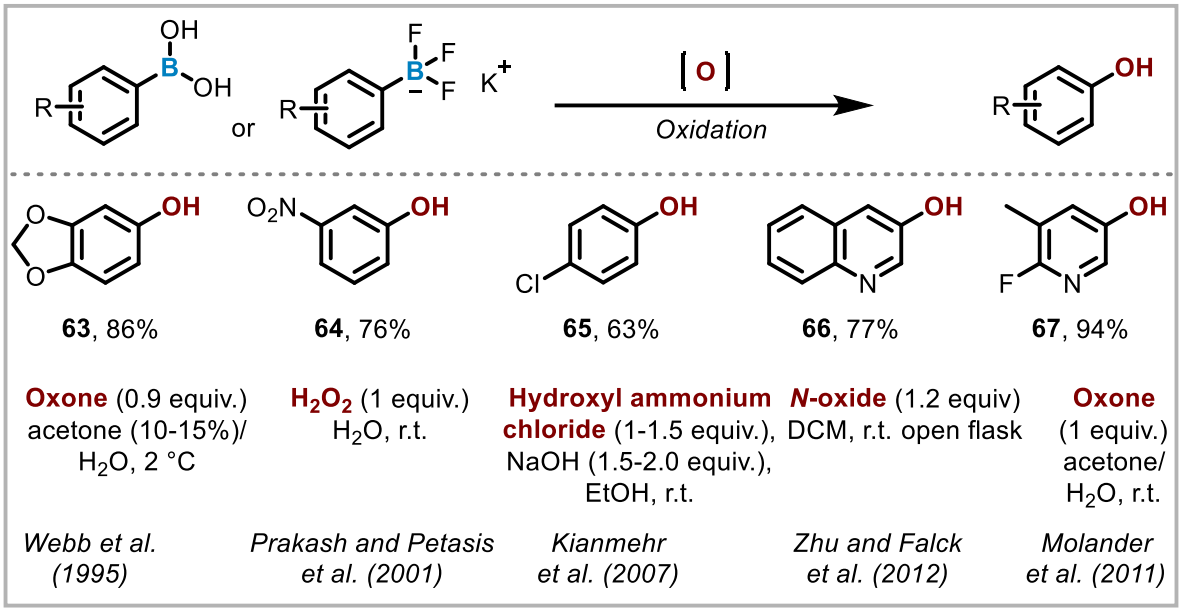
Scheme 6. *Ipso*-bromination and iodination of aryltrifluoroborates using NaBr and NaI.

2.2.3.2. Carbon–Oxygen Bond Formation

Phenols are crucial structural motifs in numerous natural products, pharmaceuticals, and polymers, as well as versatile intermediates for synthesizing complex molecules.[36] Developing practical methods for accessing polyfunctionalized phenols is therefore highly valuable. Transition-metal-free *ipso*-hydroxylation of arylboronic acids offers a mild and efficient route to phenols, often difficult to achieve through alternative methods.[25] Initial studies by Ainley and Challenger,[37] followed by Hawthorne,[38] demonstrated the conversion of phenylboronic acids to phenols using alkaline hydrogen peroxide or hydrogen peroxide, albeit with low to moderate yields. Decades later, this transformation was further explored, leading to numerous modifications that improved functional group compatibility and overall practicality (**Scheme 7**).

In 1995, Webb and Levy[39] reported the oxidation of arylboronic acids to phenols using potassium monopersulfate, commercially known as Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), in 10–15% aqueous acetone at 2°C. Both electron-rich and electron-deficient substrates provided good yields (**Scheme 7**). The reaction's efficiency was enhanced by acetone as a co-solvent, likely due to the *in-situ* formation of dimethyldioxirane. Prakash, Petasis, and co-workers[40] systematically studied the oxidation of phenylboronic acids to phenols using 30% H_2O_2 achieving good yields across various substituted arylboronic acids. Further, hydroxylamine, generated *in-situ* from hydroxylammonium chloride and sodium hydroxide, was used for hydroxylation of arylboronic acids and pinacol esters, yielding phenols in moderate to good yields at room temperature.[41] However, electron-deficient substrates showed lower reactivity, with *para*-acetyl-substituted compounds failing entirely, and the reaction required 1–2 days to complete (**Scheme 7**). In 2012, Zhu and Falck reported a highly efficient *ipso*-hydroxylation of arylboronic acids using tertiary amine *N*–oxides.[42] This method was mild, rapid, and exhibited broad functional group tolerance, with applications extending to heteroarylboronic acids and other surrogates like boronate esters and trifluoroborates. Additionally, Molander and Cavalcanti investigated the transformation of potassium aryltrifluoroborates into phenols using Oxone in an acetone/water mixture.[43] This method efficiently produced phenols within minutes, delivering excellent yields across electron-rich,

electron-deficient, and neutral substrates. Notably, heteroaryl trifluoroborates also proved compatible, yielding heterocyclic phenols in high efficiency.



Scheme 7. Hydroxylation of arylboronic acids and aryltrifluoroborates.

To achieve selective deborylative functionalizations, selective borylation is crucial as it provides access to the desired products. The ability to control the borylation step directly influences the regioselectivity of subsequent functionalization. This demonstrates the importance of developing precise borylation strategies, which will be further discussed in the context of achieving selectivity in organic synthesis (**Section 3**).

3. Selectivity in Organic Chemistry

The concept of selectivity lies at the heart of organic chemistry, particularly in the field of organic synthesis, where the precise control of reaction outcomes is essential for the efficient creation of complex molecules.[44, 45] Selectivity refers to the preference of a chemical reaction to yield one specific product over others, whether by discriminating between two substrates or reacting selectively at specific sites within a single molecule. This approach is important for achieving high yields of desired products, minimizing by-products, and ensuring the environmental and economic efficiency of synthetic processes.[46]

Several types of selectivity govern organic reactions, each with its specific focus:

Chemoselectivity: The ability to target one functional group in a molecule while leaving others unaffected.

Regioselectivity: The preference for reaction at a specific position within a molecule, especially in the presence of multiple reactive sites.

Stereoselectivity: The selective formation of one stereoisomer over others, crucial for controlling three-dimensional molecular structures.

While biological systems achieve high selectivity through enzyme-mediated processes tailored for specific substrates, synthetic chemistry employs electronic and steric properties of molecules to predict and control selectivity. For example, regioselectivity in monosubstituted benzene derivatives often follows the electronic effects of substituents, such as *ortho*-, *meta*- or *para*- preferences. Similarly, steric hindrance and sterically bulky catalytic reaction centers can direct reactivity to less hindered positions, further enhancing selectivity.[45, 47]

The demand for selective synthetic methodologies has risen significantly, driven by the need to produce pharmaceuticals, agrochemicals, and materials with specific properties while reducing waste and improving sustainability.[48] Selectivity not only ensures the efficient synthesis of desired compounds but also provides valuable mechanistic insights into reaction pathways and reactivity trends.

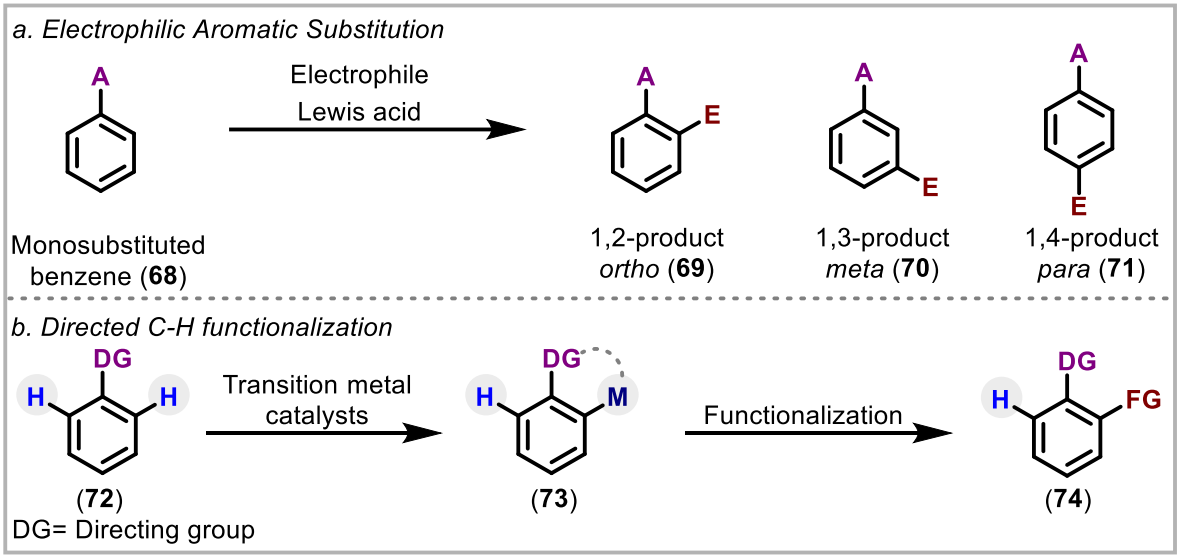
3.1. Strategies for Achieving Selectivity

3.1.1. Electrophilic Aromatic Substitution (EAS)

The functionalization of aromatic systems provides an ideal framework to explore selectivity in organic chemistry. Aromatic compounds, with their multiple reactive sites, present significant challenges in achieving regioselectivity. Two distinct approaches have been widely employed to address this: electrophilic aromatic substitution (EAS) and directing group assisted transition-metal-catalyzed reactions.

EAS relies on the inherent electronic and steric properties of the substrate to direct functionalization.[45] Substituents on the aromatic ring influence reactivity through resonance and inductive effects, guiding the reaction to *ortho*, *meta*, or *para* positions (**Scheme 8a**). For example, electron-donating groups enhance *ortho*/*para* selectivity, while electron-withdrawing groups favor *meta*-substitution.[45]

However, EAS has several limitations. First, the regioselectivity is often dictated by the existing substituents on the aromatic ring, limiting the flexibility to target non-preferred positions. Second, harsh reaction conditions, such as strong acids or high temperatures, are frequently required, which can lead to side reactions or decomposition of sensitive substrates.[49] Finally, achieving high selectivity in poly-substituted aromatic systems can be particularly challenging due to competing electronic and steric effects. These drawbacks highlight the need for alternative strategies, such as transition-metal-catalyzed methods, to overcome the limitations of traditional EAS.



Scheme 8. Strategies for achieving selectivity.

3.1.2. Directing Group-Assisted Transition-Metal-Catalyzed C–H Functionalization

The vast abundance of C–H bonds in organic molecules introduces significant challenges for achieving regioselectivity in synthetic transformations. A critical question for synthetic chemists has been: *how can specific C–H bonds be selectively activated within complex molecules containing multiple reactive sites*? To address this, directing group (DG)-mediated strategies have emerged as a powerful solution, enabling predictable and reliable functionalization at targeted C–H bonds.[50]

Directing groups orient catalysts toward specific sites by coordinating with the metal center, allowing selective activation of C–H bonds (**Scheme 8b**). This approach has employed both strongly coordinating atoms, such as nitrogen,[50b] sulfur,[50] and phosphorus,[51] and more weakly coordinating groups like ketones,[50ab] carbamates,[50b] aldehydes,[50ab] carboxylic acids,[50b] and ethers.[50c] These DGs have enabled selective *ortho*-functionalization of aromatic rings. The first instance of C–H bond activation involving a transition metal was reported in 1937 by Farkas and coworker, who described the catalytic exchange of benzene and D_2 on a platinum foil.[52] Directed C–H activation, however, gained traction after a breakthrough by Murahashi in 1955, who demonstrated cobalt-promoted C–H carbonylation of Schiff bases and azobenzenes via a five-membered cobaltacycle intermediate.[53] The subsequent Ru–

catalyzed *ortho*-alkylation of aromatic ketones, reported by Murai[54] and Chatani in 1993, popularized the directing group strategy for transition-metal-catalyzed C–H activation, which has since become a cornerstone of modern synthetic chemistry.

While directing groups provide excellent regioselectivity, their use is not without limitations. For instance, some natural products, pharmaceuticals, and complex molecules lack inherent directing groups, making their functionalization challenging.[55] Additionally, the presence of strongly coordinating nitrogen, sulfur, or phosphorus heteroatoms can compete with the directing group for catalyst binding, thereby hindering C–H activation or restricting it to bonds adjacent to these heteroatoms. Furthermore, in unsymmetrical molecules, competing C–H bonds can result in overfunctionalization or the formation of regioisomeric mixtures if reaction conditions are not carefully optimized.[55, 56] A significant drawback of these methodologies is their reliance on precious metals such as Pd, rhodium (Rh), and iridium (Ir), which are expensive, scarce, and environmentally concerning.[50,55] This reliance poses challenges for large-scale industrial applications, particularly in pharmaceutical synthesis, where traces of metals in the final product must be minimized to comply with stringent regulations.[48a]

Despite these challenges, directing group strategies remain essential in synthetic chemistry, offering remarkable control over site-selectivity in molecules. The continuous development of innovative directing groups and catalytic systems promises to expand the scope of C–H activation further, making it more robust and broadly applicable for complex molecular synthesis.

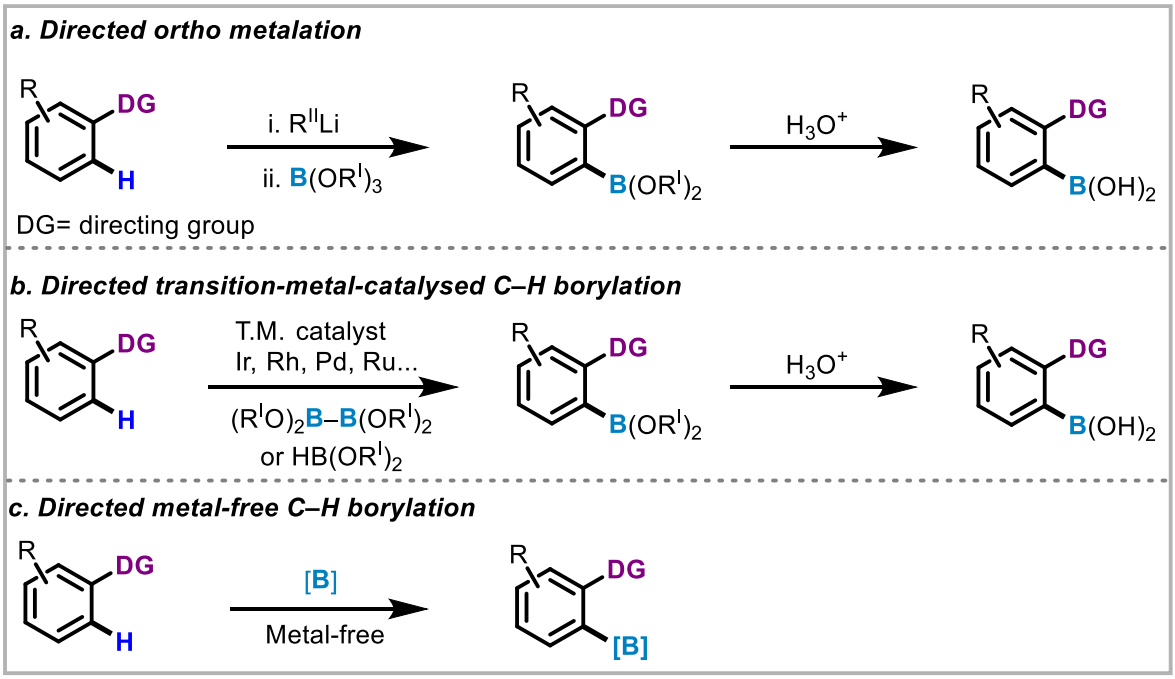
Following the discussion on selectivity in organic synthesis, it is important to highlight the role of boron chemistry in addressing these challenges. Boron-containing compounds, particularly arylboronic acids and esters, have become integral in modern synthetic methodologies due to their versatility and wide-ranging applications in pharmaceuticals, agrochemicals, and materials science.[9-11] The ability to selectively introduce boron into aromatic systems has been a cornerstone of advancements in functionalization strategies, offering tools for building complex molecular architectures with high precision. However, the synthesis of arylboron compounds remains an area of active research due to challenges in achieving regioselective functionalization, avoiding overfunctionalization, and developing sustainable methods that minimize environmental impact.

4. Strategies for the Selective Borylation

4.1 Directed *Ortho*-Metalation

One of the earliest and widely used approaches is the use of lithium–halogen exchange to generate reactive aryl–lithium intermediates, which are then quenched with boron electrophiles, such as trialkyl borates, to form boronic esters or acids.[2,14,15] Similarly, directed metallation,[57] particularly via lithiation,[2, 45] is a widely used strategy for introducing boron into the *ortho*-position of functionalized arenes (**Scheme 9a**).[58] Arenes functionalized with coordinating *ortho*-directing groups such as amines, ethers, anilides, esters, and amides are particularly well-suited to this approach, enabling the generation of arylmetal intermediates that can be trapped with borate esters to yield boronic acids or esters.[2, 58] This method has been generalized to a broad range of substrates, providing enhanced regioselectivity and facilitating access to a diverse array of boron-containing compounds.

Despite their widespread use, traditional methods for boron installation via directed metallation exhibit significant limitations.[58] Organolithium-based approaches require cryogenic conditions (−78°C to −40°C) to stabilize highly reactive intermediates, increasing operational complexity and cost. Functional group compatibility is often poor due to the harsh reactivity of organolithium, limiting substrate scope. Furthermore, the use of hazardous organolithium reagents poses safety challenges, particularly in large-scale industrial applications. These drawbacks have prompted the development of alternative catalytic methodologies.



Scheme 9. Strategies for directed C–H bond borylation: a. Directed *ortho*-metalation. b. Directed transition-metal-catalyzed C–H borylation. c. Directed metal-free C–H borylation.

4.2. Directed Transition Metal-Catalyzed C–H Borylation

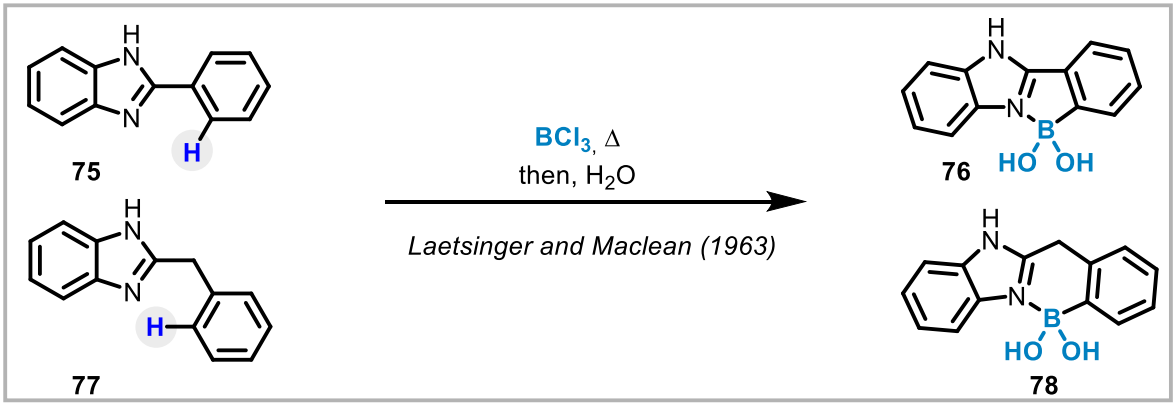
Directed transition metal-catalyzed C–H borylation is a highly efficient method for incorporating boron into aromatic systems, offering streamlined access to valuable organoboron compounds (**Scheme 9b**).[59, 60] While Ir-catalysts[59b, 60] are widely employed due to their high reactivity, other late transition metals, such as ruthenium (Ru), Rh, Pd, and rhenium (Re) have also been explored.[59] Initially, these reactions relied heavily on expensive and scarce noble metals. However, the development of first-row transition metal catalysts, including copper (Cu), iron (Fe), cobalt (Co), and nickel (Ni), has provided cost-effective and environmentally friendly alternatives.[61] The reliance on precious-metal catalysts with ligands limits large-scale synthesis and requires the removal of toxic metal traces in pharmaceuticals.[48a, 50, 55]

4.3. Directed Metal-Free C–H Borylation

A transition-metal-free approach to C–H borylation provides a practical and sustainable alternative, eliminating the need for expensive and toxic metal catalysts. Similar to metal-catalyzed borylation, directing groups have been extensively utilized in metal-free systems to achieve regioselective functionalization (**Scheme 9c**).[63] By leveraging pre-installed coordinating moieties, these strategies enable precise control over borylation site selectivity, addressing a key challenge in metal-free transformations. Among these approaches, BX_3-mediated C–H borylation has emerged as a powerful method, utilizing the strong Lewis acidity of boron trihalides (BX_3= BCl_3, BBr_3) to facilitate regioselective C–B bond formation.[63bc]

4.3.1. BX_3 Directed C–H Borylation

This section explores the development, mechanistic insights, and synthetic applications of BX_3-mediated C–H borylation, with a particular emphasis on BBr_3 as a key reagent in this transformation.

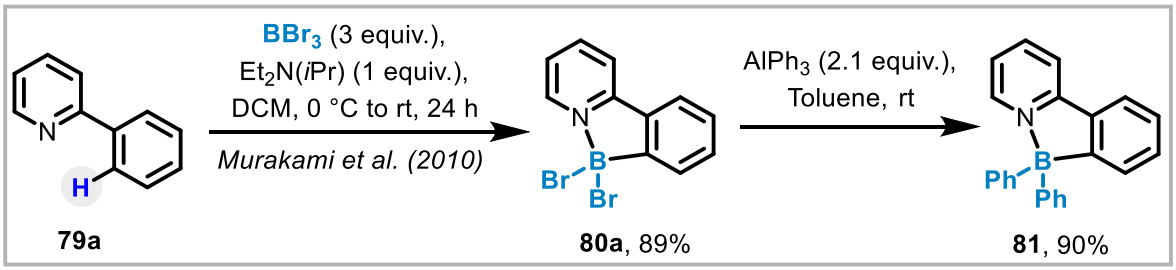


Scheme 10. Early directed C–H borylation with benzimidazole.

The first breakthrough in directing-group-assisted metal-free C–H borylation was reported by Letsingerand Macleanin,[64] demonstrating the *ortho*-borylation of compounds **75** and **77** using a benzimidazole moiety as a directing group (**Scheme 10**). This approach enabled high levels of regioselectivity, establishing a foundation for future developments in the field.

However, the reaction typically required harsh conditions, including temperatures up to 300°C and the use of BCl_3 gas, which limited its practicality.

In 2010, Murakami and co-workers reported that a pyridine ring can act as a chelating group in the electrophilic C–H borylation of 2–phenylpyridines (**79a**) with BBr_3, forming a pyridine–dibromoborane complex **80a** (**Scheme 11**).[65] This strategy was further extended to the borylation of quinoline and pyrimidine derivatives, as well as the one-pot diborylation of 1,4-di–(2–pyridyl)benzene, demonstrating its broad applicability.[65] The resulting dibromoborane complex serves as a versatile intermediate, as the bromo groups can be readily replaced with hydrogen or carbon substituents using organometallic reagents. For instance, the reaction of **80a** with $AlPh_3$ efficiently yields the tetracoordinated triaryl borane **81**, a key structure in materials science.[63, 66, 67]

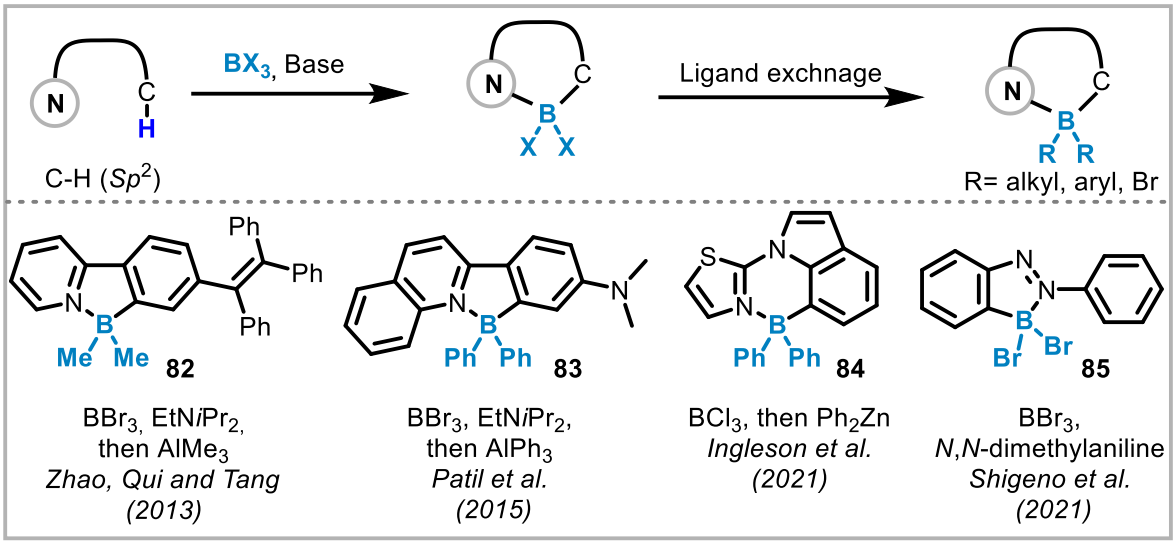


Scheme 11. Pyridine-assisted electrophilic C–H borylation of 2–phenylpyridine.

Given the importance of aza–π–conjugated systems in organic materials chemistry, research in recent years has focused on expanding this method for the synthesis of related functional materials using directed electrophilic C–H borylation under metal-free conditions (**Scheme 12**).[63b] In 2013, Zhao[66] and colleagues reported the synthesis of tetraphenylethene-based N,C-chelated four-coordinate organoboron compounds (**82**) utilizing pyridine or quinoline as directing groups. The reaction involved electrophilic aromatic borylation of 2–bromopyridine and 2–bromoquinoline derivatives with boron tribromide (BBr_3) under basic conditions. This process yielded the corresponding pyridine- and quinoline-dibromoborane complexes. These intermediates were subsequently converted to their dimethyl variants (**82**) via ligand exchange on boron using trimethylaluminum ($AlMe_3$) (**Scheme 12**). Similarly, Patil and coworkers[67] prepared a series of highly emissive molecular solids derived from *N*,C–chelated four-coordinate organoboron compounds (**83**). In these systems, the dibromoborane intermediates were modified by introducing various alkyl and phenyl groups through ligand exchange at the boron center. This approach significantly broadened the structural diversity of these organoboron derivatives.

Further expanding the scope of directed C–H borylation, Ingleson[68] and co-workers demonstrated that the C7–borylation of indoles can be achieved using a thiazole group (**84**) as a directing group, leading to the synthesis of important chromophores (**Scheme 12**). More recently, an azobenzene-directed *ortho*-C–H borylation was reported, yielding compound **85**, which was further cyclized via a Grignard reaction to produce a 1,2,3-benzodiazoborole compound.[69] The use of nitrogen as a directing group has significantly expanded the scope of this chemistry, allowing access to a wide range of scaffolds. These developments are

comprehensively discussed in Chatani's review,[63b] which provides a detailed overview of the progress and potential applications in this rapidly evolving field.

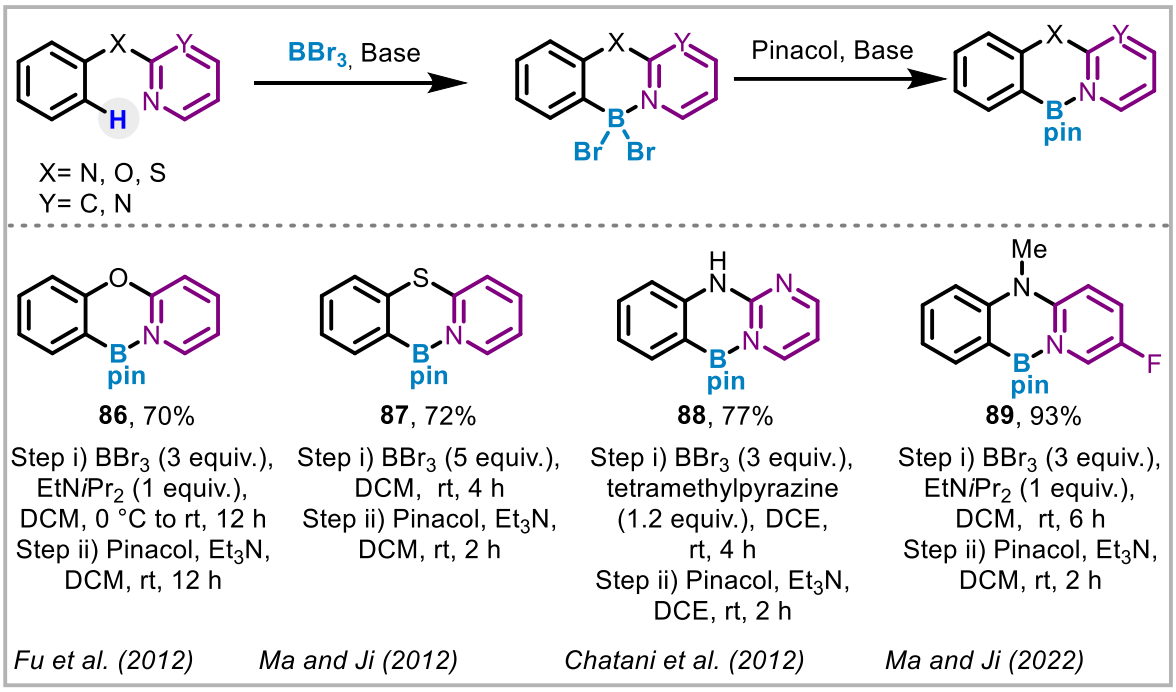


Scheme 12. Nitrogen-directed electrophilic C–H borylation and ligand exchange.

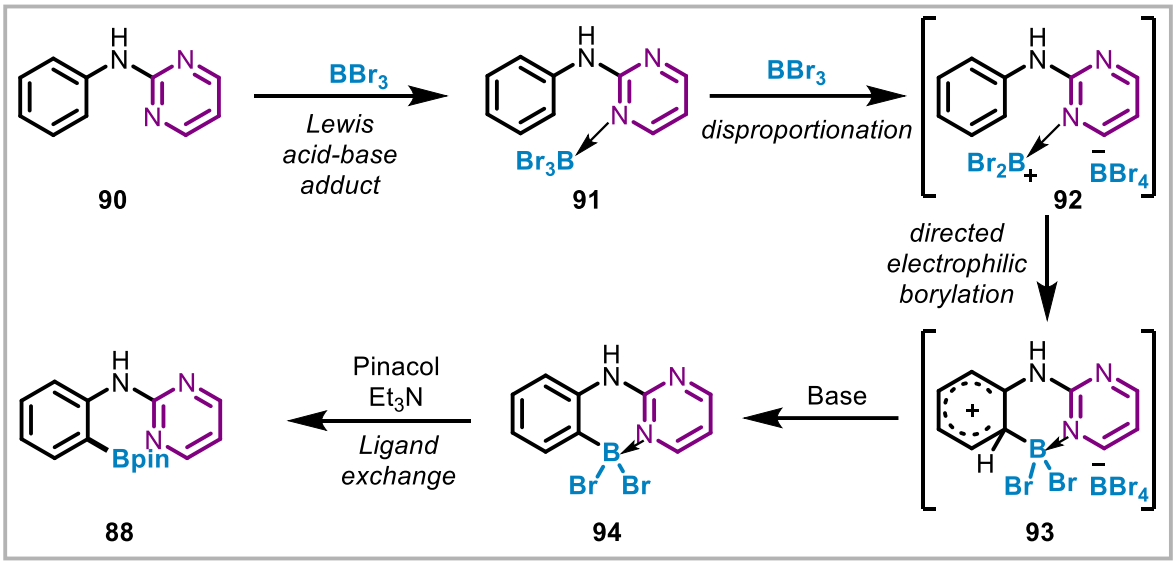
4.3.1.2. Nitrogen Directed Borylation with BBr_3

Murakami[65] and co-workers' pioneering work on the C–H borylation of 2–phenylpyridines demonstrated the exceptional ability of the pyridine moiety to act as a directing group in BBr_3 directed borylation reactions. This discovery laid the foundation for further research, prompting the exploration of pyridine and pyrimidine as versatile and removable directing groups in C–H functionalization chemistry. Building on this concept, Fu[70] and co-workers showcased its practical application by developing an efficient borylation of 2–phenoxypyridine using BBr_3, where the pyridine group played a crucial role in directing the transformation (**Scheme 13**, **86**). The resulting C–B bond was subsequently functionalized, and the directing group was efficiently removed to access functionalized phenol, highlighting the synthetic utility this strategy.

The selective *ortho*-C–H borylation of 2–phenylthiopyridines was also reported by Ma, Ji, and co-workers[71] (**Scheme 13**, **87**), with the resulting boronates undergoing Cu-catalyzed bromination, chlorination, and amination to demonstrate post-functionalization. More recently, Chatani[72] and co-workers developed a pyrimidine-directed electrophilic *ortho*-C–H borylation of 2–pyrimidylanilines (**88**), enabling the synthesis of boronates and four-coordinated triarylborane derivatives. Notably, this metal-free method operates efficiently without interference from inorganic salts, reactive functionalities, or transition-metal impurities, further highlighting its synthetic utility. Expanding on this work, Ma, Ji, and co-workers[73] further broadened the scope of *ortho*-C–H borylation by developing a method for 2–(*N*–methylanilino)–5–fluoropyridines (**89**) and 2–benzyl–5–fluoropyridines, utilizing BBr_3 as the borylating reagent and a pyridine derivative as the directing group.



Scheme 13. Nitrogen-directed electrophilic C–H borylation.

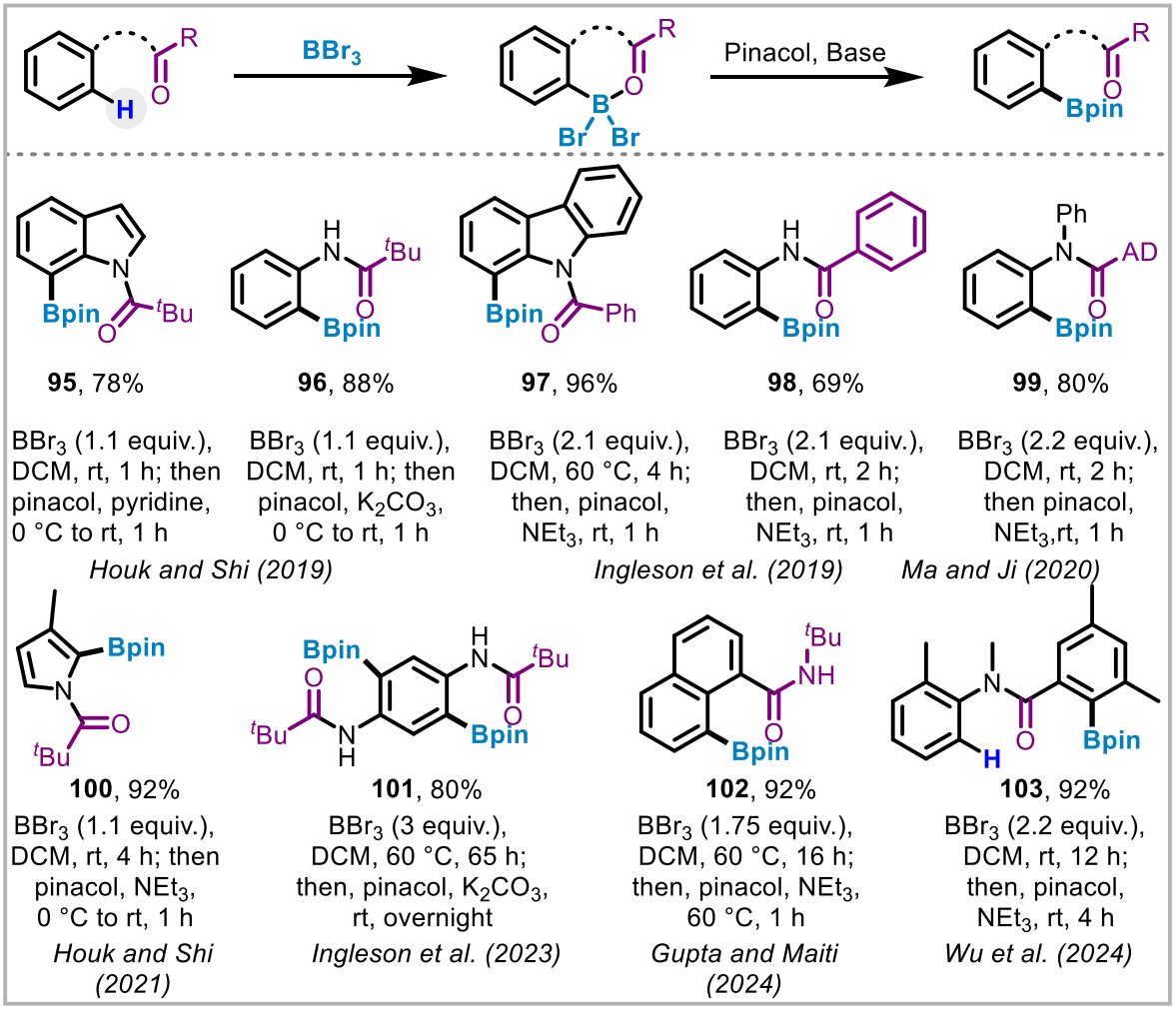


Scheme 14. Proposed mechanism for directed C–H borylation of 2-pyrimidylaniline.

The proposed mechanism for the *ortho*-C–H borylation of 2–pyrimidylanilines[72] is outlined in **Scheme 14**. Initially, a Lewis acid–base adduct forms between BBr_3 and the pyrimidyl nitrogen in **90**, facilitating activation (**91**). Subsequent bromine transfer to another BBr_3 molecule generates a highly reactive borenium species (**92**). Due to the electrophilic nature of the aniline ring in **91**, an electrophilic aromatic substitution (EAS) occurs, leading to the formation of an intermediate (**93**). Deprotonation by a base result in the formation of the complex (**94**), which, upon quenching with pinacol and triethylamine, yields the desired Bpin product (**88**). These findings highlight the efficiency of BBr_3-mediated electrophilic borylation, where the formation of a borenium species and directing group play a crucial role in enabling regioselective C–H functionalization.

4.3.1.3. Carbonyl (Oxygen) Directed Borylation

While nitrogen-based directing groups have proven effective in guiding regioselective C–H borylation, the use of carbonyl as a directing group has emerged as a powerful alternative (**Scheme 15**). Carbonyl groups not only enhance the electrophilicity of boron reagents but also provide additional stability through coordination, enabling precise functionalization. In 2019, Ingleson[74] and Houk/Shi[75] independently developed carbonyl-directed electrophilic C–H borylation employing BBr_3 as the exclusive reagent (**Scheme 15**). This approach enabled the selective C7–borylation of *N*–acylated indoles (**95**) and the *ortho*-C–H borylation of *N*–acyl aniline derivatives (**96**, **98**) and *N*–acyl carbazoles (**97**) with excellent yields. Houk/Shi further demonstrated the versatility of the resulting boron intermediates, employing them in post-functionalization reactions such as azidation, alkylation, hydroxylation, and SM coupling, broadening the scope of downstream transformations.



Scheme 15. Carbonyl (oxygen) directed electrophilic C–H borylation. (AD-Adamantyl).

Building on these findings, Ma, Ji, and co-workers[76] extended this strategy to the *ortho*-C–H borylation of diphenylamines using an adamantane–1–carbonyl (AD) directing group (**99**). The efficacy of carbonyl groups in guiding regioselectivity was further reinforced by Houk and Shi's[77] prior work, which demonstrated the successful C2–borylation of *N*–pivaloylpyrrole

(**100**). Notably, achieving site selectivity in pyrrole functionalization remains challenging, particularly in C3-substituted derivatives where competition between the C2 and C5 positions is a common issue. This study provided a significant advancement by demonstrating highly selective C2-functionalization in C3-substituted pyrroles, addressing a long-standing challenge in C–H activation strategies. In 2023, Ingleson and co-workers[78] reported a novel strategy utilizing amides as modifiable directing groups, where the amide functionality was reduced to an amine using hydrosilanes. This approach enabled a sequential one-pot electrophilic borylation-reduction process, which could subsequently be oxidized to the corresponding phenols (not depicted in the **Scheme 15**). Notably, the first example of diagonal diborylation was achieved on 1,4–dianilide (**101**), demonstrating remarkable selectivity for diagonal functionalization without the formation of side products (**Scheme 15**).

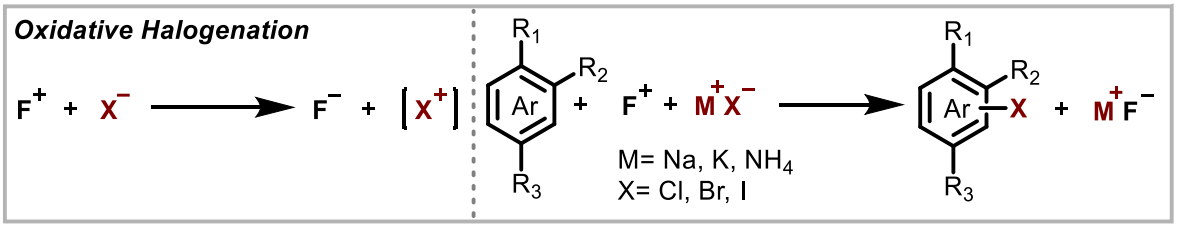
Expanding on Ingleson's earlier findings,[79] Gupta and Maiti[80] advanced this methodology to the borylation of α-naphthamides (**102**) and phenylacetic acid derivatives, including pharmaceutically relevant molecules. The successful borylation of drug compounds such as ibuprofen and indoprofen highlights the versatility and practical utility of this BBr_3 directed borylation strategy. Further advancing the field, Wu and co-workers[81] developed a chemoselective C−H borylation of *N*–phenylbenzamides, wherein borylation selectively occurred on the benzoyl moiety (**103**) rather than the aniline ring. This selectivity was attributed to the modulation of electron density, which facilitated the formation of a five-membered boracycle. By strategically increasing steric hindrance and fine-tuning electronic effects, the authors successfully directed borylation to the benzoyl ring.

Similar to nitrogen- and oxygen-based directing groups, phosphorus-[81] and sulfur-[82]containing functionalities have also been explored for BBr_3-directed C–H borylation, further expanding the scope of this strategy. These developments highlight the versatility of BBr_3 as a powerful reagent in directing group-assisted borylation, establishing it as a robust and broadly applicable approach for regioselective C–H functionalization.

By utilizing these directing groups, we have developed new chemistry, further expanding the scope of BBr_3-directed functionalizations (**Chapter 2**-**5**).

5. Oxidative Halogenation

Halogenation reactions play a crucial role in organic synthesis by providing halide intermediates essential for the preparation of various high-value compounds.[10, 83] Among these methods, oxidative halogenation has emerged as a powerful strategy for introducing halogen atoms into organic molecules under oxidative conditions, offering improved regioselectivity and controlled reactivity compared to traditional electrophilic halogenation.[84] Unlike direct halogenation, which often employs hazardous molecular halogens (e.g., Br_2, Cl_2), oxidative halogenation generates electrophilic halogen species (X^+) *in-situ* from halide salts (e.g., NaX, KX, TBAX) using an oxidizing agent.[84,85] This approach allows for greater selectivity, milder reaction conditions, and improved functional group compatibility compared to traditional electrophilic halogenation. The process typically involves the *in-situ* oxidation of halide anions (X^-) to electrophilic halogen species (X^+) (**Scheme 16**).[85]



Scheme 16. Mechanism of oxidative halogenation: *in-situ* generation of X^+ from X^-.[85a]

For instance, Selectfluor has been widely used to generate halonium (X^+) species, enabling selective halogenation of aromatic substrates (**Scheme 16**).[85a] The *in-situ* generation of X^+ allows for fine-tuning of reaction conditions, which enhances selectivity and minimizes unwanted side reactions, such as radical rearrangements or polymerization. Compared to reagents like NBS, which can produce uncontrolled Br_2 and lead to multiple bromination products, oxidative halogenation ensures a steady and controlled release of X^+, making it particularly advantageous for the selective halogenation of sensitive or complex substrates. Additionally, oxidative halogenation is more environmentally benign, as it avoids the use of toxic molecular halogens and reduces the formation of excess byproducts.[86] The concept and applications of oxidative halogenation will be further discussed in **Chapters 2** and **3**.

6. Aim of the thesis

The aim of this thesis is to develop boron-directed regioselective functionalization strategies by utilizing the unique reactivity of dibromoboracycles. The work is centered on expanding the synthetic utility of these boracycles for selective C–halogen, C–C, C–O and C–N bond formations, eliminating the need for pre-functionalized boron reagents.

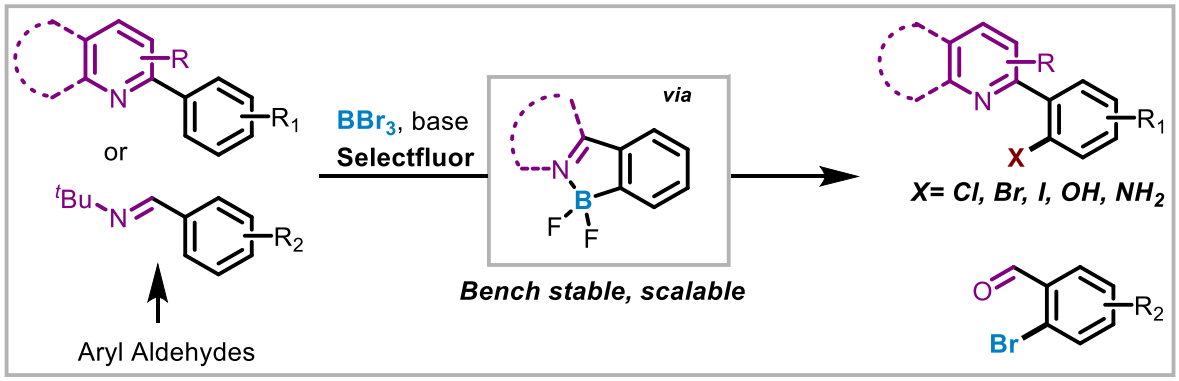
In **Chapters 2** and **3**, the goal is to develop an oxidative halodeboronation approach for regioselective *ortho*-halogenation of *N*–aryl amides, ureas, 2–aryl–*N*–heteroarenes, and aldehydes. By integrating BBr_3-directed borylation with oxidative halogenation, we aim to establish a metal-free, efficient, and selective method for *ortho*-halogenation.

Chapter 4 is focused on direct C–C bond formation using dibromoboracycles as a coupling partner, bypassing the conventional BBr_2-to-BPin transformation. The objective is to develop *ortho*-arylation and *ortho*-benzylation strategies for anilides, enabling access to valuable biaryl amides, diarylmethane amides, and dibenzoazepines. Additionally, the aim was to develop a diagonal-tetrafunctionalization of dianilides, which had not yet been explored and was not achievable using traditional methods.

In **Chapter 5**, we aim to develop stable boron reagents by designing a scalable and chromatography-free synthesis of aryl-difluoroborane (Ar–BF_2) compounds. This builds upon the intermediate observed in **Chapters 2** and **3**, where Ar–BF_2 species were identified as key intermediates in the oxidative halodeboronation process. Recognizing their potential, we sought to establish a multigram, scalable method for their synthesis, ensuring their practicality as versatile intermediates for late-stage functionalization.

Chapter 2

Oxidative Halodeboronation of 2-Aryl-*N*-Heteroarenes and Aldehydes



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This article was highlighted in Synfact, **2023**, *19*, 0554.

Author Contributions: H.S. supervised the project and oversaw all aspects of the research. G.H.S. discovered the reaction, performed the optimization studies, synthesized the substrate scope, and conducted all mechanistic investigations. Both H.S. and G.H.S. contributed to writing and editing the manuscript. H.S. served as the corresponding author.

Note: In this chapter, the reaction conditions have been adopted directly from above published work, without modification, to ensure consistency and accuracy in presenting the methodology.

1. Introduction

Achieving selective C–H functionalization in aromatic systems remains a significant challenge in organic synthesis. Developing regioselective strategies for such transformations is crucial, as it enhances efficiency, reduces byproduct formation, and simplifies purification by preventing regioisomeric mixtures.[55,56] In this work, we focus on the selective *ortho*-functionalization of 2–aryl–*N*-heteroarenes, a motif commonly found in various bioactive molecules (**Figure 1**). Given their broad synthetic and pharmaceutical relevance, these substrates serve as an excellent platform for exploring new C–H functionalization methodologies.

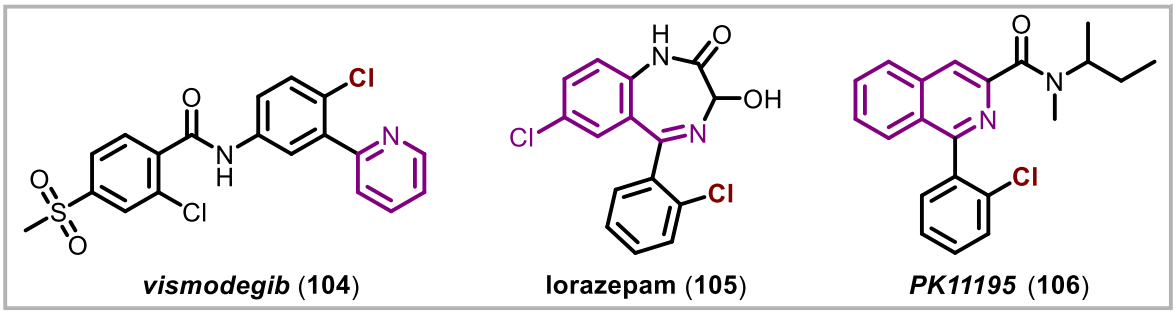
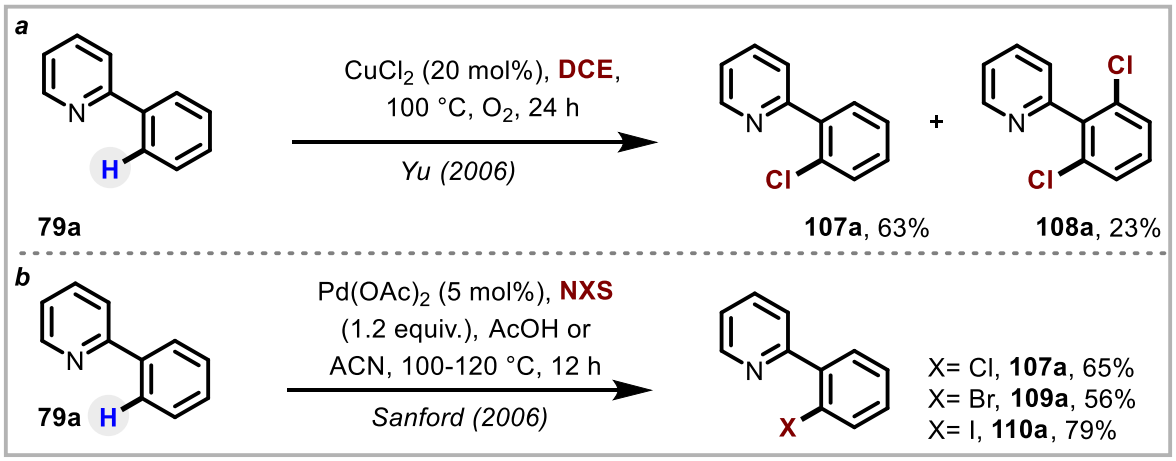


Figure 1. Biologically active *ortho*-substituted *N*-heteroarenes.

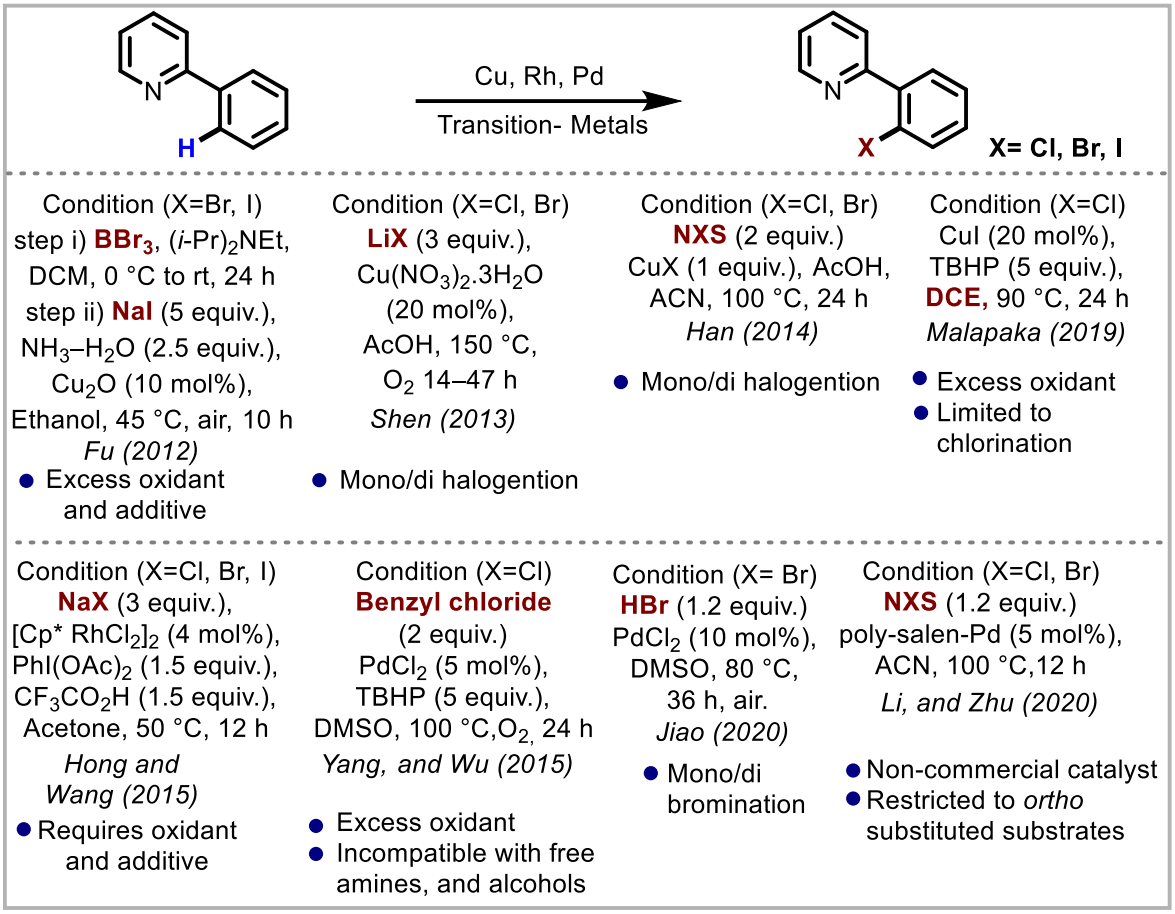
While direct regioselective aromatic C-H functionalization of 2–aryl–*N*-heteroarenes has been achieved using metal-based catalysts (Cu, Rh, Pd), these methods have predominantly targeted pyridine-based *N*-heteroarenes through nitrogen-directed chelation (**Scheme 1** and **2**).[87-101]



Scheme 1. Early reports on the *ortho*-halogenation of 2–arylpyridine.

For example, in 2006, Yu[87] reported a Cu-catalyzed chlorination protocol that employed 1,2–dichloroethane (DCE) as the chlorinating source; however, this method produced a mixture of mono- and di–chlorinated products (**Scheme 1**, **107a**-**108a**). In the same year, Sanford[88] introduced a mild Pd-catalyzed approach for the regioselective chlorination (**107a**), bromination (**109a**), and iodination (**110a**) of aromatic substrates. Inspired by these developments, Kakiuchi[89] later established a Pd-catalyzed chlorination protocol utilizing an

electrochemical oxidation strategy. Notably, when this method was applied to 2–phenylpyridine, exclusive dichlorination was observed.



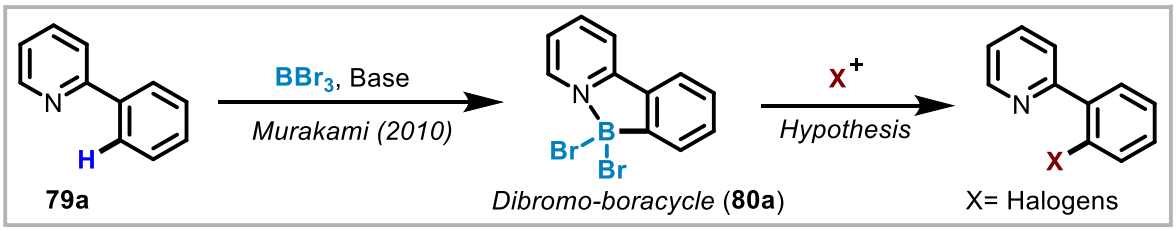
Scheme 2. State-of-the-art for the *ortho*-halogenation of 2–aryl pyridine.

Following the reports by Yu and Sanford, Fu[90] developed a method for the selective *ortho*-halogenation of 2–arylpyridines via sequential borylation and aerobic oxidative copper catalysis. In this protocol, boron tribromide (BBr_3) is used as the borylating reagent, while inorganic salts such as potassium iodide and ammonium bromide act as the halogen source (**Scheme 2**). Although the method affords good yields, it necessitates the use of excess oxidant and additional additives, which may limit its practicality. Similarly, Shen[91] and Han[92] developed Cu-catalyzed protocols employing LiX (X= Cl, Br) and NXS (X= Cl, Br) as halogenating reagents. However, these methods encountered challenges with regioselectivity, as they often produced mixtures of mono- and di-halogenated products. In addition, Han's protocol necessitates a stoichiometric amount of Cu to obtain the desired product. In 2018, Perumgani[93] et al. developed two Cu-catalyzed protocols for the *ortho*-halogenation of 2–arylpyridines, utilizing hypervalent iodine as both the halogenating reagent and oxidant. However, these methods require stoichiometric amounts of copper and hypervalent iodine, which limits their practicality for large-scale applications. Interestingly, Malapaka[94] reported that Cu-catalyzed *ortho*-chlorination of aryl pyridines can be achieved using excess *tert*–butyl hydroperoxide (TBHP) as the oxidant and DCE as the chlorinating reagent (**Scheme 2**). In 2015, Hong[95] and Wang reported a similar approach using hypervalent iodine in conjunction with a Rh-catalyst and sodium halide (X= Cl, Br, I) as the halogenating reagent, achieving excellent

yields. However, this method necessitates the use of oxidants and additives to facilitate the catalytic reaction, which may limit its practicality and functional group compatibility.
Pd has also been explored for the *ortho*-halogenation of 2–arylpyridine derivatives. Yang[96] and Wu developed a Pd-catalyzed protocol using benzyl chloride as the chlorinating reagent in the presence of an excess oxidant under an oxygen atmosphere (**Scheme 2**). However, the use of benzyl chloride can pose challenges when functional groups such as amines and alcohols are present, potentially leading to side reactions or reduced selectivity. Following this, Jiao[97] developed a protocol employing HBr as the brominating reagent; however, controlling regioselectivity remained a significant challenge in this method. To address regioselectivity issues, various synthesized Pd-precatalysts have been developed, including salen-based hypercrosslinked polymer-supported Pd catalysts,[98] Pd@MOF nanocatalysts,[99] and Pd(II) supported on polymers.[100] While these tailored catalysts aim to improve selectivity and efficiency, their preparation often involves additional synthetic steps, which can increase complexity and limit scalability.
Given the limitations of metal-catalyzed methods discussed in the literature (**Scheme 1** and **2**), it is clear that developing a metal-free, general approach for the *ortho*-halogenation of 2–aryl–*N*-heteroarenes would be highly valuable. Such a strategy would not only offer a more sustainable and cost-effective alternative but also address the challenges associated with metal catalyst requirements and regioselectivity issues.

2. Results and Discussion

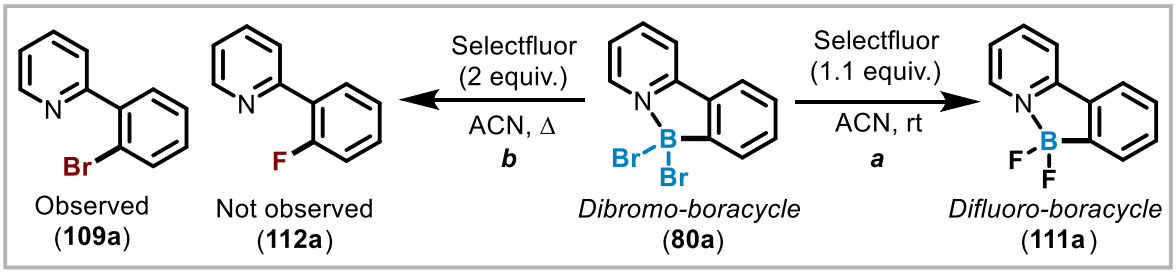
During the early stages of my PhD, I was introduced to BBr_3-mediated transformations, a field that quickly became a central focus of our research group.[102] BBr_3 has been successfully employed in directed borylation strategies, particularly for the selective C–H borylation of aromatic compounds (**Chapter 1**, **section 4.3.1**).[63] Building on these developments, we aimed to expand the borylation protocol into halogenation reactions exploring the potential for oxidative halogenation. In this context, our initial hypothesis was that a tetracoordinated dibromo boracycle (**80a**), generated via BBr_3 activation, could serve as a reactive intermediate for oxidative halogenation,[84,85] offering a selective and efficient route to *ortho*-halogenation (**Scheme 3**).



Scheme 3. Murakami's[65] findings and our hypothesis.

To validate our hypothesis of oxidative halodeboronation, we selected 2–phenylpyridine boracycle (**80a**) as a model substrate and employed Selectfluor[85] as an oxidant (**Scheme 4**). Under the initial reaction conditions (**Scheme 4a**), we observed the formation of a difluoroboracycle (**111a**), indicating a ligand exchange process on boron rather than direct deborylative fluorination (**112a**). With increased loading of Selectfluor, we observed selective

oxidative bromination (**Scheme 4b**, **109a**), aligning with literature reports that establish Selectfluor as an effective oxidant.



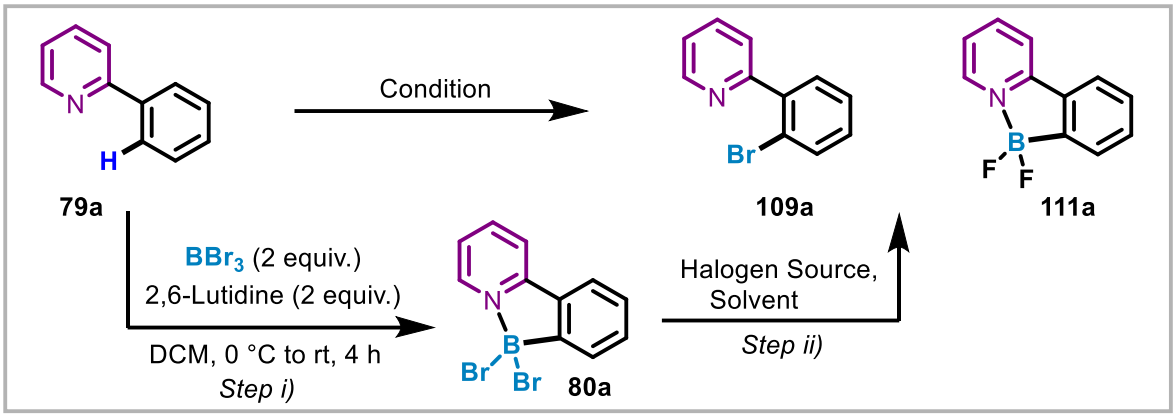
Scheme 4. Intial results.

Next, with initial results in hand, our approach involved modifying established borylation protocols to achieve efficient substrate activation and subsequent transformations. To this end, we modified Murakami's[65] borylation protocol and adopted Chatani's[103] method for the borylation. We discovered that treating the starting material (**79a**) with 2.0 equiv. of BBr_3 and 2,6-lutidine in DCM at room temperature for 4 hours resulted in complete conversion of (**79a**) into the corresponding dibromoboracycle (**80a**).

With the optimized conditions for the synthesis of **80a** established, we proceeded to investigate the bromide-to-fluoride ligand exchange (**Table 1**). Initial experiments revealed that both solubility and the fluorine source significantly influenced the efficiency of the exchange process. In our first attempt, treating **80a** with 1.0 equiv. of Selectfluor in ACN at room temperature resulted in the formation of the product **111a** (**Table 1**, entry 1). Increasing the reaction temperature to 55 °C led to the formation of **109a** in approximately 10% yield, while **111a** remained the major product (81%) (**Table 1**, entry 2). To enhance the formation of **109a**, we increased the Selectfluor loading to 2.0 equiv. at 55 °C, which improved the yield of **109a** to 79%, with **111a** no longer observed under these conditions (**Table 1**, entry 3). However, during these trials, we noticed precipitate formation, suggesting that solubility issues persisted. To address this, we introduced a biphasic ACN-water solvent system, which resulted in a homogeneous reaction mixture. Under these conditions, **109a** was isolated in 94% yield within 3 hours at 55 °C (**Table 1**, entry 4). Notably, in this aqueous-based system, the required Selectfluor loading could be reduced to 1.0 equiv., yielding **109a** in 96% (**Table 1**, entry 5).

Next, we explored the effect of alternative fluorine sources. When NFSI was employed, the reaction delivered **109a** in 87% yield (**Table 1**, entry 6). In contrast, when using a nucleophilic fluorine source such as KF, only **111a** was observed, albeit in 63% yield (**Table 1**, entry 7), suggesting that electrophilic fluorine sources are crucial for oxidative bromination.

Table 1: Optimization of the reaction conditions.

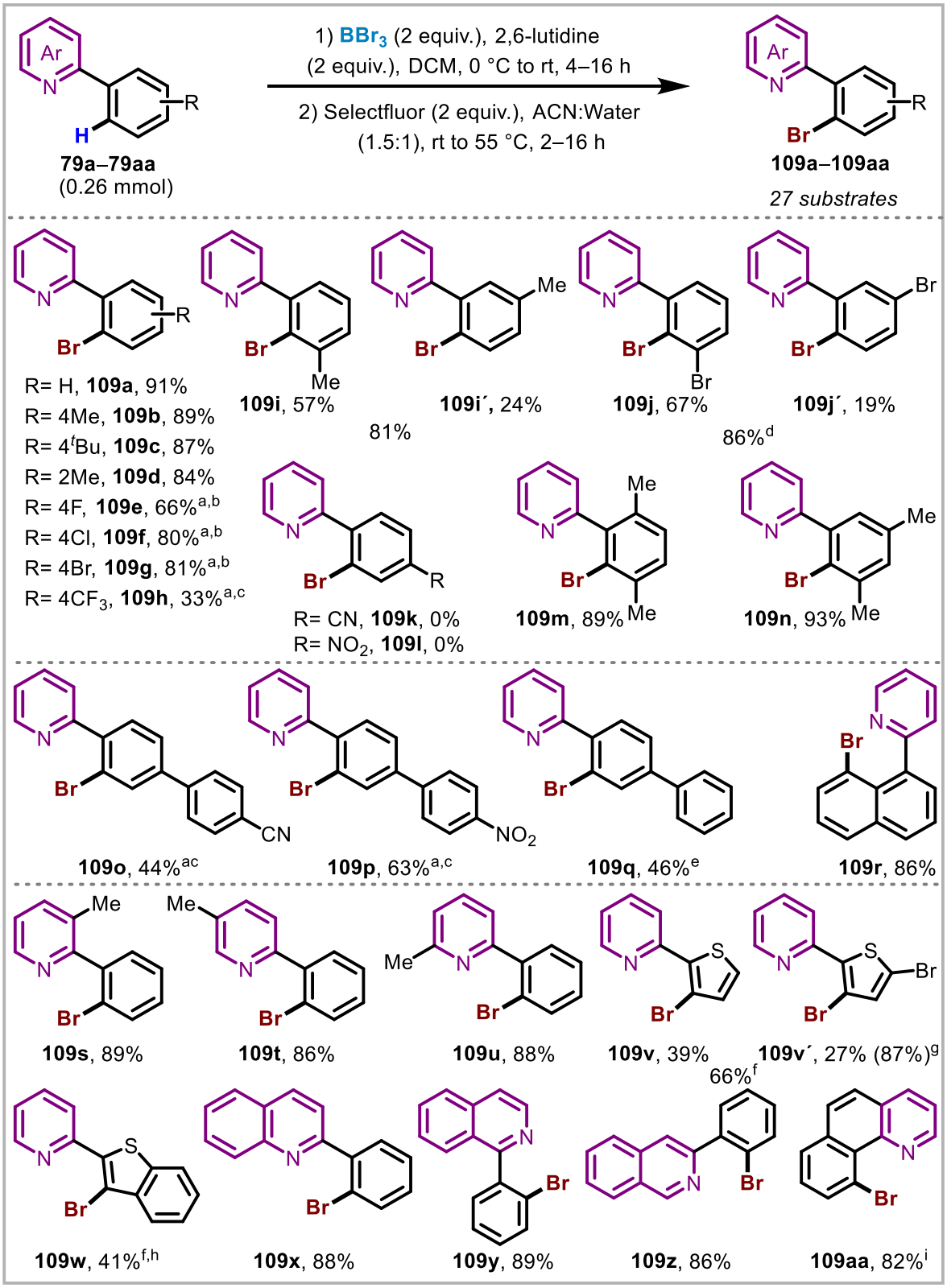


Entry	Halogen source (equiv.)	Solvent	Time (h)	Temp. (°C)	Yield (%)[e] 109a	Yield (%)[e,f] 111a
1	Selectfluor(1)	ACN	1	rt	0	96
2	Selectfluor (1)	ACN	6	55	>10	81
3	Selectfluor (2)	ACN	6	55	79	
4	Selectfluor (2)	ACN:Water	3	55	94	
5	**Selectfluor (1)**	**ACN:Water**	**3**	**55**	**96**	
6	NFSI (2)	ACN:Water	6	55	87	
7	KF (2)	ACN:Water	16	55	0	63
8	Selectfluor (1)	ACN:Water	12	55	64	
9	Selectfluor (1.5)	ACN:Water	12	55	80	
10[a]	**Selectfluor (2)**	**ACN:Water**	**4**	**55**	**91**	
11	NBS (2)	ACN:Water	16	55	67	
12[b]	Selectfluor (2)	ACN:Water	4	55	0	
13[c]	Selectfluor (2)	ACN:Water	4	55	0	
14[d]	----	ACN:Water	12	55	0	

[a]**Reaction conditions:** i) **80a** (0.15 mmol), Selectfluor (0.15 mmol), in 1 mL ACN and 0.5 mL water at rt to 55 °C, 3 h; Entry 8-14 one pot synthesis: i) **79a** (0.26 mmol), BBr_3 (0.52 mmol), and 2,6-lutidine (0.52 mmol), in 0.5 mL DCM at 0 °C to rt, 4 h; ii) Selectfluor (0.52 mmol), in 1.5 mL ACN and 1 mL water at rt to 55 °C, 4 h; [b]BCl_3 was used instead BBr_3, starting material **79a** was recovered; [c]$BF_3.OEt_2$ was used instead BBr_3; crude yields; [d]Starting material **80a** was decomposed. [e]Isolated yields [f]purified by pentane wash.

We then investigated the possibility of conducting the reaction in a one-pot fashion, starting directly from **79a**. Slight modifications to the reaction conditions allowed for a successful transformation, with 2.0 equiv. of Selectfluor affording **109a** in 91% yield (**Table 1**, entries 8–10). The requirement for a higher Selectfluor loading in this sequence is likely due to the presence of residual BBr_3 in the reaction mixture, which may compete with the fluorination process. Additionally, we examined whether other bromine sources could promote the

transformation. When NBS was used, **109a** was obtained in 67% yield (**Table 1**, entry 11), indicating that alternative bromine sources are compatible but less efficient than Selectfluor.
Finally, we explored the influence of different boron sources on the transformation. Using either BCl_3 or BF_3 resulted in no observable reactivity, with the starting material remaining intact (**Table 1**, entries 12 and 13). Moreover, when the reaction was conducted in the absence of Selectfluor, the starting material underwent decomposition, and no desired product was obtained (**Table 1**, entry 14).
With an optimized protocol for the regioselective bromination of **79a** in hand, we next explored the substrate scope to evaluate the functional group tolerance under the established conditions. A diverse range of electron-donating and electron-withdrawing substituents on the phenyl ring of the substrates were well tolerated (**Scheme 5**). Electron-donating groups, such as 4–methyl, 4–*t*–butyl, and 2–methyl, were compatible, affording the corresponding brominated products **109b**, **109c**, and **109d** in 89%, 87%, and 84% yield, respectively. Halogen-substituted phenyl substrates also exhibited good reactivity under the optimized conditions. The corresponding fluoro-, chloro-, and bromo-substituted derivatives **109e**, **109f**, and **109g** were obtained in 66%, 80%, and 81% yield, respectively, demonstrating the method's compatibility with halogen functional groups (**Scheme 5**).
Meta-substituted substrates exhibited regioselectivity under the optimized conditions, leading to the formation of two regioisomers due to the inherent directing effects of the substituents. For instance, *meta*-methylated (**109i**) and *meta*-brominated (**109j**) substrates afforded regioisomers (**109i/109i'** in a 2.3:1 ratio and **109j/109j'** in a 3.5:1 ratio) with excellent combined yields of 81% and 86%, respectively. The observed reactivity arises from the *ortho*/*para*-directing nature of the methyl and bromo substituents, which favor electrophilic substitution at the most electronically and sterically accessible positions. Substrates bearing electron-withdrawing groups showed varying reactivity. For instance, a *para*-CF_3 group afforded the brominated product **109h** in 33% yield. However, strongly deactivating groups like cyano (**109k**) and nitro (**109l**) completely suppressed product formation. This could be due to the electron-withdrawing nature of these groups, which significantly reduces the electron density on the aromatic ring, making it much less reactive toward electrophilic borylation. Interestingly, under modified conditions, biphenyl derivatives bearing cyano and nitro groups were successfully converted to the corresponding brominated products in moderate yields (**109o** 44% and **109p** 63%). Additionally, substrates bearing dimethyl groups on the phenyl ring underwent selective monobromination, delivering the expected brominated products **109m** and **109n** in 89% and 93% yield, respectively, highlighting the tolerance of the method toward disubstituted arenes and the steric influence on site selectivity (**Scheme 5**).
The method was further extended to polycyclic arenes, demonstrating its versatility. Under controlled conditions, a biphenyl substrate (**79q**) underwent selective monobromination, yielding **109q** in 46%, as excess Selectfluor was found to promote over-bromination on the 1´–phenyl ring.

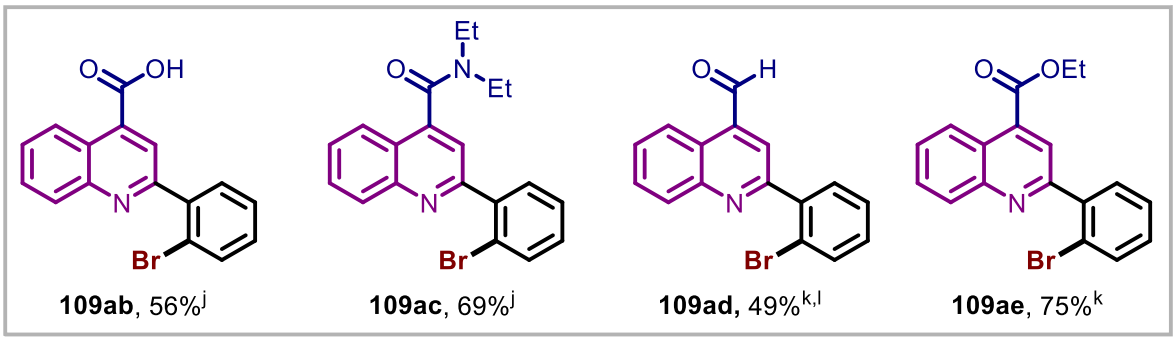


Scheme 5. [a]3 equiv. of BBr_3 and 3.5 equiv. of Selectfluor were used. [b]first step 6 h, second step 6 h. [c] first step 16 h, second step 8 h. [d]3 equiv. of BBr_3 and 3 equiv. of Selectfluor were used. [e]2 equiv. of BBr_3 and 1 equiv. of Selectfluor were used, first step 20 h, second step 16 h. [f]2 equiv. of BBr_3 and 1 equiv. of Selectfluor were used, first step 3 h. [g]2.5 equiv. of Selectfluor in 2 mL ACN and 0.5 mL water, rt to 55 °C, 2 h. [h]second step 2 h. [i]First step 16 h.

In the case of a naphthyl-substituted analogue (**79r**), bromination occurred exclusively at the 8-position, rather than the *beta*-position of the naphthyl ring, affording **109r** in 86% yield. The observed regioselectivity is attributed to the difference in ring strain and electronic properties between the six-membered boracycle and the five-membered boracycle.

We next explored the effect of substituents on the pyridine ring. Methyl groups at the 3-, 5-, and 6-positions underwent smooth bromination, affording **109s**, **109t**, and **109u** in 89%, 86%, and 88% yield, respectively. However, an electron-rich 2–(thiophen–2–yl)pyridine substrate led to a mixture of products (**109v** 39% and **109v'** 27%), giving an overall yield of 66%. By slightly modifying the reaction conditions, selective 3,5-dibromination of the thiophene derivative was achieved, yielding **109v'** in 87%. Similarly, exclusive monobromination was observed in the benzo[*b*]thiophen–2–yl pyridine substrate (**79w**), producing **109w** in 41% yield. The protocol was further expanded to other heterocyclic systems, including quinoline, isoquinoline, and benzo[*h*]quinoline, all of which underwent smooth bromination to afford the desired products in excellent yields (**109x** 88%, **109y** 89%, **109z** 86%, and **109aa** 82%).

To further explore the scope of this protocol, we examined its applicability to pharmaceutically relevant cinchophen derivatives (**Scheme 6**). The methodology demonstrated broad functional group compatibility, including acid, amide, aldehyde, and ester functionalities. The corresponding brominated products were obtained in yields of 56% (**109ab**, acid), 69% (**109ac**, amide), 49% (**109ad**, aldehyde), and 75% (**109ae**, ester) (**Scheme 6**). Notably, the regioselective bromination of cinchophen derivatives underscores the potential of this approach for modifying bioactive *N*-heterocycles, enabling further structural diversification. This makes the protocol particularly valuable for downstream applications, including transition metal-catalyzed cross-coupling reactions.

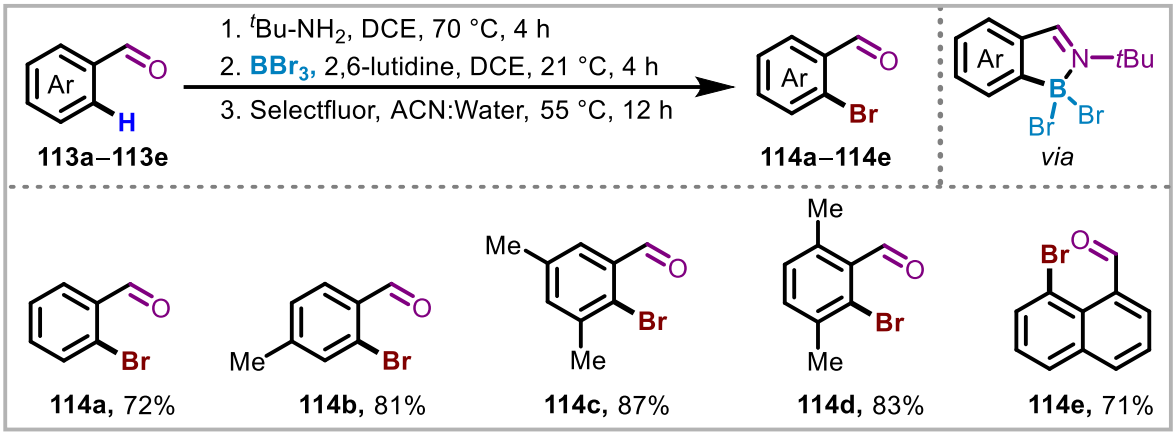


109ab, 56%[j] **109ac**, 69%[j] **109ad,** 49%[k,l] **109ae**, 75%[k]

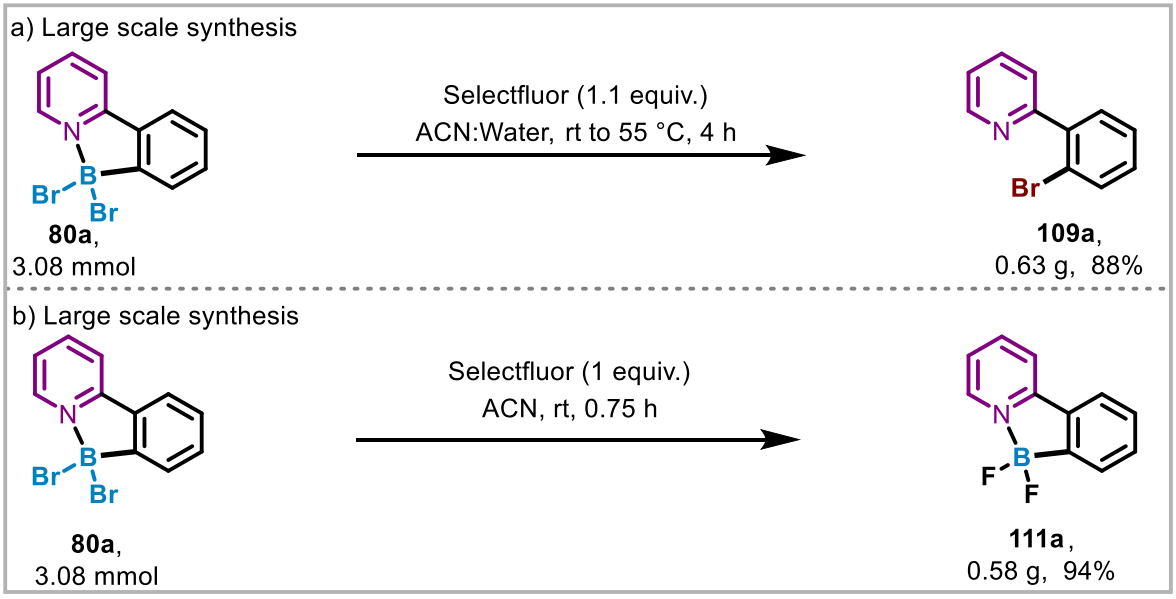
Scheme 6: Functional group tolerance of pharmaceutically relevant Cinchophen derivatives (**109ab**– **109ae**): Reaction conditions: [j]For acid– i) **79ab** (0.2 mmol), BBr_3 (0.8 mmol), 2,6-lutidine (0.5 mmol), DCM, 0 °C to rt 6 h; ii) Selectfluor (0.8 mmol), in 1.5 mL ACN and 0.5 mL water, rt to 55 °C, 16 h; [j]For amide– i) **79ac** (0.2 mmol), BBr_3 (0.8 mmol), 2,6-lutidine (0.6 mmol), DCM, 0 °C to rt 16 h; ii) Selectfluor (0.8 mmol), in 1.5 mL ACN and 1 mL water, rt to 55 °C, 8 h; [k]For aldehyde and ester– i) **79ad**/ **79ae** (0.2 mmol), BBr_3 (0.6 mmol), 2,6-lutidine (0.6 mmol), DCM, 0 °C to rt 16 h; ii) Selectfluor (0.8 mmol), in 1.5 mL ACN and 1 mL water, rt to 55 °C, 7 h. [l]Second step: 4 h.

We next examined transient arylimines as substrates for our oxidative halogenation strategy (**Scheme 7**). Acting as masked aldehydes, transient imines allow the direct utilization of commercially available aromatic aldehydes in regioselective bromination.[(103)] A variety of

benzaldehyde derivatives (**113a–113e**) reacted efficiently under these conditions, furnishing exclusively *ortho*-brominated aldehydes (**114a–114e**) in excellent yields (**Scheme 7**). This method represents the first metal-free protocol for *ortho*-selective bromination of aldehydes, bypassing the need for transition-metal catalysts that are typically required for such transformations. This mild and selective method offers a practical alternative for the late-stage functionalization of aldehyde-containing molecules and advanced intermediates.



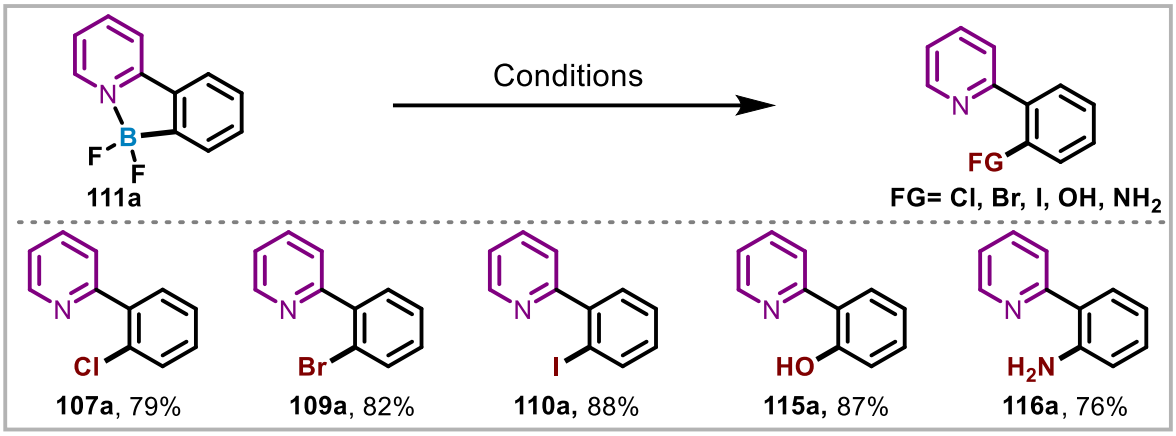
Scheme 7. Reaction conditions: step i) **113a** (0.26 mmol), ^{t}Bu-NH$_2$ (1.04 mmol) in 0.5 mL DCE, 70 ^{o}C, 4 h; step ii) BBr$_3$ (0.65 mmol), 2,6-lutidine (0.65 mmol), DCE, 21 ^{o}C, 4 h; step iii) Selectfluor (0.65 mmol), in 1.5 mL ACN and 1 mL water, 55 ^{o}C, 12 h.



Scheme 8. Large scale experiments. Reaction conditions (a): **80a** (3.08 mmol), Selectfluor (3.38 mmol), in 20 mL ACN and 10 mL water, rt to 55 ^{o}C, 4 h. Reaction conditions (b): **80a** (3.08 mmol), Selectfluor (3.08 mmol), in 20 mL dry ACN, rt 0.75 h.

To demonstrate the scalability and synthetic utility of our protocol, a scaled-up reaction of **80a** was performed, yielding the brominated product **109a** exclusively in 88% yield (**Scheme 8a**). This result highlights the efficiency and adaptability of the method for large-scale synthesis. Furthermore, compound **111a** was readily synthesized on large scale, with a straightforward purification process requiring only filtration (**Scheme 8b**).

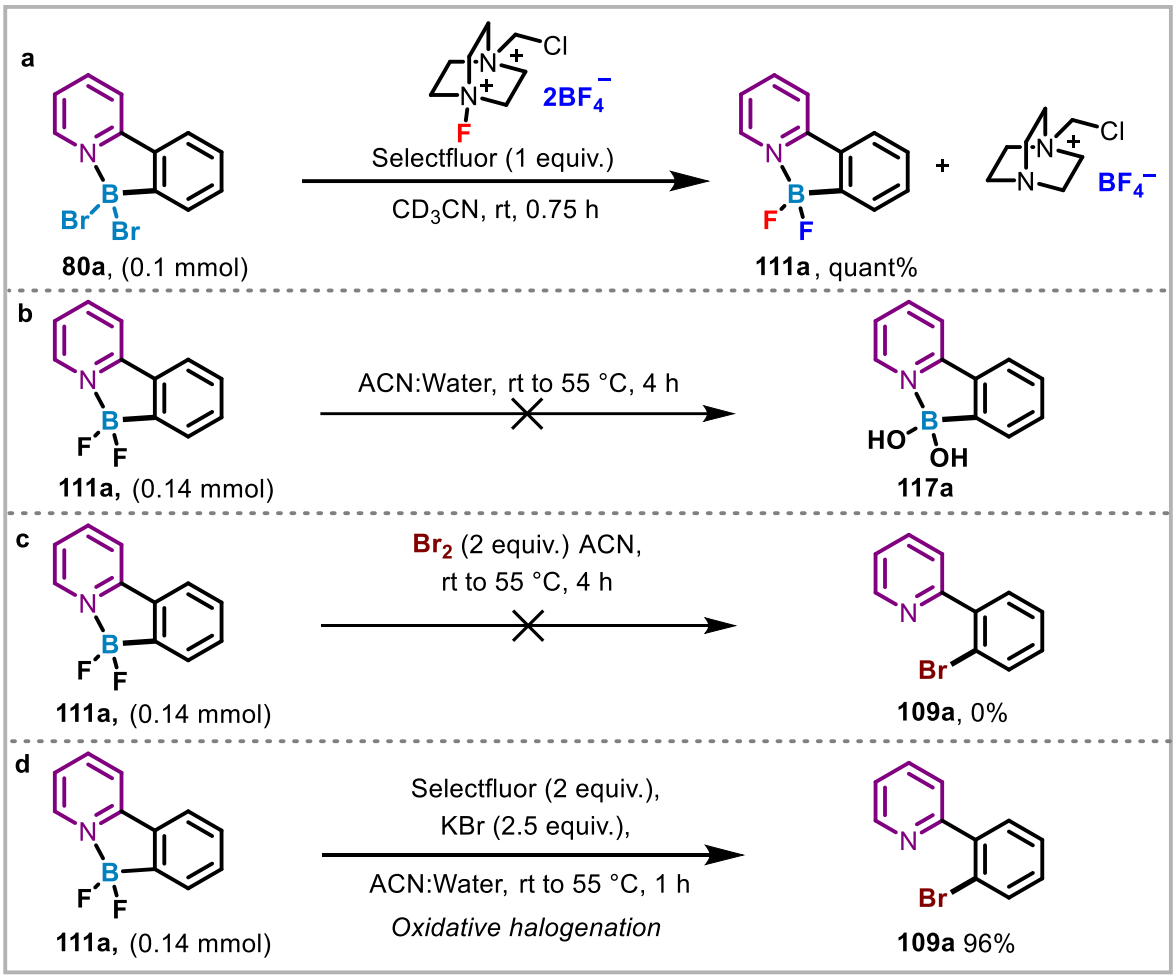
Given the ease of accessing **111a**, we next explored its reactivity profile. Remarkably, **111a** proved to be a highly versatile intermediate, participating in a range of functionalization reactions (**Scheme 9**). For instance, metal-free halogenation of **111a** furnished chloro (**107a**), bromo (**109a**), and iodo (**110a**) derivatives in excellent yields. Oxidation of **111a** with oxone led to the hydroxylated derivative (**115a**) in 87% yield, while Cu-catalyzed amination[90] provided the corresponding amine (**116a**) in 76% yield.



Scheme 9. Functionalization of 2-(2-(difluoroboraneyl)aryl)pyridine (**111a**): Reaction conditions: For **107a**: TCICA (0.66 equiv.), in 1 mL ACN and 0.5 mL water, rt to 55 °C, 3 h. For **109a**, **110a**: i) **111a** (0.2 mmol), NBS/NIS (0.4 mmol), in 1 mL ACN and 0.5 mL water, rt to 55 °C, 3 h. Reaction conditions (**115a**): **111a** (0.2 mmol), Oxone (0.2 mmol), in 0.5 mL acetone and 0.5 mL water, rt to 55 °C, 1 h. Reaction conditions (**116a**): **111a** (0.2 mmol), NaN_3 (0.3 mmol), $Cu(OAc)_2.H_2O$ (20 mol%), in 1 mL methanol, rt to 80 °C, 1.5 h.

To gain further insight into the bromide-to-fluoride ligand exchange and the subsequent C–B bond cleavage, a series of control experiments were conducted (**Scheme 10**). Notably, intermediate **111a** was observed to form quantitatively with just 1 equiv. of Selectfluor, suggesting that one fluorine originates from the FNR_3^+ species in Selectfluor, while the other fluorine is incorporated from BF_4^- (**Scheme 10a**). With the formation of **111a** confirmed, we next examined the role of water in the reaction. Subjecting **111a** to an aqueous reaction mixture revealed that boronic acid formation (**117a**) does not occur, leaving **111a** unchanged (**Scheme 10b**). This indicates that hydrolysis of **111a** is not a contributing factor in the observed reactivity.

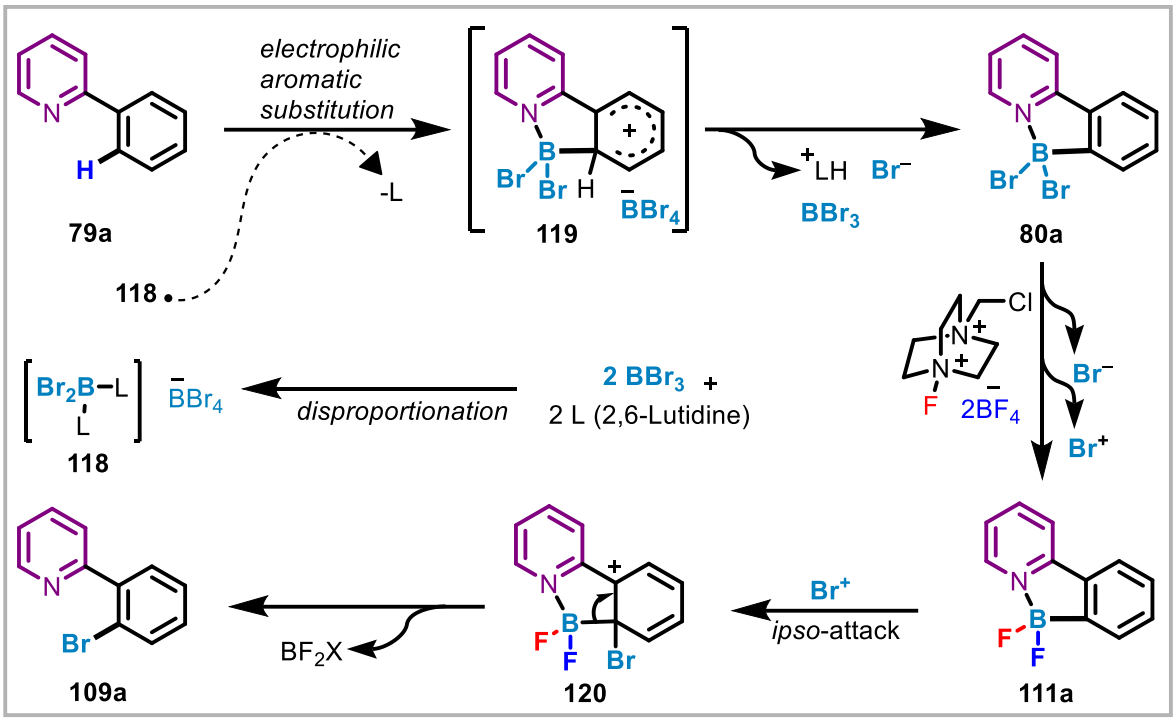
Furthermore, exposure of **111a** to bromine did not lead to the formation of the brominated product **109a**, suggesting that **111a** is unreactive towards molecular bromine (**Scheme 10c**). This prompted us to investigate whether the reaction proceeds through a radical or cationic bromine species. To further investigate the nature of the bromination process, **111a** was subjected to an oxidative halogenation system[85ab] designed to generate a preformed solution of Br^+. Under these conditions, the reaction led to the exclusive formation of **109a** in 96% yield (**Scheme 10d**). This result strongly suggests that the *ipso*-functionalization proceeds via an electrophilic bromination pathway, where Br^+, generated through oxidative halogenation, serves as the key brominating species.



Scheme 10. Control experiments: Condition a: **80a** (0.1 mmol), Selectfluor (0.1 mmol), in 0.5 mL CD_3CN, rt, 0.75 h; Condition b: **111a** (0.14 mmol), in 0.5 mL ACN and 0.5 mL Water, rt to 55 °C, 4 h. Condition c: **111a** (0.14 mmol), Br_2 (0.28 mmol) in 1 mL ACN, rt to 55 °C, 4 h. Condition d: **111a** (0.14 mmol), Selectfluor (0.28 mmol), KBr (0.35 mmol), in 0.5 mL ACN and 0.5 mL water, rt to 55 °C, 1 h.

Building on our mechanistic findings, we propose a pathway that accounts for the observed reactivity (**Scheme 11**). The transformation begins with the base promoted formation of the highly electrophilic boron species **118**, which undergoes regioselective electrophilic aromatic substitution with **79a**, leading to the formation of the boracycle **119**. Subsequent base-promoted aromatization converts **119** into the boron complex **80a**.

As suggested by our control experiments, Selectfluor facilitates a ligand exchange process, converting **80a** into **111a**, while also generating a cationic bromine species. This electrophilic Br^+ species subsequently engages in *ipso*-substitution with the C–B bond of **111a**, forming intermediate **120**, which furnish the desired brominated product **109a**.



Scheme 11. Proposed mechanism.

3. Conclusion

In this work, we have developed a regioselective, efficient, and practical BBr_3-mediated functionalization strategy for 2–aryl–*N*-heteroarenes via an aryl–BF_2 complex. This methodology accommodates a broad range of 2-aryl–*N*-heteroarenes and aromatic aldehydes under mild and operationally simple conditions, offering an alternative to traditional metal-catalyzed halogenation methods. Mechanistic investigations revealed that the transformation proceeds through a fluoride-to-bromide ligand exchange on boron, followed by C–B bond cleavage facilitated by cationic bromine, providing key insights into boron-mediated halogenation pathways.

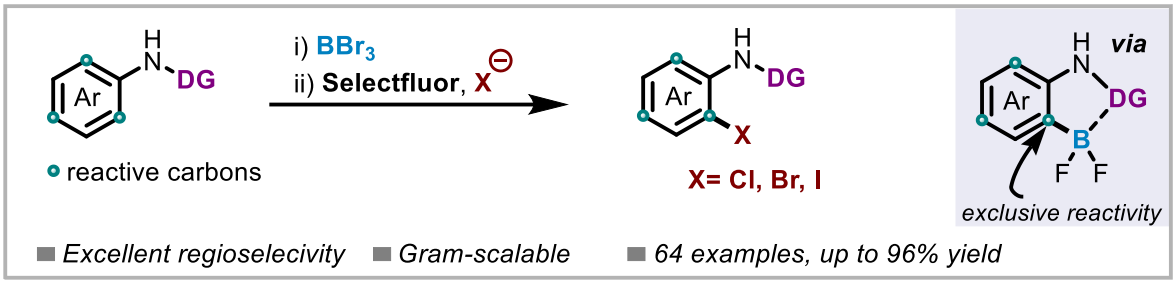
Compared to existing halogenation approaches, our protocol eliminates the need for pre-functionalized boron reagents, demonstrating that dibromoboracycles can be directly leveraged for selective halogenation without requiring conversion into stable boronic esters. This work not only expands the scope of BBr_3-mediated borylation but also establishes the synthetic utility of aryl–BF_2 compound, which was previously underexplored in direct functionalization strategies. Furthermore, the synthesis of a scalable, bench-stable aryl–BF_2 broadens the applicability of boron-based intermediates, creating new opportunities in regioselective transformations.

Despite these advancements, challenges remain in extending this methodology to certain electronically demanding substrates and optimizing conditions for broader halogenation applications. These challenges were addressed in **Chapter 3** by modifying the oxidative halogenation protocol, demonstrating improved efficacy and broader substrate compatibility.

Ultimately, this study contributes to the growing body of research in boron chemistry, providing a foundation for further developments in selective C–H functionalization and cross-coupling methodologies.

Chapter 3

Regioselective *Ortho*-Halogenation of *N*-Aryl Amides and Ureas via Oxidative Halodeboronation



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Author Contributions: H. S. supervised the overall project, while G. H. S. conceived the idea and designed the study in collaboration with G. S. G. Experimental work was carried out by G. H. S. and G. S. G.

F. M. A. N. and L. O. contributed to the crystal structure analysis, and P. O. N. conducted the computational study. G. S. G., F. M. A. N., L. O., and P. O. N. provided valuable insights on the manuscript. H. S. and G. H. S. co-wrote the manuscript.

Note: In this chapter, the reaction conditions have been adopted directly from above published work, without modification, to ensure consistency and accuracy in presenting the methodology.

1. Introduction

Amides are fundamental structural motifs present in a diverse range of natural products and biologically active compounds. Notably, approximately 25% of all known drugs feature an amide functionality, with several incorporating an *N*–aryl amide core, as seen in atorvastatin, teriflunomide and prilocaine (**Figure 1**).[104-106] Given the significance of amides in medicinal chemistry, methods enabling precise modifications in proximity to the amide group are highly valuable, as even minor structural changes can profoundly impact the chemical and physical properties of a compound. In this context, regioselective *ortho*-halogenation of *N*–aryl amides provides a powerful strategy for late-stage diversification, allowing direct functionalization without the need for pre-halogenated aniline precursors. Halogens, being versatile synthetic handles, offer significant potential for facilitating various functional group transformations, thereby enabling the development of novel and more effective pharmaceutical agents.[10, 83]

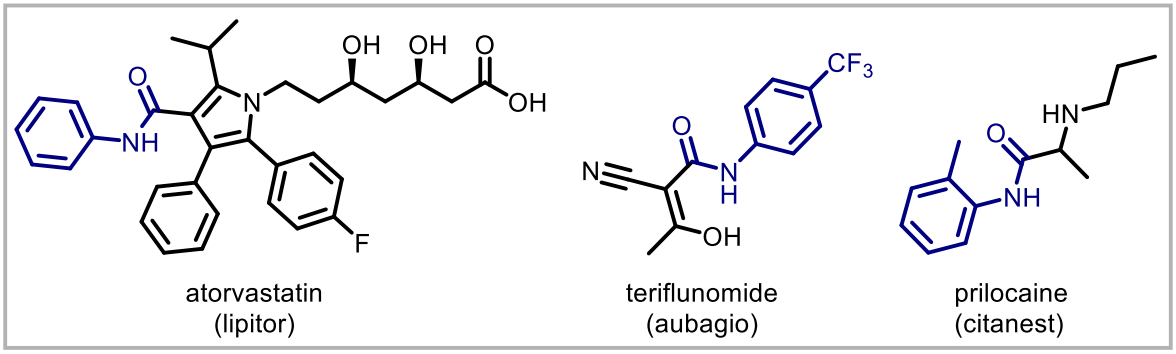
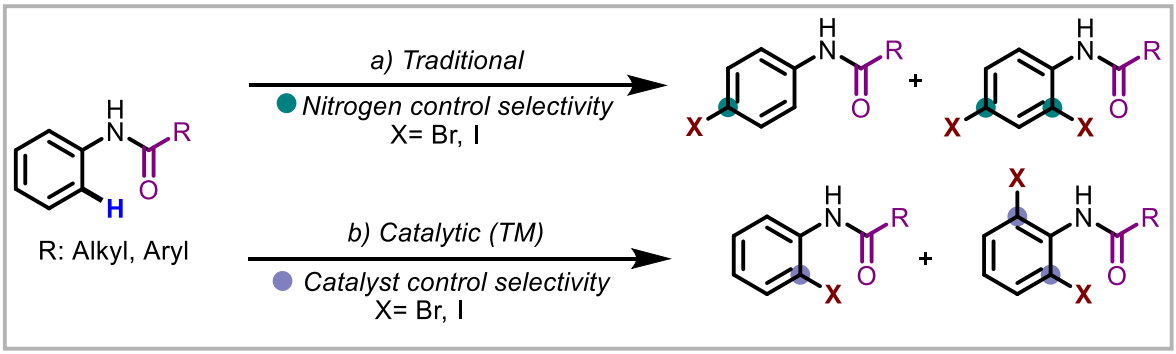


Figure 1. Amide motif in bioactive molecules.

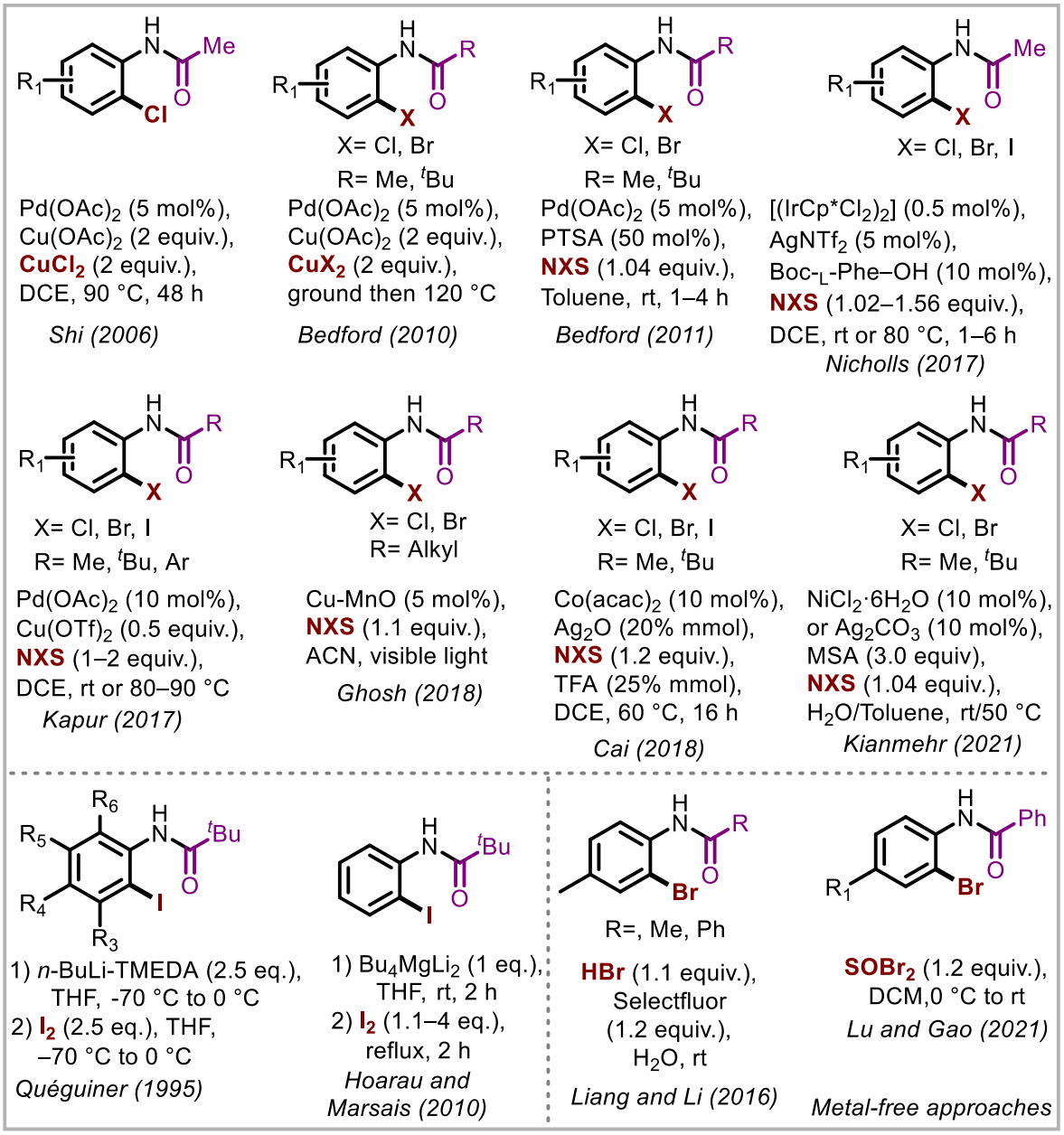
The selective *ortho*-halogenation of anilides has long been a challenge in synthetic chemistry. Traditional electrophilic halogenation methods[107-109] often lead to mixtures of *para*- and *ortho*/*para*-substituted products due to the inherent electronic effects of the amide group (**Scheme 1**). To address this, transition metal-catalyzed C–H activation has been developed as a powerful strategy to achieve regioselective halogenation.[107-118]



Scheme 1. Strategies for *ortho*-halogenation of *N*–aryl amides.

While these metal-catalyzed methods offer improved selectivity, they come with significant limitations (**Scheme 1**). The requirement for precious metals, stoichiometric additives and inert atmosphere conditions can complicate the reaction setup and reduce overall synthetic

efficiency. Additionally, catalysts such as Pd, Ir, Co, and Cu have been widely used to facilitate *ortho*-halogenation using reagents like *N*–halosuccinimides (NXS) and copper halide salts (**Scheme 2**). However, these approaches are often limited to *meta*- and *para*-substituted anilides, as *ortho*-selectivity becomes difficult to control in more electron-rich substrates.



Scheme 2. Literature reports on *ortho*-halogenation of *N*–aryl amides.

For example, In 2006, Shi[117] developed a Pd-mediated *ortho*-halogenation of acetanilides using stoichiometric copper halides as the halogen source and copper acetate as an oxidant (**Scheme 2**). However, when NXS were used as the halogenating reagent, the reaction resulted in both *ortho*- and *para*-halogenation, highlighting the challenge of controlling regioselectivity. Building on this, Bedford[107] reported Pd-catalyzed approaches; however, they suffered from competing EAS pathways, leading to undesired regioisomers.

In 2017, Nicholls[112] introduced an Ir-catalyzed halogenation of acetanilides, which demonstrated excellent substrate scope. However, the method faced the same challenge of *ortho*/*para* halogenation, limiting its regioselectivity. Seeking to improve on this, Kapur[113] developed a Pd-Cu catalytic system using NXS as halogenating reagents, achieving high yields. Despite this, *meta*-substituted substrates resulted in two regioisomers, complicating selectivity, although unwanted dihalogenation was not observed.

Further advancements were made by Ghosh[118] and Cai,[114] who employed visible-light Cu–MnO and Co-catalysis for anilide halogenation (**Scheme 2**). However, both protocols suffered from issues of dihalogenation, reducing their synthetic precision. Among the reported methods, Kianmehr's[116] approach proved to be highly selective. Using a Ni-silver catalytic system with NXS and methanesulfonic acid, his protocol efficiently achieved *ortho*-halogenation with minimal side reactions. Notably, this strategy was also successfully extended to the halogenation of carbamates, further demonstrating its broad applicability.

Overall, a major drawback of transition metal-catalyzed halogenation lies in its competition with EAS. In many cases, *para*-dihalogenation becomes a dominant side reaction, leading to undesired byproducts. This competing reactivity limits the scope of existing methodologies, making it challenging to achieve a truly selective and efficient *ortho*-halogenation process.

On the other hand, lithium-mediated protocols developed by Quéguiner,[110a] Hoarau, and Marsais,[110b] offers an alternative strategy for *ortho*-halogenation. However, these methods are limited by a narrow substrate scope and required cryogenic temperatures to maintain selectivity.

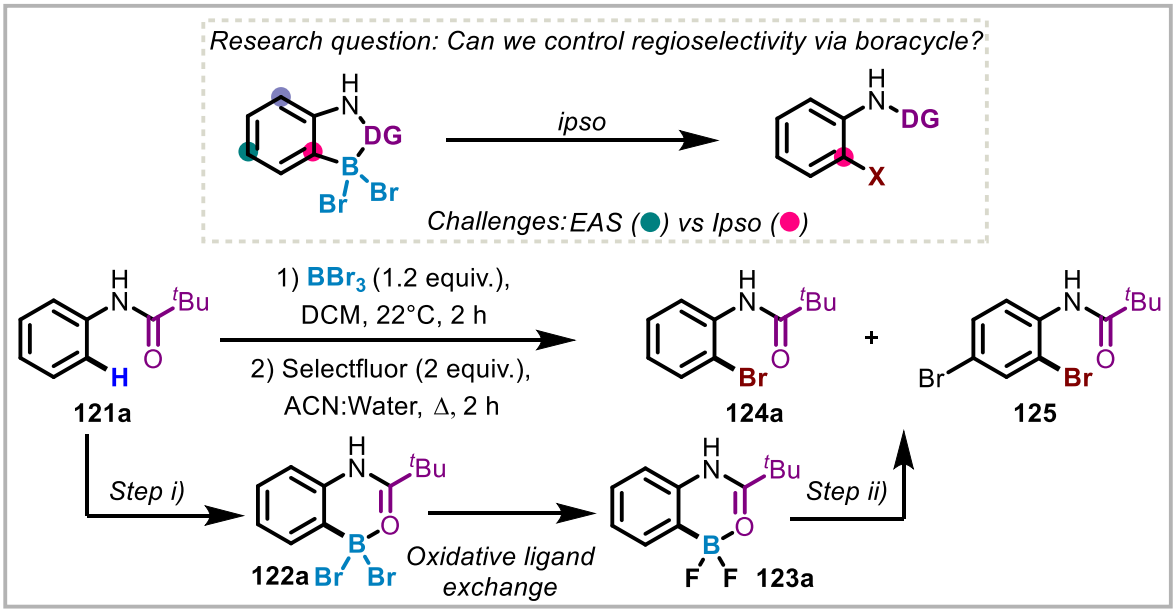
A metal-free approach for bromination was developed by Liang and Li,[109] utilizing HBr as the brominating source and Selectfluor as the oxidant. While this strategy eliminated the need for transition metals, it was largely limited to *para*-substituted substrates, restricting its broader applicability. Building on this, Lu and Gao[115] introduced a protocol for the halogenation of anilides using $SOBr_2$ as the brominating reagent. However, this method also suffered from regioselectivity issues, favoring *para* substitution and generating regioisomeric mixtures when applied to *meta*-substituted substrates. These challenges highlight the need for a new strategy that overcomes these limitations while maintaining high selectivity and practicality.

In this chapter, we address these drawbacks by developing a regioselective halogenation approach that ensures precise *ortho*-functionalization while expanding substrate scope and applicability.

2. Results and Discussion

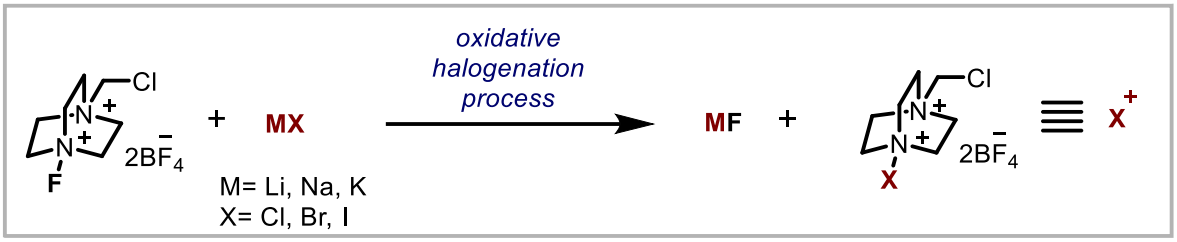
Building on our success in developing a protocol for 2–aryl–*N*-heteroarenes, we were eager to explore its applicability to *N*–aryl amides, leveraging the carbonyl as a directing group. The challenges posed by existing halogenation strategies, particularly issues with selectivity, motivated us to seek an alternative approach that would offer precise control over regioselectivity. Rather than relying on traditional EAS, we envisioned a strategy where boron installation on the aromatic ring could fundamentally alter its reactivity, enabling *ipso*-substitution via oxidative halodeboronation (**Scheme 3**). This approach, we hypothesized, would allow boron to dictate selectivity over nitrogen, overcoming the limitations observed in previous methods (**Scheme 1** and **2**).

To put this hypothesis to the test, we selected *N*–phenylpivalamide (**121a**) as our model substrate. Our initial experiments involved a sequential addition of BBr_3 and Selectfluor, anticipating the formation of a BBr_2 complex (**122a**), which would undergo oxidative ligand exchange with Selectfluor to yield a BF_2 complex (**123a**) and a cationic bromine species (**Scheme 3**). Ideally, this pathway would lead to the formation of the *ortho*-brominated anilide (**124a)** through *ipso*-substitution. However, our initial results unexpectedly yielded a mixture of regioisomers (**124a** and **125**). This suggested that the electronically rich anilide substrate was more challenging than anticipated, leading to competing side reactions. A similar reactivity pattern was observed in **Chapter 2**, where electron-rich thiophene substrate also exhibited side reactions due to their high electronic density, further highlighting the influence of substrate electronics on the halodeboronation process. Selectfluor is known to oxidize bromide ions (Br^-) to bromine cations (Br^+), which can exist as hypobromous acid (HOBr) in aqueous media.[119] This oxidation process is rapid and can lead to the formation of bromine radicals under certain conditions.[85c] The presence of these reactive bromine species can result in uncontrolled halogenation, leading to side products such as **125**.



Scheme 3. Research question and preliminary results .

To overcome this challenge, we hypothesized that controlling the halogenation process by generating the halogen source *ex-situ* would minimize radical formation and ensure selective reactivity (**Scheme 4**). Instead of directly introducing Selectfluor, which we observed to cause uncontrolled oxidation and side reactions, we envisioned that pre-mixing it with halide salts would produce a more controlled halogenating species, leading to improved selectivity.



Scheme 4. *Ex-situ* generation of halogenating species for controlled electrophilic halogenation.

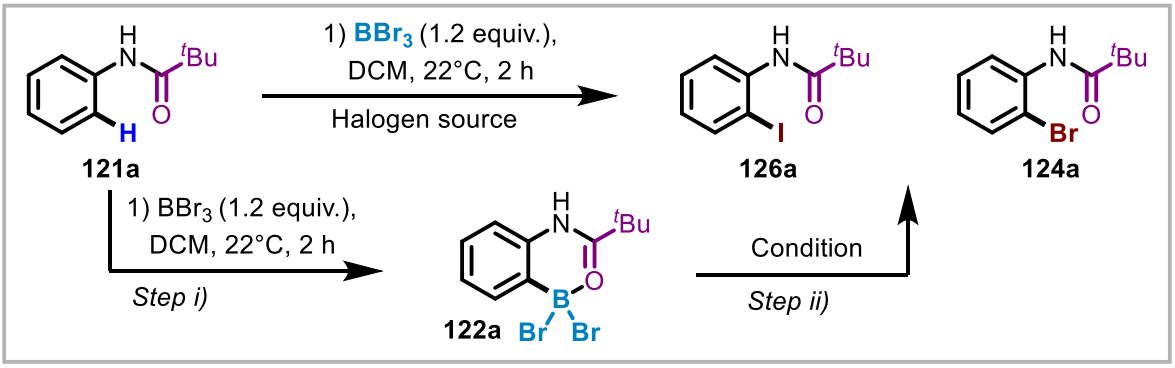
To test our hypothesis, we pre-mixed Selectfluor (1 equiv.) with potassium iodide (1.2 equiv.) before introducing it to a solution of **122a** in ACN-water system at 60 °C. As anticipated, this modification significantly improved selectivity, yielding the *ortho*-iodinated product (**122a**) exclusively in 41% yield (**Table 1**, entry 2). To further improve the yield, we increased the loading of Selectfluor and KI, which successfully enhanced the formation of **126a**, achieving 93% yield (**Table 1**, entry 3 vs. entries 1–2). We then explored various inorganic and organic iodine sources, confirming that KI provided the highest efficiency in this transformation (**Table 1**, entry 3 vs. entries 4–6). Notably, in the absence of BBr_3, no product formation was observed (**Table 1**, entry 7), highlighting the crucial role of the six-membered boron cycle in enabling this reaction.

Next, when boracycle **122a** was subjected to direct electrophilic iodination, the reaction proceeded with significantly lower yields (**Table 1**, entries 8–10) or failed entirely (**Table 1**, entry 11). This result highlights the importance of the BF_2 boracycle (**123a**) in facilitating the transformation, as it is generated only in the presence of a fluorinating reagent, further explaining the reduced efficiency observed with direct electrophilic halogenating agents.

The method was further extended to a bromination protocol, where using TBAB as the brominating source proved effective, delivering the selective *ortho*-brominated product **124a** in a 78% yield (**Table 1**, entry 12). However, employing inorganic bromide sources such as LiBr, NaBr, and KBr resulted in a mixture of mono- and dibromo compounds.

The observed discrepancy in bromination selectivity between tetrabutylammonium bromide (TBAB) and inorganic bromide salts (LiBr, NaBr, KBr) can be attributed to differences in their solubility or oxidation with Selectfluor. Inorganic bromide salts, due to their differing solubility and ion-pairing properties in the ACN-water system, may undergo less controlled oxidation with Selectfluor. This can lead to incomplete oxidation, generating a mixture of reactive bromine species, including bromine radicals, which can result in over-bromination. In contrast, TBAB, with its bulky organic cation, exhibits enhanced solubility. This facilitates a more controlled oxidation, promoting the formation of the desired electrophilic brominating species and improving selectivity.

Table 1. Selected Reaction Optimization (0.22 mmol Scale)[a]

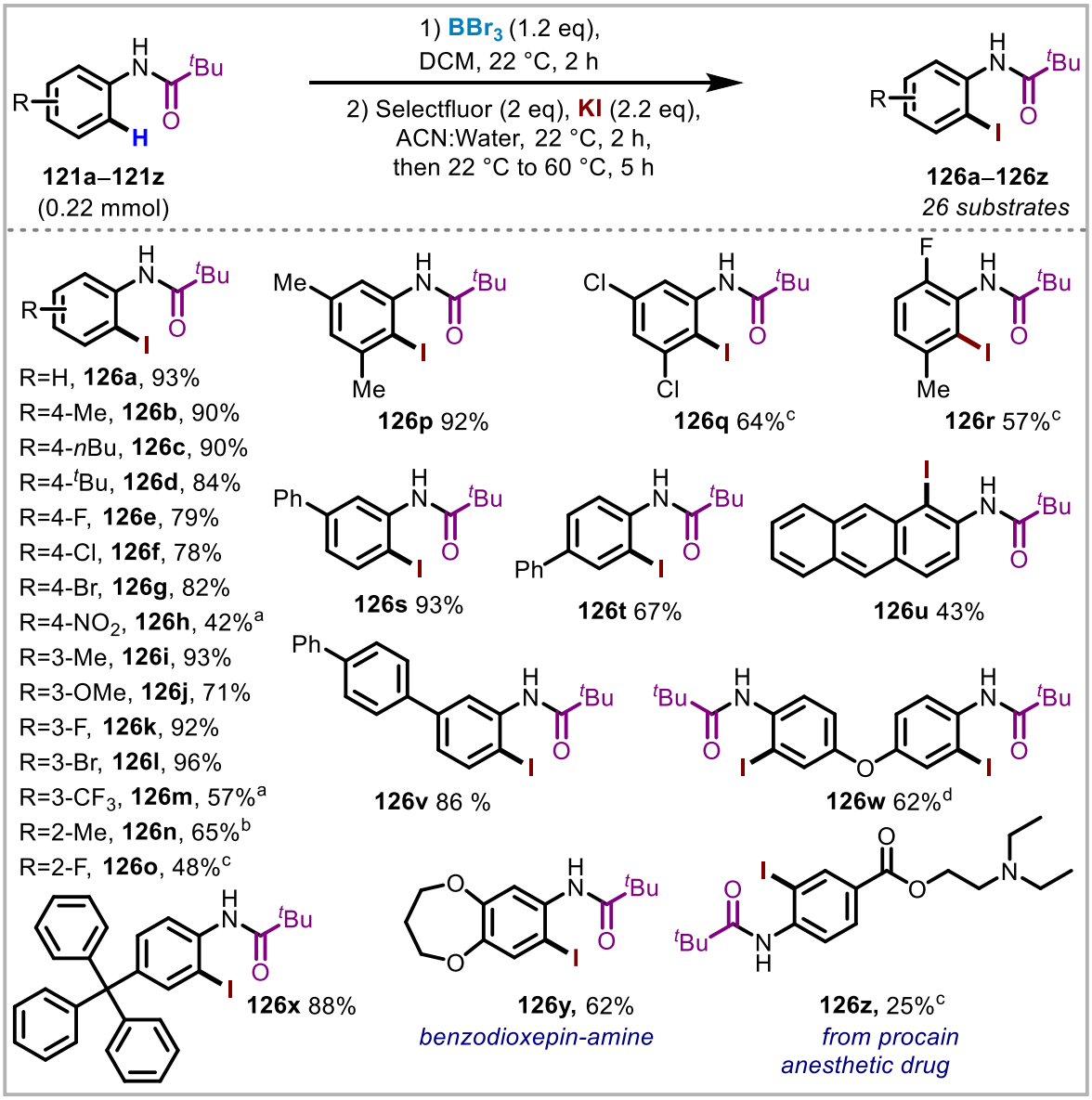


Entry	Halogen source (equiv.)	Oxidant (equiv.)	Solvent	Time (h)	Yield 126a[(d)]
1	KI (1.2)	Selectfluor (1)	ACN:Water	5	41%
2	KI (1.7)	Selectfluor (1.5)	ACN:Water	5	66%
3[a]	**KI (2.2)**	**Selectfluor (2)**	**ACN:Water**	**5**	**93%**
4	LiI (2.2)	Selectfluor (2)	ACN:Water	5	91%
5	NaI (2.2)	Selectfluor (2)	ACN:Water	5	84%
6	TBAI (2.2)	Selectfluor (2)	ACN:Water	5	91%
7[b]	KI (2.2)	Selectfluor (2)	ACN:Water	5	0%
8	NIS (1)	-----	ACN:Water	5	14%
9	ICl (1)	-----	ACN:Water	5	12%
10	Barluenga´s reagent (1)	-----	ACN:Water	5	17%
11	I_2 (2)	-----	ACN:Water	5	0%
12[c]	**TBAB**	**Selectfluor (2)**	**ACN:Water**	**2.5**	**78%**

[a]**Reaction conditions iodination:** Step i) **121a** (0.22 mmol), BBr_3 (0.26 mmol), in 0.5 mL anhydrous DCM at 22 °C, 2 h; Step ii) Selectfluor (0.44 mmol), KI (0.48 mmol) in 1.5 mL ACN and 1 mL water at 22 °C, 2 h then 60 °C for 5 h; [b]Without BBr_3; Barluenga´s reagent= Bis(pyridine)iodonium(I) tetrafluoroborate. [c]Reaction condition for bromination (**124a**): Step i) **121a** (0.22 mmol), BBr_3 (0.26 mmol), in 0.5 mL anhydrous DCM at 22 °C, 2 h; Step ii) Selectfluor (0.44 mmol), TBAB (0.48 mmol) in 1.5 mL ACN and 1 mL water at 22 °C, 2 h then 0 °C to 22 °C for 2.5 h. [d]Isolated yields.

With the optimized reaction conditions established, we explored the substrate scope. A range of *para*-substituted *N*–aryl amides, including electron-donating, halogenated, and electron-withdrawing groups, underwent *ortho*-iodination efficiently, affording products **126a**–**126h** in moderate to excellent yields (**Scheme 5**, 42–93%,). Similarly, *meta*-substituted substrates bearing methyl, strongly donating methoxy, halogens, and trifluoromethyl (–CF_3) were well tolerated, yielding the desired iodinated products **126i**–**126m** in good to excellent yields (57–96%). However, for electron-withdrawing groups such as –NO_2 and –CF_3, the electron-

deficient nature of the system necessitated the use of excess BBr_3 to facilitate the borylation step.



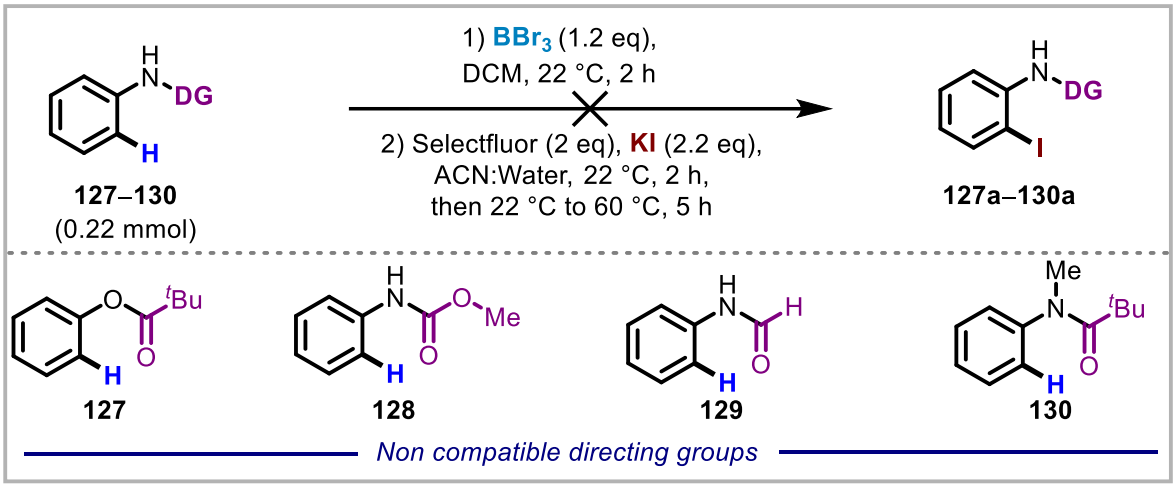
Scheme 5. Reaction scope for pivalamides. Iodination (**121a–121z** 0.22 mmol): [a]2.2 mmol of BBr_3. [b]step-1 for 16 h. [c]Step-1 at 40 °C, 16 h. [d]0.48 mmol of BBr_3, 0.88 mmol of Selectfluor, 0.92 mmol of KI.

In contrast, *ortho*-substituted substrates **121n** and **121o** exhibited sluggish reactivity, likely due to steric hindrance interfering with the amide's ability to adopt the planar conformation required for boracycle formation. However, adjusting the reaction time and temperature in the borylation step successfully overcame this challenge, yielding **126n** in 65% and **126o** in 48%. Disubstituted *N*–aryl amides also performed well, providing products **126p**–**126r** in good to excellent yields (57–92%).

Additionally, extended aromatic systems (**121s**–**121u**) and structurally intricate substrates (**121v** and **121x**) exhibited good compatibility with the reaction, affording the desired products in moderate to excellent yields without any side reactions on the phenyl rings. Notably, using the same conditions, diiodination of the oxydibenzene substrate **121w** proceeded efficiently,

yielding **126w** in 62%. Compound **121y**, featuring an unsymmetrical *N*–aryl ring, exclusively yielded a single isomer in 62% (**126y**). Similarly, the biologically active procaine derivative **121z**, despite its electron-deficient nature, provided the desired product (**126z**), albeit in a lower yield. The reduced yield was a result of ester hydrolysis occurring in the presence of BBr_3 during the initial borylation step (**Scheme 5**).

While the protocol successfully accommodated various anilides, other directing groups such as pivalates, carbamate, formamide and tertiary anilide failed to yield the desired products (**Scheme 6**). Hydrolysis was observed for substrates **127** and **128**, while **129** did not undergo borylation and remained unreacted. Notably, although boracycle formation was observed for substrate **130**, no deborylative halogenation was detected. These findings indicate that secondary amides play a key role in promoting the deborylative halogenation step, while tertiary amides may present a fundamental limitation in the oxidative halodeboronation process.

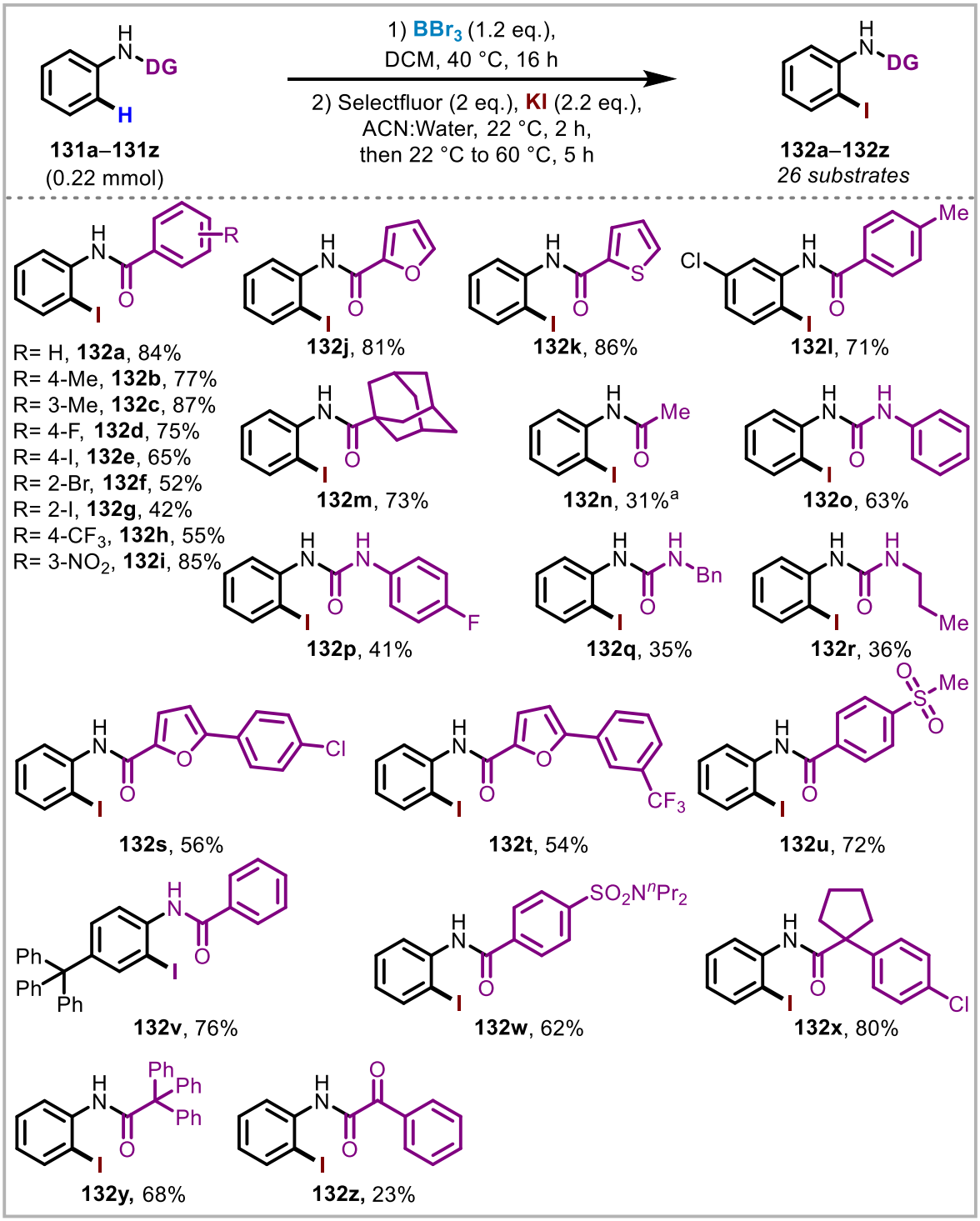


Scheme 6. Non-compatible directing groups in oxidative halodeboronation.

Next, we explored the protocol by employing benzoyl as the directing group. With slight modifications to the reaction conditions, including heating at 40 °C, the reaction demonstrated broad compatibility, delivering *ortho*-iodinated products with excellent regioselectivity and good to excellent yields (**Scheme 7**). Electron-donating groups at both *para* and *meta* positions (**131a–131c**) were well tolerated, affording the desired iodinated products in yields ranging from 77–87%. Similarly, halogen-substituted substrates at the *para* and *ortho*-positions provided iodinated products in moderate to good yields (**132d–132g**, 42–75%). These di-halogenated compounds are particularly valuable due to their potential for facile cyclization in the synthesis of biologically active molecules (see **Scheme 11**).[120]

Furthermore, electron-withdrawing groups on the benzoyl directing group did not hinder the reaction, yielding **132h** (55%) and **132i** (85%), respectively. Electron-rich heteroaromatic substrates were also well tolerated, producing the desired iodinated products without side reactions (**132j** 81%, **132k** 86%). An important observation for the products **132j** and **132k** was the absence of iodination on the heteroarene part, which had been observed in **Chapter 2**.

The absence of halogenation on the heteroaromatic ring suggests that the oxidative deborylative halogenation is highly selective.



Scheme 7. Reaction scope, iodination: [a]BBr_3 (0.66 mmol), 60 °C, 24 h.

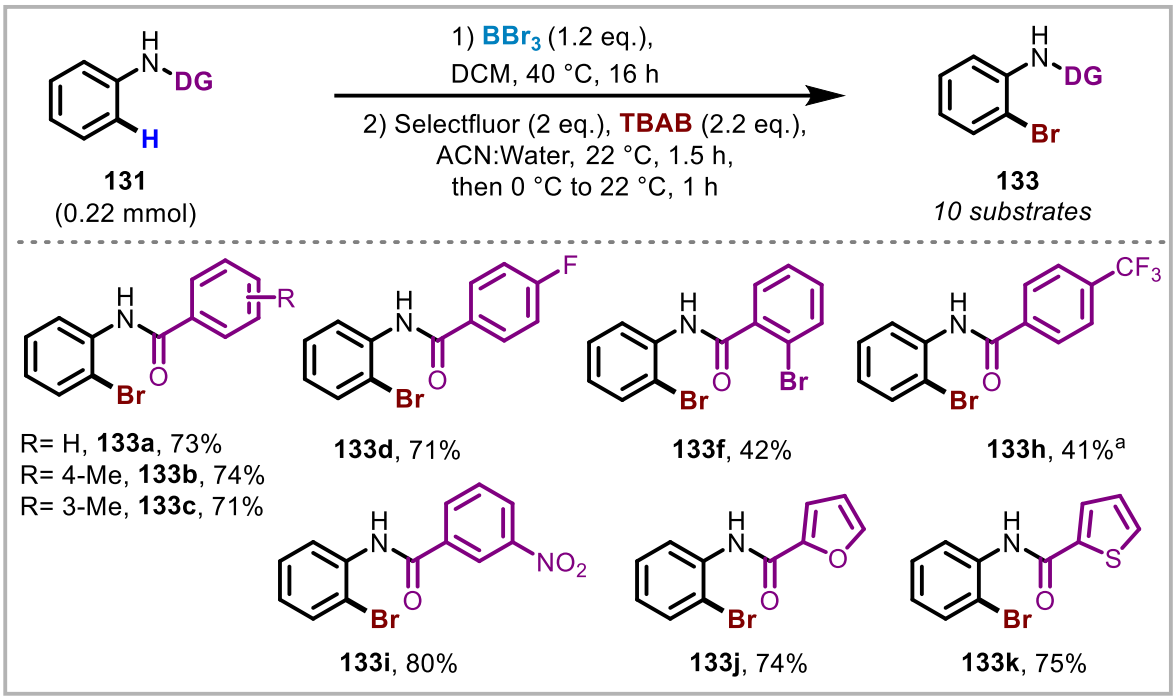
Next, substitutions on the aniline moiety proceeded efficiently under the optimized conditions (**132l** 71%). Notably, alkyl-based directing groups, including adamantane–1–carboxamide and acetamide, successfully furnished the iodinated products, albeit with varying efficiency (**132m** 73%, **132n** 31%). The lower yield for substrate **131n** can be attributed to the unreacted starting material during the borylation step. This could be due to the formation of an enolate under

the BBr_3 conditions, which potentially interfered with the borylation process. Despite increasing the reaction temperature to 60 °C, we did not observe full conversion in the first step.

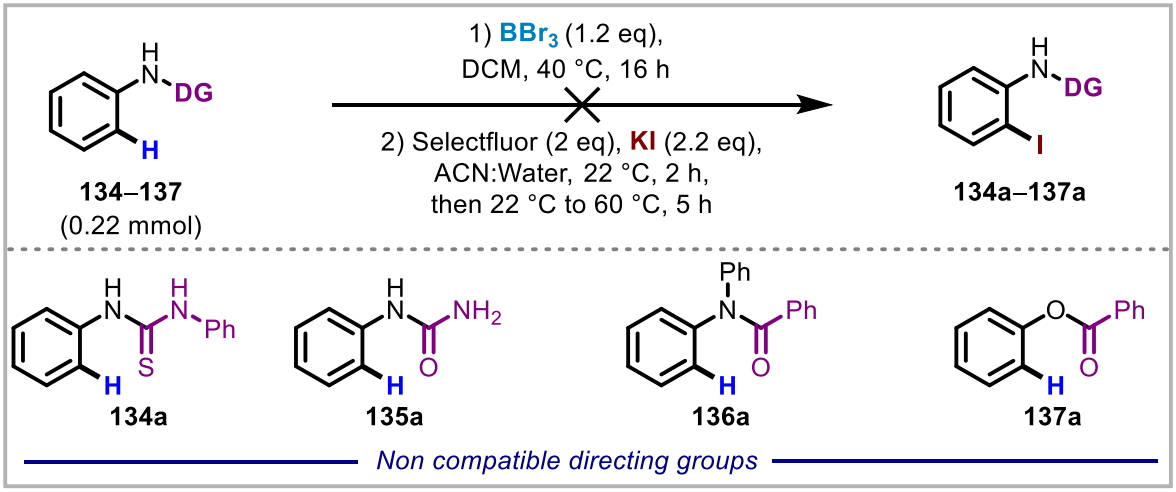
Furthermore, we investigated urea substrates in the context of deborylative iodination. Ureas represent a more complex class of substrates in BBr_3 chemistry due to their polarity, which can lead to challenges in purification (**Scheme 7).** However, the reaction proceeded efficiently with a variety of ureas, yielding low to moderate amounts of the corresponding iodinated products. These included phenyl (**132o**, 63%), *p*-fluorophenyl (**132p**, 41%), benzyl (**132q**, 35%), and propyl (**132r**, 36%) substituents. The lower yields were due to incomplete conversion of the starting material during the first step. In the case of *N*–propyl and *N*–benzyl substituents, partial dealkylation may have occurred, along with the presence of unreacted starting material, which contributed to the reduced yields. Notably, this work marks the first successful borylation and iodination of *N*–aryl ureas using BBr_3.

Encouraged by these promising results, we next explored the application of our protocol to late-stage diversification on a series of bioactive molecules and other relevant substrates (**Scheme 7**, **131s**–**131z**). The deborylative iodination process performed exceptionally well with sodium channel inhibitors,[121] maintaining good tolerance for various functional groups, including furan heterocycles and the $–CF_3$ group (**Scheme 7**, **132s** 56%, **132t** 54%). Additionally, we successfully applied the protocol to a vismodegib derivative precursor (**132u** 72%), a complex *p*–trityl anilide (**132v** 76%), and a probenecid derivative[122] (**132w** 62%), demonstrating the versatility and robustness of our approach. Notably, even sterically hindered amide substrates,[123] such as **131x** and **131y**, were successfully transformed under our conditions, yielding valuable and challenging products in good to excellent yields (**132x** 80%, **132y** 68%). Furthermore, substrates with two coordinating sites, such as **131z**, also afforded the desired iodination product, although in a lower yield (**132z** 23%). These results highlight the broad applicability of our method to complex small and biologically relevant substrates, opening up possibilities for advanced structural modifications in drug development.

Building on the success of our iodination protocol, we next extend the reaction to bromination, aiming to demonstrate the broader generality of the oxidative halodeboronation method (**Scheme 8**). To achieve this, we used TBAB as the bromine source and employed similar approach, with stirring at room temperature for a short period of time. The bromination was highly effective across a variety of substrates, including those with electron-donating groups (**133a**–**133c**, 71–74%), halogens (**133d** 71%, **133f** 42%), electron-withdrawing groups (**133h** 41%, **133i** 80%), and heteroaromatics (**133j** 74%, **133k** 75%). Notably, substrate **133f**, with its halogen group, is of particular interest due to its potential for intramolecular cyclization (see **Scheme 10**). The ability to brominate this substrate selectively opens avenues for the formation of cyclic scaffolds, which are commonly found in biologically active compounds.



Scheme 8. Substrates scope, Bromination: [a]step-2 at 40 °C, 1.5 h.

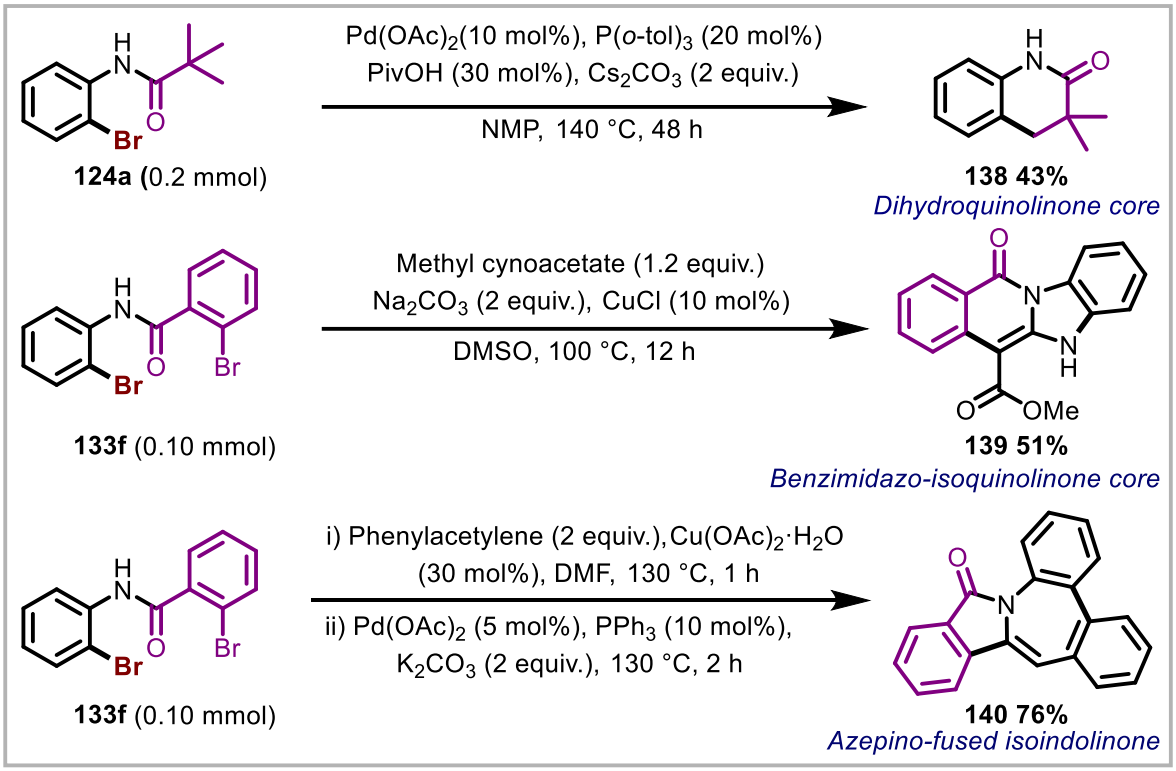


Scheme 9. Non-compatible directing groups in oxidative halodeboronation.

While the protocol successfully accommodated a variety of directing groups, including benzoyl, acyl, ureas, and dicarbonyl, other substrates such as thiourea, 1–phenyl urea, tertiary anilide, and benzoate did not yield the desired products (**Scheme 9**). In the case of substrates **134a** and **135a**, no borylation was observed, while hydrolysis occurred with substrate **137a**. A similar issue was encountered with the *tertiary* amide-containing substrate **136a**, which failed to produce the desired outcome. These results we can conclude that not all directing groups are compatible with the BBr_3-directed borylation protocol, highlighting the need for further optimization and exploration of alternative conditions.

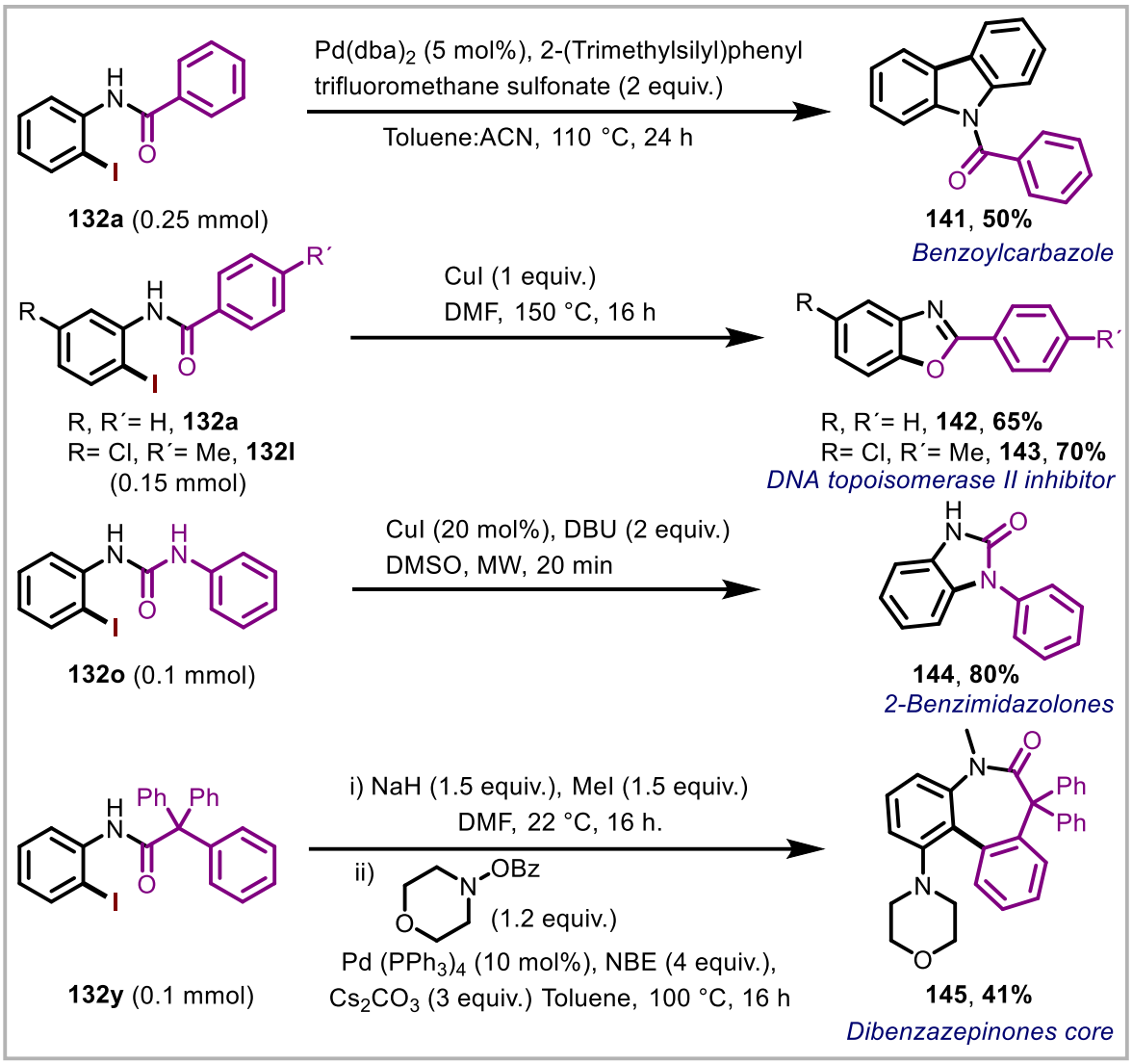
To further demonstrate the utility of our synthesized halogenated products, we explored a series of transformations that showcase their potential in building complex bioactive scaffolds (**Scheme 10** and **11**). Initially, the biologically active 3,4–dihydroquinolinone derivative **138** was prepared from substrate **124a** via a previously established Pd-catalyzed coupling

method,[124] providing the target compound in a 43% yield. Next, we applied the deborylative halogenation strategy to produce benzimidazo-isoquinolinone core[120a] **139** and azepino-fused isoindolinone core[120b] **140** from substrate **133f** in 51% and 76% yields, respectively (**Scheme 10**). These heterocyclic cores are key structural features commonly found in a variety of biologically active compounds.



Scheme 10. Diversification of brominated substrates.

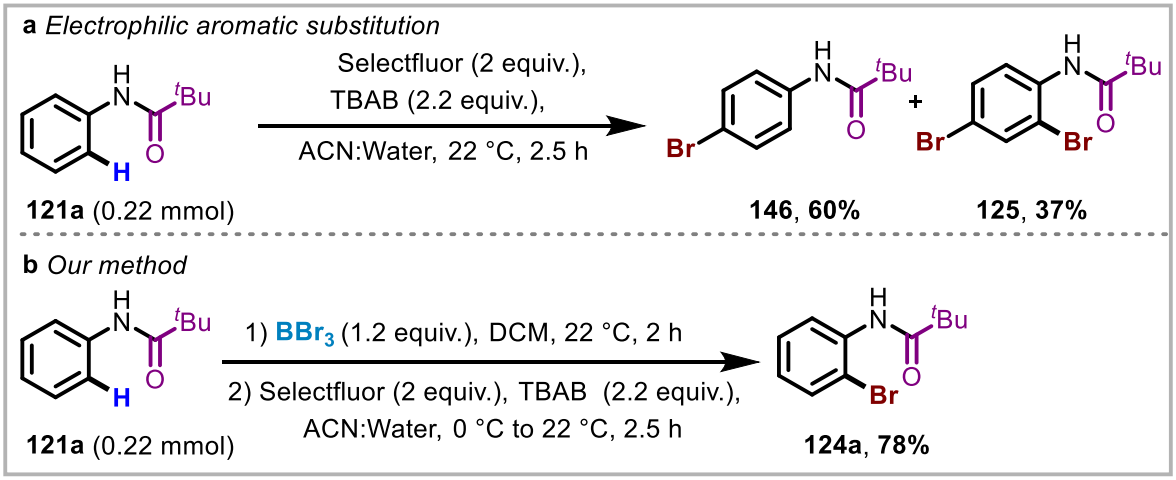
Additionally, we utilized our iodinated products for the synthesis of other valuable biologically active compounds, such as the benzoyl carbazole **141** and benzoxazole core **142**–**143**, which were synthesized through established Pd-aryne[125] and Cu-catalyzed methods[126] from substrates **132a** and **132l**, yielding 50%, 65%, and 70% respectively (**Scheme 11**). In another Cu-catalyzed reaction,[127] iodo urea **132o** was successfully converted into 2–benzimidazolones **144** in 80% yield, further demonstrating the ability of our halogenated ureas to serve as key building blocks for various heterocyclic transformations (**Scheme 11**).
Finally, we showcased the versatility of our approach by synthesizing the dibenzazepinones core[128] **145** from **132y**, achieving a yield of 41%. These examples highlight the broad applicability and versatility of our halogenated products, making them valuable intermediates for the construction of complex, bioactive molecules.



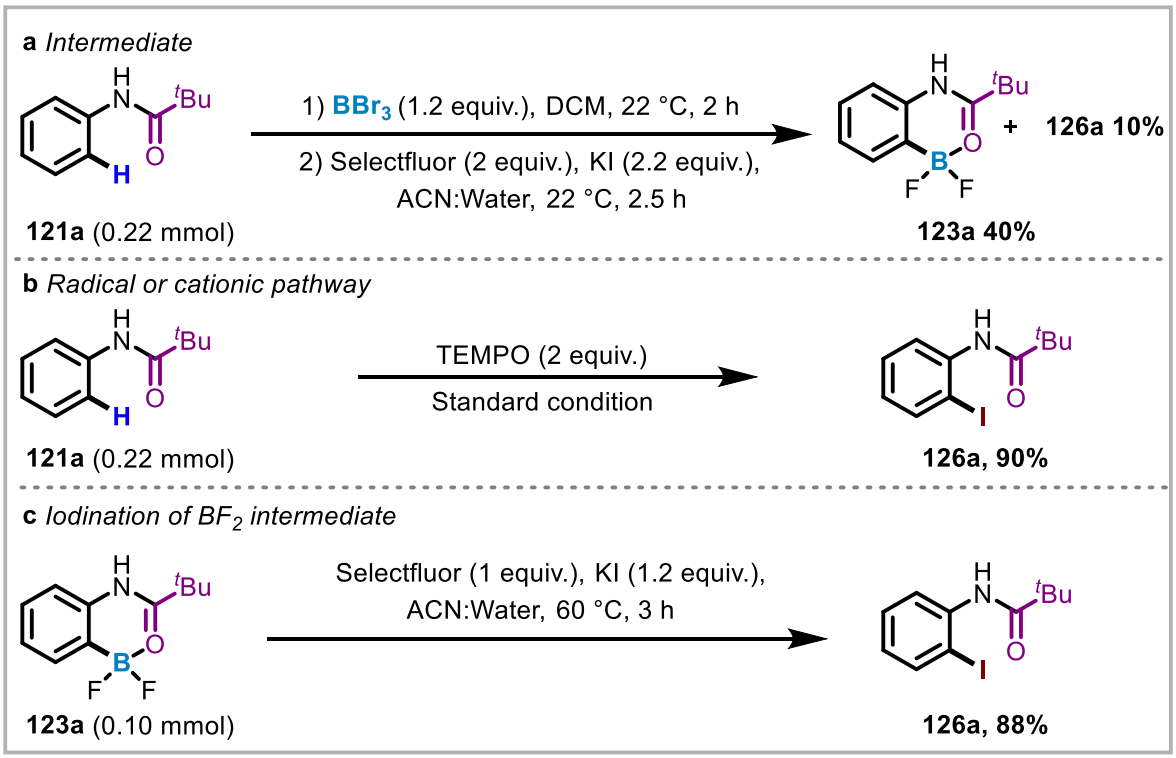
Scheme 11. Diversification of iodinated substrates.

To further analyze the selectivity of our oxidative halogenation protocol we performed a number of control experiments (**Scheme 12**). In the presence of Selectfluor and a bromine source, TBAB, we observed a typical EAS reaction on substrate **121a** (**Scheme 12a**). This reaction produced a mixture of brominated products (**146** and **125)** with no regioselectivity for the *ortho*-bromination, suggesting that under these conditions, the reactivity follows the traditional EAS pathway (**Scheme 12a**).

However, when the same reaction was conducted with the inclusion of a boron handle, the outcome was markedly different. The presence of the boron complex the reactivity shifted entirely, resulting in exclusive *ortho*-bromination, with product **124a** isolated in 78% yield (**Scheme 12b**). This shift in reactivity underscores the boron complex (**122a**) role in directing halogenation, favoring *ipso*-substitution over the typical EAS pathway. Notably, regioselectivity is dictated by the boron functionality rather than the electron-donating amide group, ensuring exclusive mono-bromination. These findings provide strong evidence that our oxidative deborylative halogenation protocol achieves high selectivity, with the boron guiding the reaction toward mono-substitution, even in the presence of excess halogenating reagent.



Scheme 12. *Ipso* vs EAS reactivity.

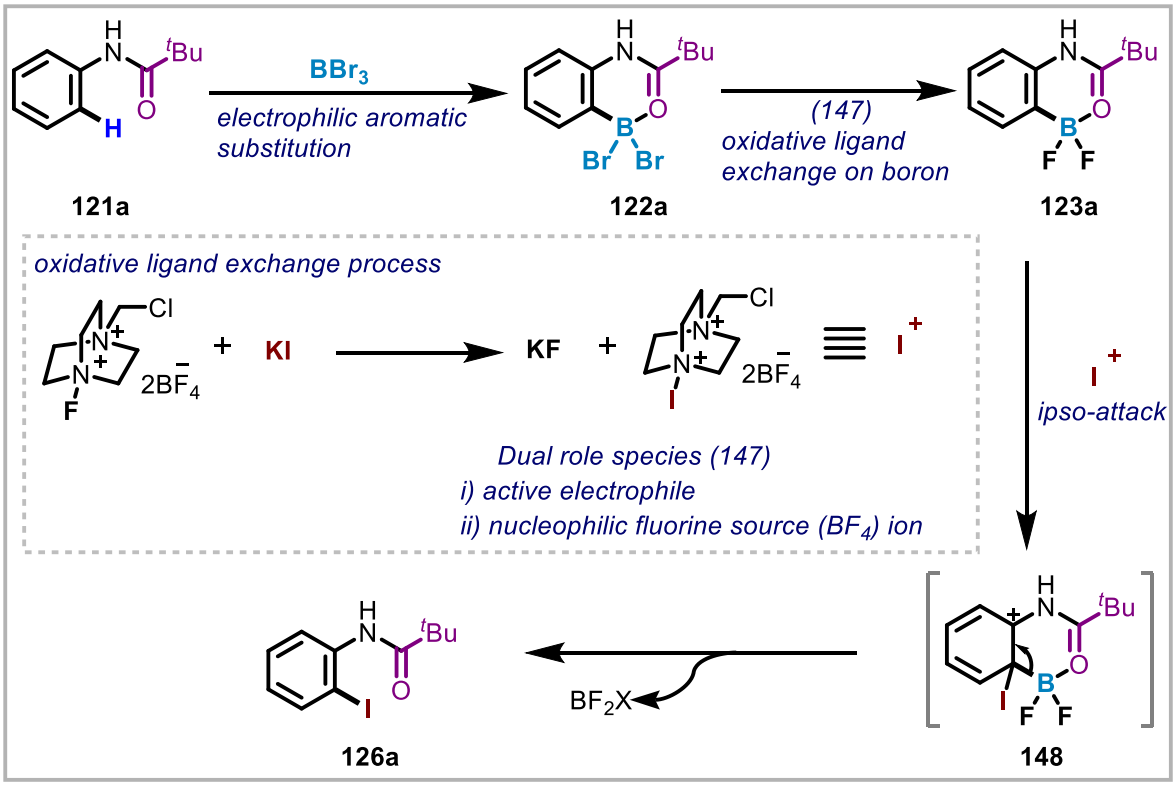


Scheme 13. Control experiments.

To gain mechanistic insights into the bromide-to-fluoride ion exchange and the cleavage of the C–B bond, we performed a series of experimental and computational studies. Two critical steps were identified for further investigation: (i) the formation of the difluoroborane species and (ii) the occurrence of ionic *ipso*-addition. To confirm the formation of the difluoroborane species **123a**, we stirred the reaction at room temperature, quenched it early, and successfully isolated **123a** in 40% yield, along with 10% of **126a** (**Scheme 13a**). This result supports the formation of intermediate **123a**, which was further confirmed by a single crystal X-ray structure. To probe the mechanism of radical or ionic *ipso*-addition, we carried out the reaction in the presence of the radical scavenger TEMPO (**Scheme 13b**). Interestingly, the

presence of excess TEMPO did not alter the reaction outcome, with the desired iodinated product still obtained in 90% yield. Additionally, to further investigate the reactivity and support the proposed mechanism, we subjected the **123a** to the oxidative halodeboronation reaction conditions (**Scheme 13c**). The **123a** also formed the desired product, further supporting the observation that ligand exchange occurs and the halodeboronation proceeds via the difluoroborane species.

To explain the observed reactivity, we propose a mechanism (**Scheme 14**) based on control experiments and DFT studies. The mechanism begins with electrophilic aromatic substitution, leading to the formation of boracycle **122a** in the presence of boron tribromide. The bromo-boracycle **122a** then undergoes conversion to the fluoro-boracycle **123a** in the presence of the oxidative system (**147**). In the traditional oxidative process, Selectfluor oxidizes the halogen anion (X^-) into the corresponding halogen cation (X^+). However, in our case, the oxidative conditions serve a dual role: they not only generate the electrophilic halogen species but also provide the nucleophilic fluoride ions for the ligand exchange on boron. The fluoro-boracycle then undergoes an *ipso* addition with cationic iodine, forming intermediate **148**. Subsequent deborylation leads to the desired iodinated product **126a**.



Scheme 14. Proposed mechanism.

3. Conclusion

In conclusion, we have developed a highly regioselective, efficient, and practical method for the *ortho*-halogenation of *N*–aryl amides and ureas, utilizing a boron handle as a directing group. This protocol demonstrates broad applicability, enabling halogenation across a range of carbonyl-containing directing groups, including benzoyl, acyl, and ureas. The key innovation in our approach lies in the dual role of Selectfluor, functioning both as an oxidant and fluoride source, facilitating regioselective deborylative *ortho*-halogenation.

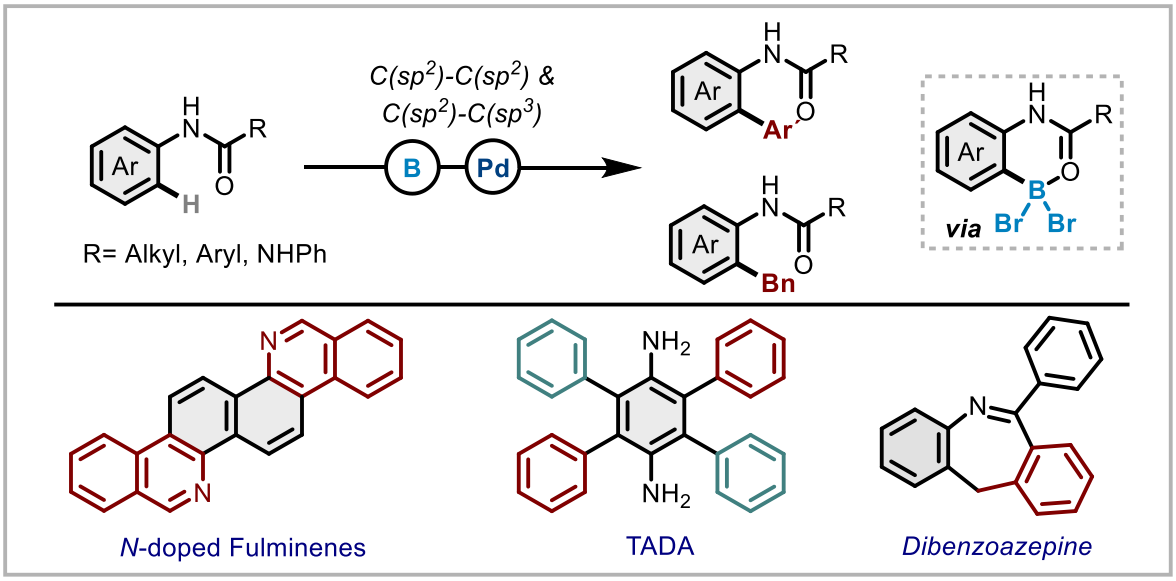
Mechanistic studies, supported by DFT calculations and control experiments, reveal that the reaction proceeds via oxidative ligand exchange on boron, followed by *ipso*-addition with a halogen cation, leading to the desired product through deborylation. Notably, the unique reactivity of the boron species provides a distinct and selective pathway for halogenation, offering significant advantages in the functionalization of *N*–aryl amides.

Outlook: Late-Stage Functionalization and Future Directions

Beyond its synthetic utility, this method holds great promise for late-stage functionalization, particularly in the modification of complex molecules containing diverse directing groups. By leveraging boron-mediated halogenation, this approach enables the selective installation of halogens on structurally intricate substrates, offering a powerful tool for streamlining synthetic routes. The ability to directly functionalize complex scaffolds without extensive prefunctionalization expands the potential applications of this methodology in organic synthesis.

Chapter 4

Ortho-Arylation and Benzylation of *N*-aryl Amides via BBr_3-Derived Dibromoboracycles



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Author Contributions: H. S. supervised the overall project, while G. H. S. conceived the idea and designed the study. Experimental work was carried out by G. H. S. and G. S. G.
H. S. and G. H. S. co-wrote the manuscript.

Benzylation:

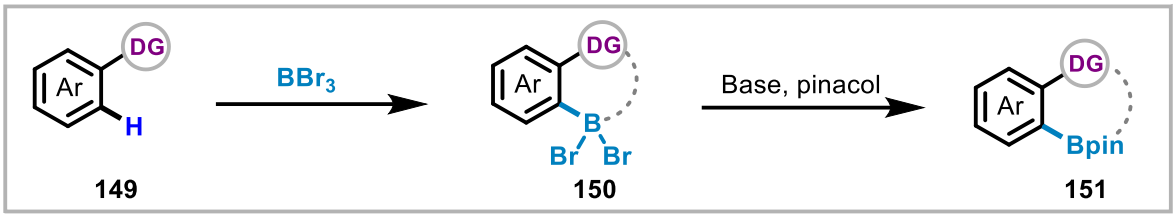
Shinde, G. H.; Castlind, H.; Ghotekar, G. S.; Amombo Noa, F. M.; Öhrström, L.; Sundén, H. Site Selective Boron Directed *Ortho*-Benzylation of *N*–Aryl Amides: Access to Structurally Diversified Dibenzoazepines. *Org. Lett.* **2025**, 27, 207–211.

Author Contributions: H. S. supervised the overall project. G. H. S. designed the study. Experimental work was carried out by G. H. S., H. C. and G. S. G.
H. S. and G. H. S. co-wrote the manuscript.

Note: In this chapter, the reaction conditions have been adopted directly from above published work, without modification, to ensure consistency and accuracy in presenting the methodology.

1. Introduction

The development of efficient and selective C–H functionalization strategies has revolutionized modern synthetic chemistry, offering streamlined access to complex molecular architectures.[55, 56] Despite these advancements, many conventional methodologies remain limited by their reliance on stoichiometric oxidants and additives, excess reagents, or harsh reaction conditions. Additionally, achieving precise regioselectivity continues to pose a significant challenge. In this context, we hypothesized that dibromoboracycles (BBr_2-boracycles) could serve as versatile intermediates for cross-coupling reactions (**Scheme 1**, **50**). Unlike traditional boron-mediated transformations, which typically require conversion of BBr_2 to Bpin (**151**) for functionalization,[63bc] our approach seeks to directly utilize BBr_2-boracycles in selective cross-coupling reactions.



Scheme 1. Traditional approach in BBr_3-mediated borylation strategies.

Traditional Suzuki couplings rely on pre-functionalized boron reagents, such as boronic acids, boronate esters, and organotrifluoroborates, which have been widely employed for C(sp^2)–C(sp^2) and C(sp^2)–C(sp^3) bond formation (**Figure 1**).[11] Among these, organotrifluoroborates have gained prominence due to their stability and efficiency in cross-coupling reactions.[12] Inspired by their success, we envisioned that the tetravalent **150** developed in the **chapter 3** could serve as novel coupling partners in SMC-reaction. By leveraging the unique reactivity of BBr_2-boracycles, this approach aims to expand the utility of boron-mediated cross-couplings, offering a new strategy for site-selective functionalization.

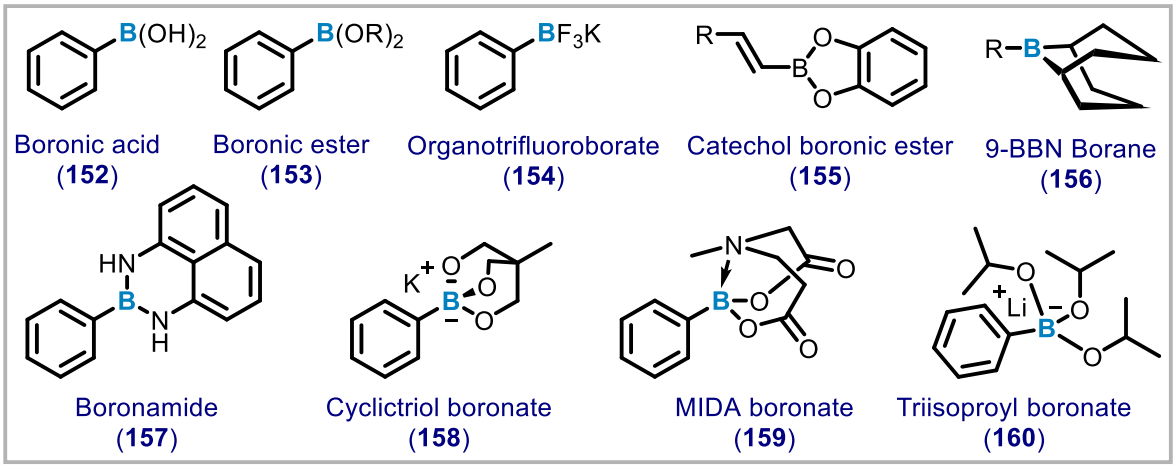
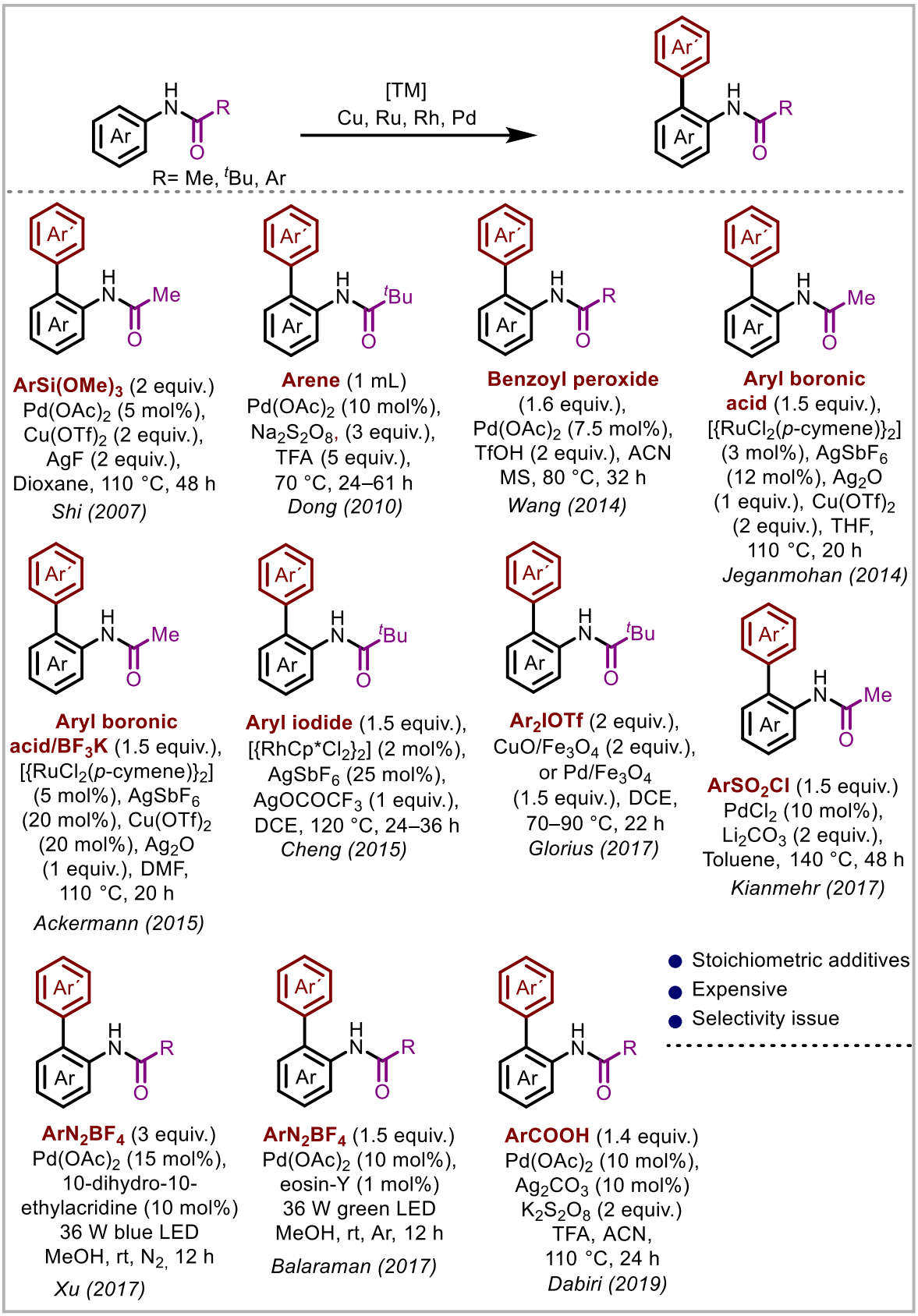


Figure 1. Most popular boron reagents in Suzuki-Miyaura cross-coupling.

Before discussing our optimization of conditions for the use of BBr_2-boracycles in cross-coupling reactions, it is important to review the existing methods developed for the arylation of anilides. This will not only provide context for the challenges in the field but also highlight the need for a new methodology that addresses the limitations of current approaches.

The development of methods for *ortho*-arylation has garnered significant attention, particularly for the functionalization of *N*–aryl amides. Transition-metal catalysts, including Cu, Ru, Rh, and Pd, have been extensively explored for this purpose (**Scheme 2**).[129-139] While these strategies have demonstrated significant progress, they are often hindered by inherent limitations. Many protocols necessitate stoichiometric oxidants, an excess of electrophilic arenes, and elevated reaction temperatures, all of which can compromise efficiency and functional group tolerance. Furthermore, achieving high site selectivity remains challenging, and the reliance on expensive and resource-limited metal catalysts restricts the broader applicability of these methods. For instance, Shi[129] developed a protocol for the *ortho*-arylation of acetanilides using trialkoxyarylsilanes via direct C–H functionalization. While this strategy provides access to biaryl scaffolds, it is hampered by the need for stoichiometric copper oxidants and silver additives, adding to cost and waste generation (**Scheme 2**). Moreover, when applied to benzamides, the reaction exhibited diminished efficiency, resulting in lower yields, thereby highlighting the substrate limitations of this approach. In 2010, Dong[130] developed an *ortho*-arylation strategy for phenylacetamides, benzamides, and anilides using simple arenes as coupling partners, with $Na_2S_2O_8$ serving as an oxidant (**Scheme 2**). While this method eliminates the need for pre-functionalized aryl donors, it suffers from regioselectivity issues, particularly when applied to 4–methoxy–substituted arenes.

Later, Wang[131] introduced a Pd-catalyzed decarboxylative *ortho*-arylation of amides using aryl acylperoxides via C–H activation. This method provided moderate to good yields, but halogenated anilide substrates required an additional oxidant to drive the reaction to completion (**Scheme 2**). Notably, when applied to urea substrates, no reaction was observed highlighting the limitations of this strategy in accommodating a broader range of directing groups. Jeganmohan[132] and Ackermann[133] developed a robust Ru(II)-catalyzed strategy for the oxidative C–H arylation of anilides using boron-based arylating reagents (**Scheme 2**). While these methods expanded the scope of direct arylation, they required additional additives and silver salts to maintain catalytic efficiency. Furthermore, Jeganmohan's approach exhibited sluggish reactivity with pivalamides, while Ackermann's protocol delivered only low to moderate yields for several substrates. A general limitation of Ru-catalysis in C–H functionalization is its reliance on high catalyst loadings and longer reaction times.



Scheme 2. State-of-the-art for the *ortho*-arylation of *N*-aryl amides.

Building on these advancements, Cheng[134] developed an efficient and highly regioselective method for the synthesis of *ortho*-arylated anilide derivatives. This approach utilized a Rh-catalyzed C–H activation process, enabling direct coupling of *N*–phenylpivalamides with iodobenzenes. While the method achieved excellent yields, substrates bearing electron-withdrawing groups required significantly longer reaction times.

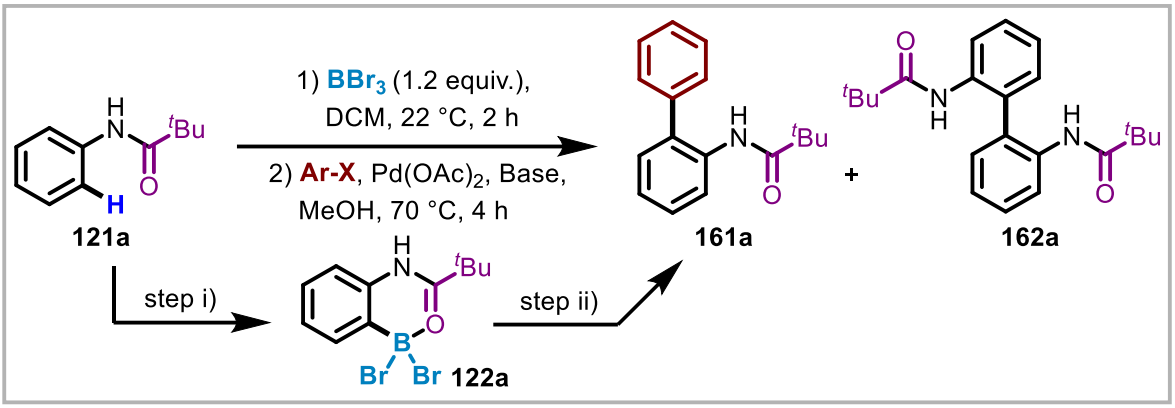
In 2017, Glorius[135] and Kianmehr[136] independently developed protocols for *ortho*-arylation of anilides. However, both reports faced challenges with regioselectivity, and side reactions were observed, which limited the overall efficiency and control of the reactions (**Scheme 2**). Interestingly, Xu[137] and Balaraman[138] developed a light-mediated *ortho*-arylation of anilides using aryldiazonium tetrafluoroborates as a convenient aryl group donor, achieving excellent yields. Among the various protocols, these two showed good substrate scope with simple reaction conditions. However, one limitation with the use of aryldiazonium salts is their reactivity with complex aryl groups, which may lead to issues such as poor selectivity or side reactions, limiting their applicability in more challenging substrates. Additionally, the handling and stability of aryldiazonium salts can be problematic in certain cases, as they are often sensitive to moisture and temperature. Recently, Dabiri[139] disclosed an efficient *ortho*-C–H bond arylation of anilides using benzoic acids as aryl sources. This synthetic method enables the preparation of a broad range of 2–aryl anilides from inexpensive and readily available starting materials. The approach exhibits good substrate tolerance, accommodating both electron-donating and electron-withdrawing substituents on both coupling participants. However, similar to other Pd-catalyzed methods, it still requires silver salts and an oxidant for optimal reaction conditions.

While significant progress has been made in the development of methods for the *ortho*-arylation of anilides, the direct benzylation of anilides remains largely unexplored. Unlike arylation, which has benefited from a variety of transition-metal-catalyzed approaches, there is currently no established methodology for the direct benzylation of anilides. This gap in the literature presents a unique opportunity to develop a novel strategy that leverages the reactivity of dibromoboracycles (BBr_2-boracycles) to achieve selective benzylation.

2. Results and Discussion

Motivated by the lack of direct methods for benzylation and the inherent drawbacks associated with existing arylation methods, we aimed to develop a novel approach for the *ortho*-arylation and benzylation of anilides. In this section, we present our findings on both transformations, including the optimization of reaction conditions, the scope of the methodology, and mechanistic insights into the role of BBr_2-boracycles in facilitating these processes.

Table 1: Optimization of the reaction conditions for arylation



Entry	Catalyst (mol%)	Base (equiv.)	Yield[e] (161a)	Yield[e] (162a)
1[a]	**$Pd(OAc)_2$ (1)**	**K_2CO_3 (3)**	**89%[f]**	**3%[f]**
2[b]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	84%[f]	6%[f]
3	$Pd(OAc)_2$ (5)	K_2CO_3 (3)	88%	6%
4	$PdCl_2(dppf)$ (1)	K_2CO_3 (3)	86%	3%
5	$PdCl_2(PPh_3)_2$ (1)	K_2CO_3 (3)	85%	6%
6	$Pd(PPh_3)_4$ (1)	K_2CO_3 (3)	46%	5%
7	----	K_2CO_3 (3)	0%	0%
8[c]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	51%	4%
9	$Pd(OAc)_2$ (1)	K_2CO_3 (2)	3%	0%
10	$Pd(OAc)_2$ (1)	----	0%	0%
11	$Pd(OAc)_2$ (1)	Na_2CO_3 (3)	85%	4%
12	$Pd(OAc)_2$ (1)	Cs_2CO_3 (3)	69%	5%
13[d]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	45%	3%

[a]**Reaction conditions:** Step i) **121a** (0.15 mmol), BBr_3 (0.18 mmol), in 0.5 mL anhydrous DCM at 22 °C, 2 h; Step ii) Iodobenzene (0.18 mmol), K_2CO_3 (0.45 mmol), $Pd(OAc)_2$ (1 mol%), in 1.5 mL MeOH at 22 °C to 70 °C for 4 h; [b]Bromobenzene instead of iodobenzene; [c]Step 2 at RT 22 h; [d]Ethanol as solvent; [e]GC yields, *o*-xylene as an internal standard; [f]Isolated yields; entries 3-13 Iodobenzene was used.

Our initial screening employed 1.2 equiv. of iodobenzene in the presence of 1 mol% $Pd(OAc)_2$ and K_2CO_3 as a base, which efficiently facilitated the cross-coupling reaction, affording the desired *ortho*-arylated product **161a** in an excellent 89% yield. Notably, only a minor amount

(3%) of the homo-coupled byproduct **162a** was observed (**Table 1**, entry 1). When bromobenzene was used as the electrophile, the reaction still proceeded smoothly, yielding **161a** in 84%; however, an increased formation of the homo-coupled byproduct **162a** (6%) was noted. Given the superior selectivity observed with iodobenzene, we opted to further explore the SMC reaction using this electrophile as the preferred coupling partner.

To further refine the reaction conditions, we next investigated the effect of the Pd-catalyst. Increasing the catalyst loading to 5 mol% $Pd(OAc)_2$ (**Table 1**, entry 3) neither improved the yield nor enhanced the selectivity, establishing 1 mol% $Pd(OAc)_2$ as the optimal catalyst loading for this transformation. A comparative study of various Pd-catalysts revealed that Pd(II) catalysts outperformed Pd(0) species, with $Pd(OAc)_2$ delivering superior results (**Table 1**, entries 4, 5, 6 vs. entry 1). Notably, in the absence of a Pd, no product formation was observed (**Table 1**, entry 7), ruling out the possibility of an uncatalyzed *ipso* addition pathway.

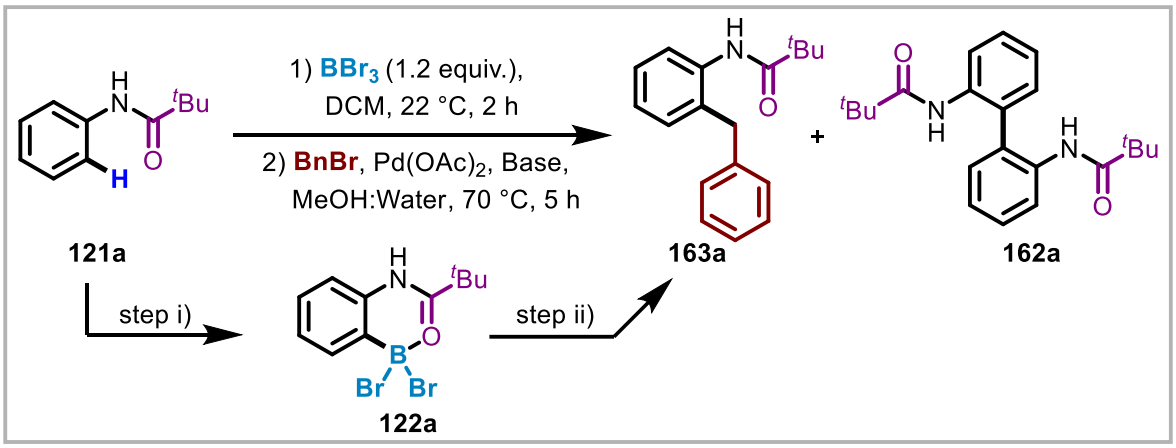
Temperature screening demonstrated that room-temperature conditions led to a sluggish reaction, affording the desired product in only 51% yield (**Table 1**, entry 8), confirming the necessity of elevated temperatures for efficient cross-coupling. The role of the base was also examined, revealing that reducing the base loading significantly diminished the yield, while its complete exclusion led to no product formation (**Table 1**, entries 9–10,). Among the bases tested, K_2CO_3 emerged as the most effective, outperforming Na_2CO_3 and Cs_2CO_3 (**Table 1**, entry 1 vs. entries 11–12).

The choice of solvent was found to be equally critical for the reaction outcome. While switching from methanol to ethanol resulted in a sluggish reaction with only 45% yield (**Table 1**, entry 13), other solvents, including ACN, THF, ethyl acetate, and toluene, completely suppressed product formation. This observation emphasizes the crucial role of methanol in facilitating the transformation, likely due to its involvement in the ligand exchange process, which is essential for effective cross-coupling.

To evaluate the feasibility of our envisioned C(sp^2)–C(sp^3) cross-coupling strategy, we initially subjected the dibromoboracycle derived from pivalamide (**121a**) to arylation conditions with benzyl bromide. The reaction, conducted at 70 °C in 1.5 mL of alkaline methanol, yielded the desired benzylation product (**163a**) in 49%, alongside a homocoupled side product (**162a**) in 17% (**Table 2**, entry 1). This outcome suggested competing reactivity between C(sp^2)–C(sp^3) bond formation and undesired C(sp^2)–C(sp^2) homocoupling. Additionally, a side reaction between methanol and benzyl bromide was observed, which further reduced the efficiency of the transformation. To mitigate these issues, we introduced water as a co-solvent, which significantly improved the reaction outcome, increasing the yield of **163a** to 91% while reducing the formation of **162a** to trace amounts (**Table 2**, entry 2). To further explore the scope of the benzylation reaction, benzyl chloride and benzyl alcohol were evaluated as alternative benzyl sources. While benzyl chloride proved to be a viable reagent, it led to an 80% yield of **163a**, accompanied by an increased formation of the homocoupled byproduct **162a** (**Table 2**, entry 3). The higher occurrence of **162a** is likely due to the slower reaction rate of benzyl chloride compared to benzyl bromide, which prolonged the reaction time and allowed greater homocoupling. In contrast, benzyl alcohol showed no reactivity under the

optimized conditions, with no detectable formation of **163a** observed (**Table 2**, entry 4). These optimization efforts were primarily aimed at minimizing the formation of the homocoupled byproduct (**162a**), a challenge encountered in arylation condition. By carefully tuning the solvent system and reagent stoichiometry, we successfully suppressed unwanted homocoupling while significantly improving the efficiency and selectivity of the benzylation reaction.

Table 2: Optimization of the reaction conditions for benzylation

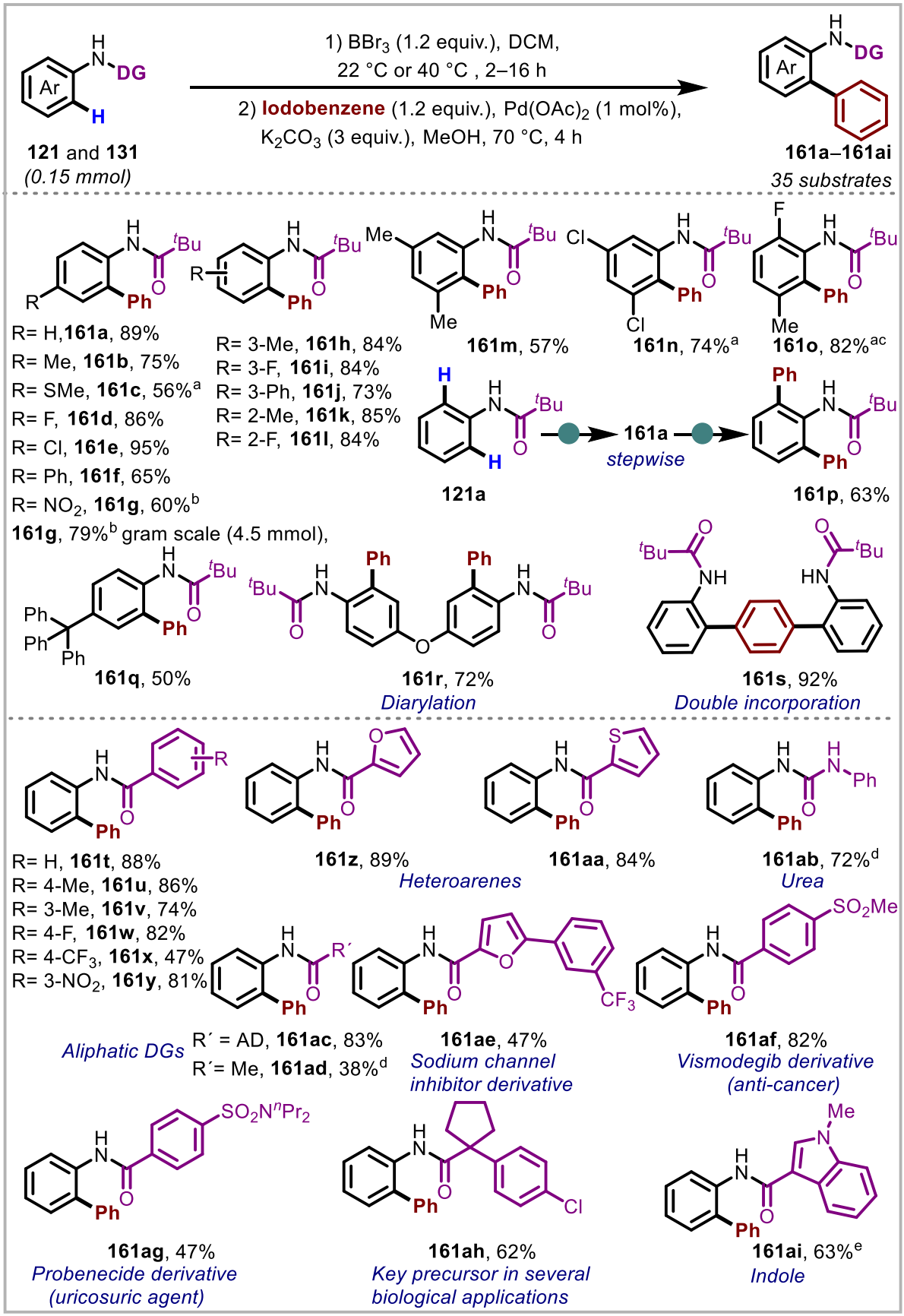


Entry	Catalyst (mol%)	Solvent	Yield[(e)] (163a)	Yield[(e)] (162a)
1	$Pd(OAc)_2$ (5)	MeOH	49%	17%
2[a]	$Pd(OAc)_2$ (5)	MeOH:Water	91%	trace
3[b,c]	$Pd(OAc)_2$ (5)	MeOH:Water	80%	14%
4 [c,d]	$Pd(OAc)_2$ (5)	MeOH:Water	0%	0%

[a]**Reaction conditions:** Step (i) **121a** (0.15 mmol), BBr_3 (0.18 mmol), in 0.5 mL anhydrous DCM at 22 °C, 2 h; Step (ii) benzyl bromide (0.225 mmol), K_2CO_3 (0.45 mmol), $Pd(OAc)_2$ (5 mol%), in 0.8 mL MeOH and 0.8 mL Water 70 °C for 5 h. [b]Benzyl chloride instead of Benzyl bromide. [c]Step (ii) time 16 h.[d]Benzyl alcohol instead of Benzyl bromide. [e]Isolated yields.

Substrate Scope for Arylation: *N*–Aryl Component

With the optimized reaction conditions in hand for arylation and benzylation, we next explored the substrate scope to assess the generality of our protocol. Beginning with arylation, a diverse range of *para*-substituted *N*–phenyl pivalamides was examined, affording the corresponding *ortho*-arylated products (**161a**–**161g**) in good to excellent yields (**Scheme 3**, 56%–95%). For instance, *para*-fluoro- and *para*-chloro-substituted pivaloyl anilides were well tolerated, delivering **161d** and **161e** in 86% and 95% yield, respectively.



Scheme 3. Reaction scope for arylation- *N*-aryl part: **161a–161s** step 1 at 22 °C, 2 h; [a]step 1 at 40 °C for 16 h. [b]step 1 at 22 °C, 24 h. [c]step 2 for 12 h. entry **161t–161ai** step 1 at 40 °C 16 h. [d] step 1 at 60 °C for 24 h. [e]step 2 for 6 h.

Similarly, electron-donating groups performed well, with the electron-withdrawing *p*-nitro-substituted product **161g** obtained in 79% yield, even on a gram scale.

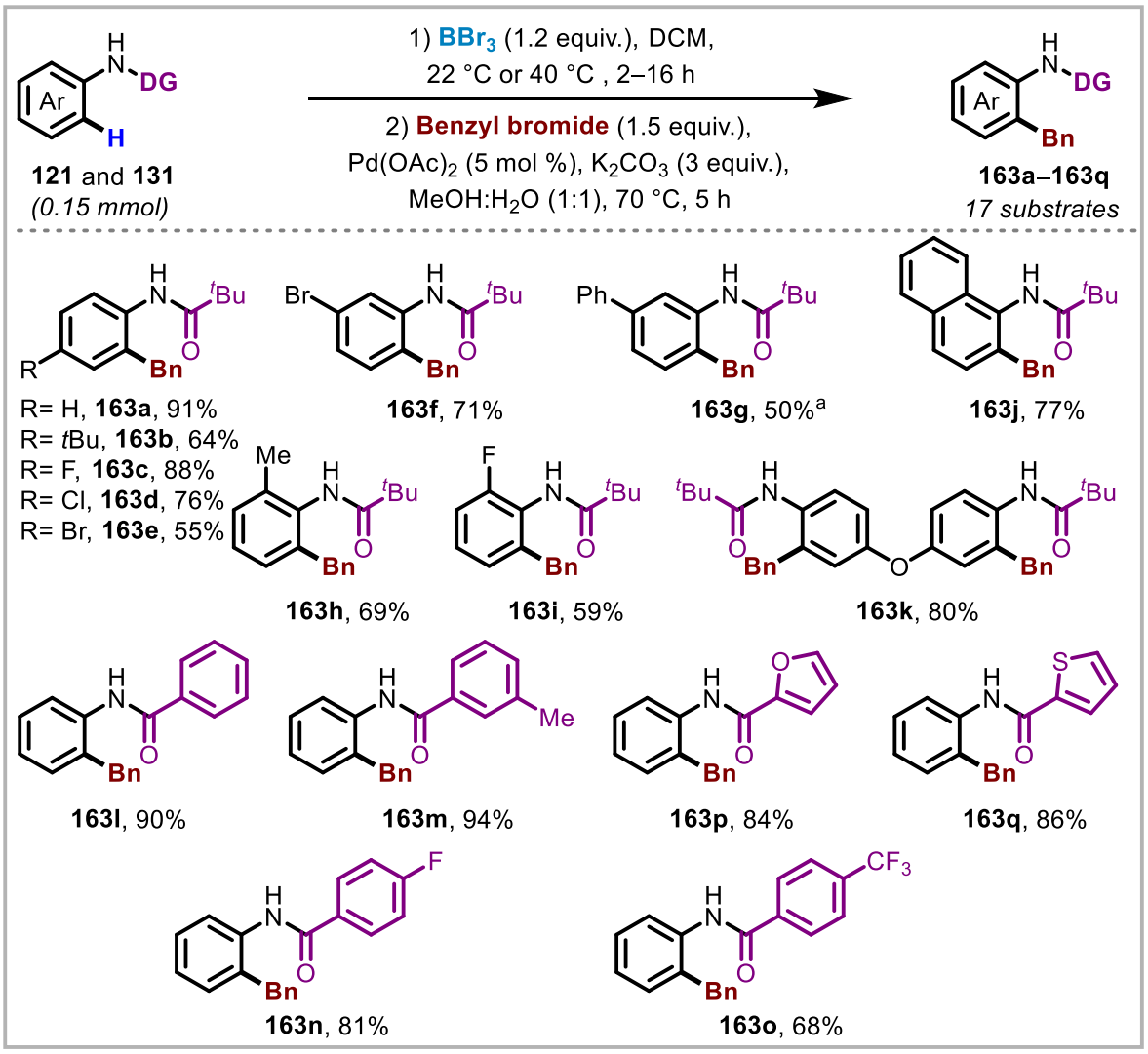
Beyond *para*-substituted substrates, *ortho*- and *meta*-substituted anilides bearing methyl, phenyl, or fluoro groups were also efficiently arylated, providing the desired products **161h**–**161l** in 73%–85% yield. Importantly, in the case of *meta*-substituted anilides, a single regioisomer was consistently observed, with arylation occurring exclusively at the position *para* to the *meta*-substituent, and no product was detected at the *ortho*-position. This high regioselectivity can be attributed to electronic effects, where the electronic nature of the *meta*-substituent influences the electron density distribution in the aromatic ring, making the *para*-position more favorable for the borylation reaction. Such selective functionalization is particularly advantageous in complex molecule synthesis, as it allows for precise control over substitution patterns without the need for additional directing groups or protective strategies. Furthermore, the reaction demonstrated excellent compatibility with disubstituted substrates (**161m**–**161o**). Notably, diarylation could also be achieved, as demonstrated by the conversion of **IV-1a** into **161p** in 63% yield (**Scheme 3**). Expanding the scope further, *N*–(4–tritylphenyl)pivalamide was successfully arylated, delivering **161q** in 50% yield. A particularly noteworthy feature of this protocol is its ability to achieve diarylation under similar conditions. For instance, substrate bearing two pivalamide groups, was efficiently transformed into **161r** in 72% yield. Moreover, employing 1,4–diiodobenzene as the coupling partner facilitated double arylation, furnishing **161s** in an impressive 92% yield.

Next, the scope of the reaction was explored for a series of benzamide-based directing groups. Notably, the transformation proved compatible with various substituents, including methyl, fluoro, $-CF_3$, and $-NO_2$, positioned at the *para* and *meta* positions of the benzamide aryl ring, delivering the corresponding products **161t**–**161y** in good to excellent yields (47%–88%). Expanding the substrate scope further, heteroaromatic substrates such as furan and thiophene exhibited high reactivity, affording the desired products **161z** and **161aa** in excellent yields of 89% and 84%, respectively (**Scheme 3**).

It is particularly noteworthy that a substrate containing a urea moiety also performed well, yielding the arylated product **161ab** in a significant 72% yield, despite the potential for urea to chelate Pd and interfere with the catalytic cycle (see **Table 3**). Additionally, alternative acyl groups were tested to assess the reaction's versatility. For example, an adamantyl-based directing group was well accommodated, providing **161ac** in an 83% yield. The acetyl group was also compatible with BBr_3, though with a lower efficiency, affording **161ad** in a 38% yield. The widespread presence of the anilide functional group in biologically active compound highlights the significance of developing efficient methods for their functionalization. Many pharmaceuticals and bioactive compounds incorporate this moiety, making site-selective modifications highly valuable for medicinal chemistry and drug discovery. By demonstrating that the present arylation method is compatible with pharmaceutically relevant substrates, we highlight its potential utility in late-stage functionalization. Encouragingly, these structurally diverse substrates were well tolerated, delivering the desired arylated products **161ae**–**161ai** in good to excellent yields (**Scheme 3**, 47%–82%).

Substrate Scope for Benzylation: *N*–Aryl Component

We next explored the substrate scope to evaluate the generality of this *ortho*-benzylation strategy (**Scheme 4**). Initially, a range of pivalamides was examined, demonstrating excellent functional group tolerance.



Scheme 4. Reaction scope for benzylation- *N*-aryl part: Condition for (**163a–163k**): step 1 at 22 °C, 2 h. Condition for (**163l–163q**): step 1 at 40 °C for 16 h. [a]Step 2 at 70 °C for 16 h.

Both electron-donating and electron-withdrawing substituents at the *para* position were well accommodated, affording the desired benzylation products with yields ranging from moderate to excellent (**163a–163e**, 55–88%). Similarly, *meta*- and *ortho*-substituted substrates provided products in 59–71% yield (**163f–1631i**). Notably, bromo-substituted substrates, which are generally reactive in Pd-catalyzed reaction, remained intact, yielding the desired benzylation products in 55% and 71%, respectively (**163e** and **163f**). Additionally, an extended aromatic system successfully underwent benzylation, affording **163j** in 77% yield, while double benzylation proceeded efficiently, yielding **163k** in 80%.

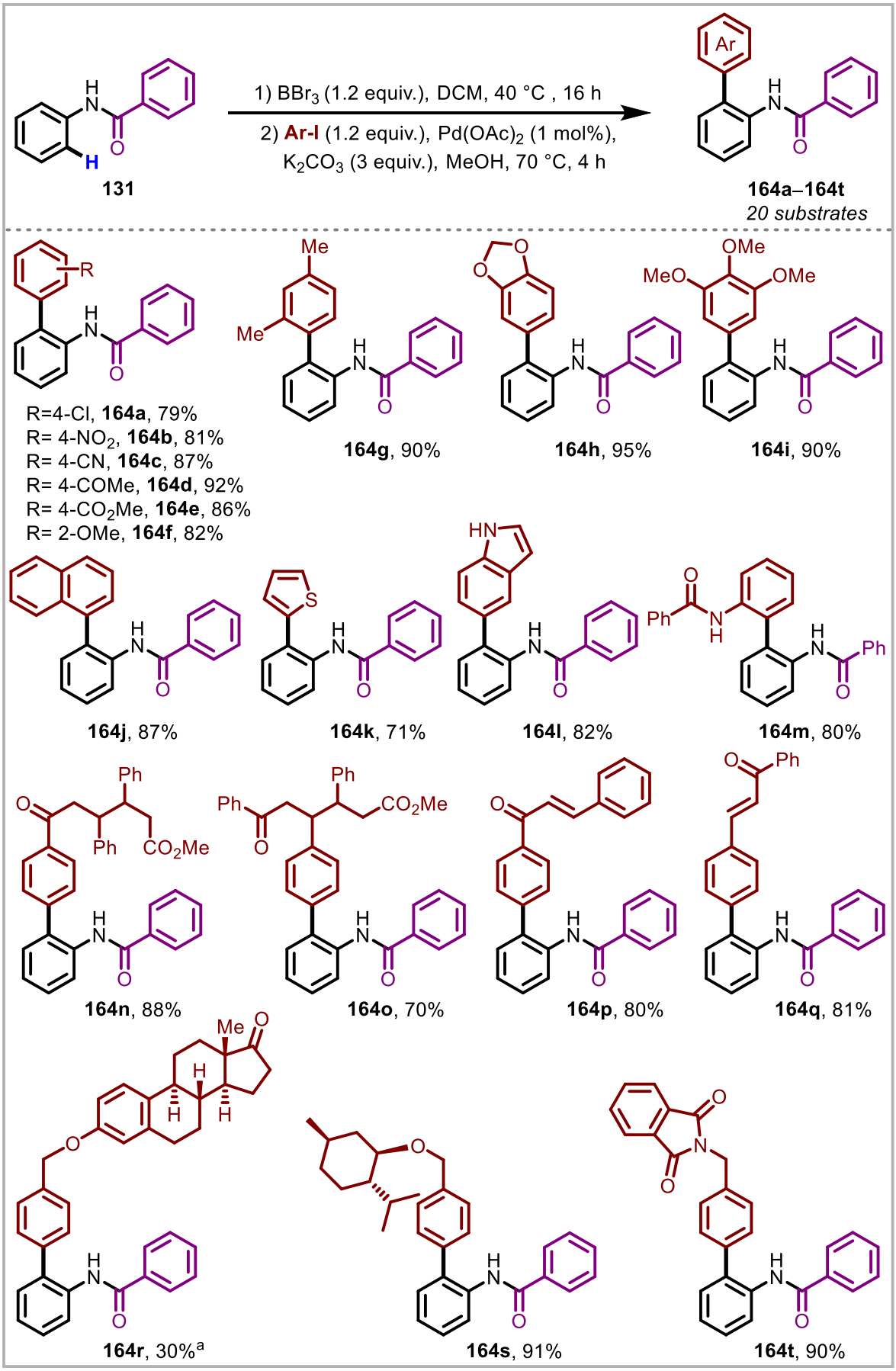
To further assess the selectivity and versatility of this method, we investigated benzanilides aiming to explore site-selective benzylation at the aniline portion of the ring (**Scheme 4**). The optimized conditions were well-suited for a variety of substituents, including methyl, fluoro, and trifluoromethyl, delivering the benzylated products (**163l**–**163o**) in moderate to excellent yields (**Scheme 4**, 68% to 94%). Furthermore, heterocyclic anilides displayed excellent reactivity, producing the desired benzylation products in 84% and 86% yields, respectively (**163p**–**163q**).

Despite the excellent performance of the reaction, purification posed a significant challenge. If the starting material **121** and **131** remained unreacted in the initial borylation step, it carried over into the subsequent benzylation step. Additionally, some degree of protodeborylation could occur during the reaction, regenerating the starting material and further complicating purification. The minimal polarity difference between the unreacted starting material and the desired product made their separation challenging. However, this issue was effectively addressed by employing a high-capacity column, which facilitated efficient purification. Alternatively, manual column chromatography with increased column height provided sufficient resolution to separate trace amounts of the starting material from the product.

Substrate Scope for Arylation: Aryl Iodide Component

After thoroughly investigating the reactivity of various aniline-based substrates and directing groups for arylation and benzylation, we next focused on the reactivity of different aryl iodides and benzyl bromides. Remarkably, the reaction displayed high tolerance to a broad range of functional groups. A diverse array of aryl iodides, including those bearing -chloro, -cyano, -nitro, -ketone, and -ester functional groups at the *para* position, smoothly participated in the reaction, yielding the desired products in excellent yields (**Scheme 5**, **164a**–**164e**, 79%–92%). Furthermore, substrates bearing electron-donating methoxy groups at the *ortho*-position, as well as disubstituted, trisubstituted, and naphthyl-containing aryl iodides, all demonstrated excellent reactivity, producing products **164f**–**164j** in 82%–95% yield, demonstrating its ability to handle more sterically hindered and electronically diverse substrates.

Heteroaromatic substrates, such as thiophene, unprotected indole, and amide derivatives, were also effectively tolerated, delivering the desired products in excellent yields (**Scheme 5**, **164k**–**164m**, 71%–82%). For example, the 5-iodo-1*H*-indole underwent smooth coupling with benzanilide (**131a**) to yield the indole derivative **164l** in 82% yield. Our investigation continued with oxotriphenylhexanoate (OTHO) molecules, which were originally discovered by our group as low molecular weight gelators that can self-assemble into three-dimensional networks in solution.[140]



Scheme 5. Reaction scope for arylation- aryl iodides: [a] 1.3 equiv. of aryl iodide.

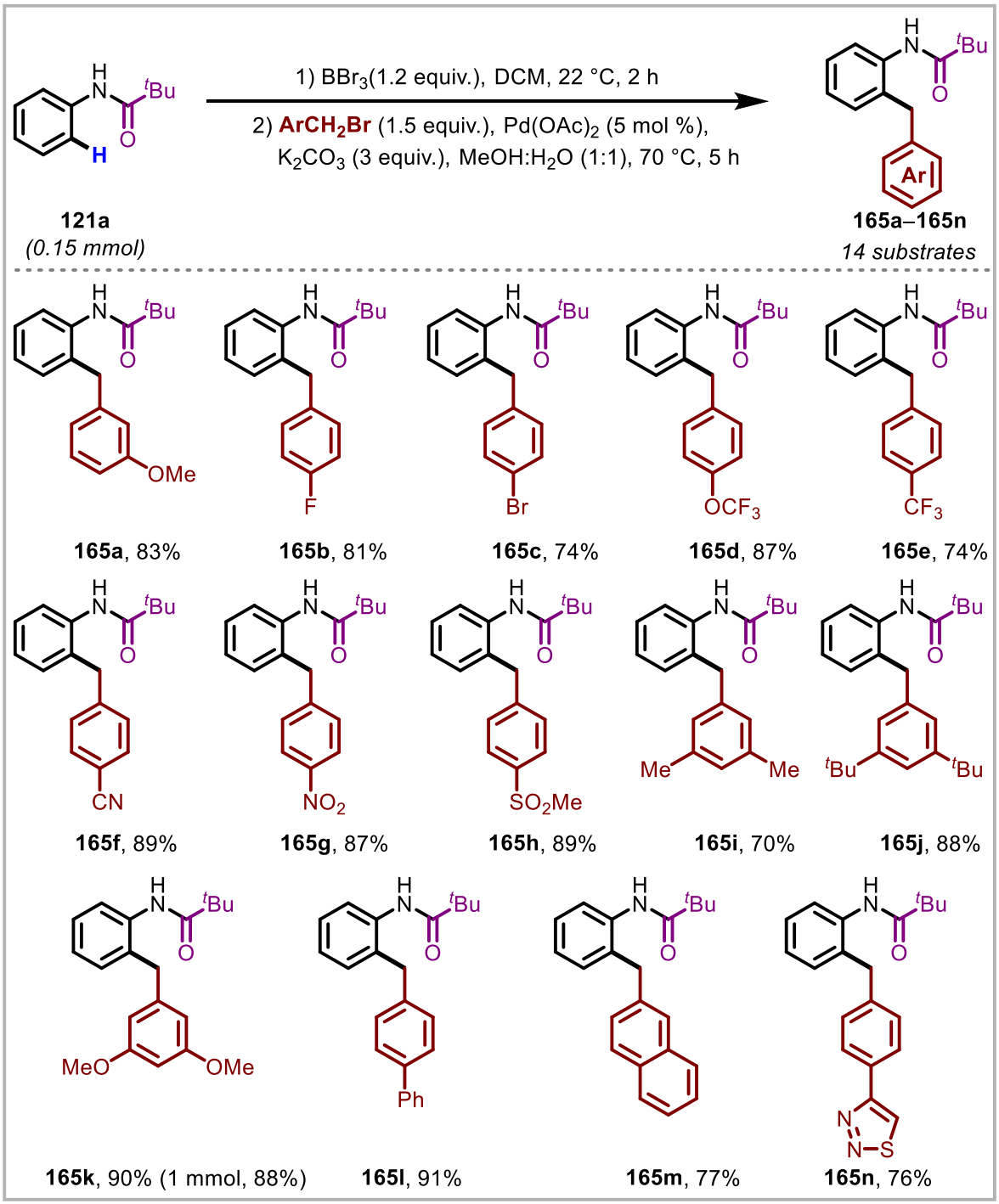
These molecules are known to undergo cyclization under BBr_3 conditions;[10] however, under our optimized reaction conditions, no such reactivity was observed. Instead, the desired products **164n** and **164o** were obtained in excellent yields of 88% and 70%, respectively (**Scheme 5**). This result emphasizes the effectiveness of our method in facilitating the synthesis of complex molecules.

Further studies revealed that iodide-containing chalcone substrates were also compatible with our reaction conditions, yielding products **164p** and **164q** in 80% and 81% yield, respectively, without any undesired Heck-type side reactions. Lastly, we extended our investigation to more complex substrates with pharmaceutical relevance, including estrone, L-menthol, and phthalimide derivatives. Encouragingly, despite being challenging, these substrates were well tolerated, with the desired products **164r**–**164t** isolated in yields ranging from low to excellent (**Scheme 5**, 30%–91%).

Substrate Scope for Benzylation: Benzyl Bromide Component

Building on the successful benzylation of various anilides, we next explored the scope of the benzyl bromide component using *N*–phenylpivalamide (**121a**) as the substrate (**Scheme 6**). Benzyl bromides bearing methoxy, halogen, and trifluoromethoxy ($-OCF_3$) substituents were well tolerated under the optimized conditions, affording the corresponding products (**Scheme 6**, **165a**–**165d**) in 74–87% yield. Similarly, benzylation with electron-withdrawing groups at the para position proceeded efficiently, yielding the desired products (**165e**–**165h**) in 74–89% yield. These results highlight the broad applicability of this strategy, demonstrating excellent functional group tolerance across a range of electronic environments.

Further extending the substrate scope, disubstituted benzyl bromides and extended aromatic systems were also well accommodated, furnishing the benzylated products (**Scheme 6**, **165i**–**165m**) in 70–91% yield. Notably, a scale-up reaction conducted on a 1 mmol scale for the synthesis of **165k** proceeded with high efficiency, highlighting the robustness and practicality of the method. Additionally, the introduction of a heterocyclic thiadiazole moiety via benzyl bromide was successfully achieved, delivering **165n** in 76% yield without compromising reaction efficiency.

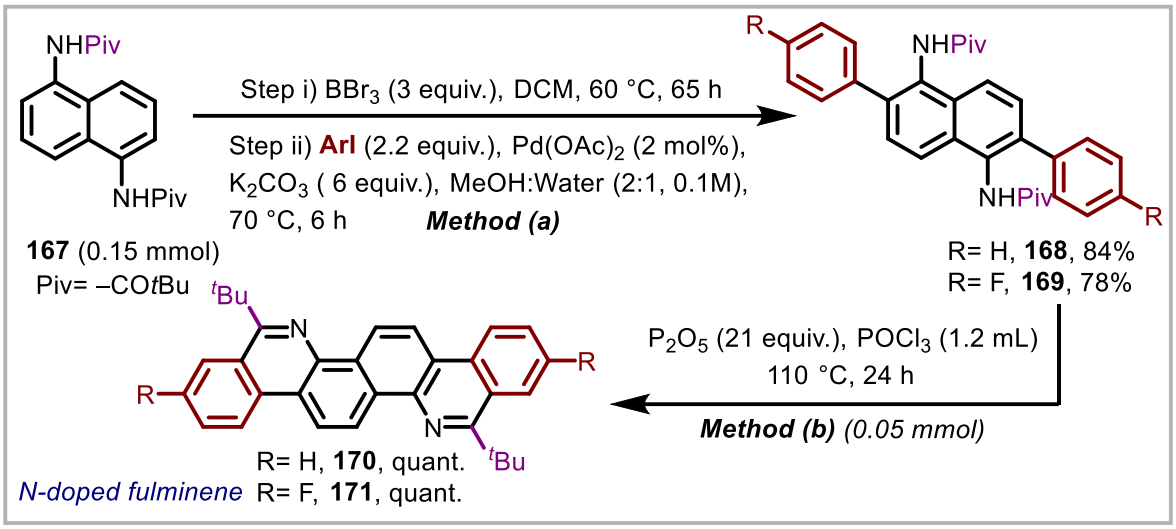


Scheme 6. Reaction scope for benzylation- benzyl part.

Application: Diagonal difunctionalization

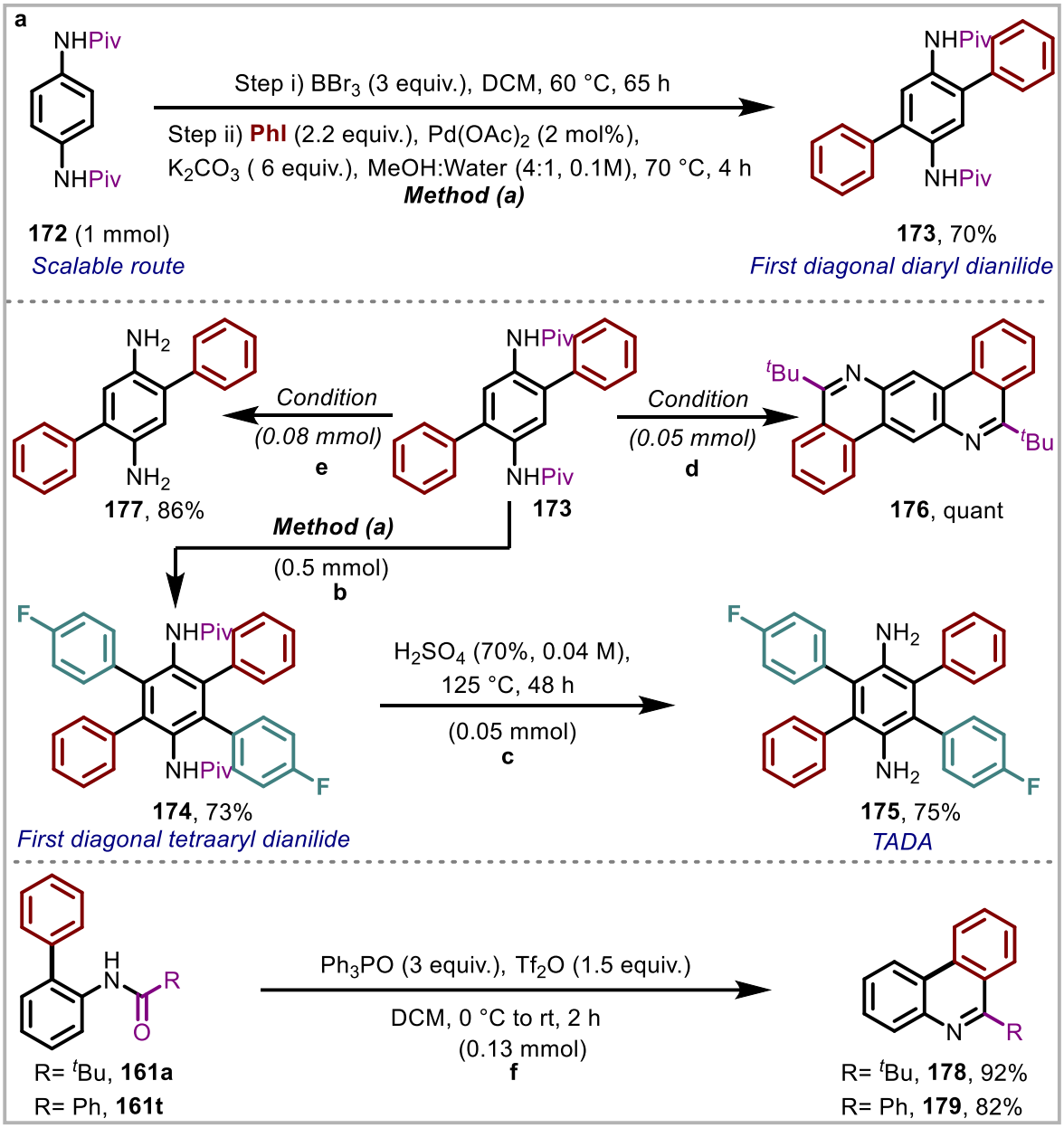
After successfully demonstrating the broad substrate scope and functional group compatibility of our protocol, we next explored its potential applications in polycyclic aromatic hydrocarbons (PAHs). PAHs are highly regarded in materials chemistry for their diverse roles, ranging from organic field-effect transistors (OFETs) to catalysis.[141] In particular, *N*,*N*′–(1,4–phenylene)diamides have proven to be valuable starting materials for the synthesis of compounds utilized in these advanced applications. To explore the potential of our developed method for the diagonal functionalization of *N*,*N*′–(1,4–phenylene)diamides, we subjected a

naphthalene-derived dianilide **167** to our two-step reaction conditions. This treatment resulted in the successful diphenyl-functionalization of dianilide **168** with an 84% yield (**Scheme 7**). Notably, the phenyl group is readily alterable; for example, treating **167** with 4-fluoroiodobenzene produced the fluorinated diagonally arylated compound **169** in 78% yield. With these two diarylated dianilides in hand, we proceeded to demonstrate their utility as starting materials for the synthesis of *N*–doped fulminene derivatives **170** and **171** (**Scheme 7**). Notably, we successfully synthesized *N*–doped fulminene from diarylated products in quantitative yields.



Scheme 7. Aplications: Synthesis of diagonal diaryl systems and synthesis of *N*-doped fulminene.

Building on the success of the diagonal di-arylation, we applied our approach to the synthesis of tetraaryl di-pivalamides, specifically targeting tetraarylbenzenediamines (TADA) (**Schemes 8a–c**). The two-step procedure was initiated by the diagonal installation of two aryl units on **172**, yielding the desired product **173** in 70% yield (**Scheme 8a**). Intermediate **173** was further subjected to a second diagonal di-arylation, leading to the formation of diagonal tetraaryl dipivalamide **174**, which was isolated in 73% yield (**Scheme 8b**). Tetraaryl dipivalamide **174** was then hydrolyzed using sulfuric acid to yield the TADA derivative **175** in 75% yield (**Scheme 8c**). Additionally, compound **173** was found to be a valuable precursor for the synthesis of extended heteroaromatic systems. Treatment with P_2O_5 and $POCl_3$ afforded the *N*–doped benzo[*k*]tetraphene **176** in quantitative yield (**Scheme 8d**). Upon deprotection, compound **173** led to the formation of diagonal diarylbenzenediamine **177**, which was isolated in 86% yield (**Scheme 8e**). Lastly, phenanthridine derivatives **178** and **179** were successfully synthesized by subjecting **161a** and **161t** to reaction conditions with Ph_3PO and Tf_2O, achieving yields of 92% and 82%, respectively (**Scheme 8f**).

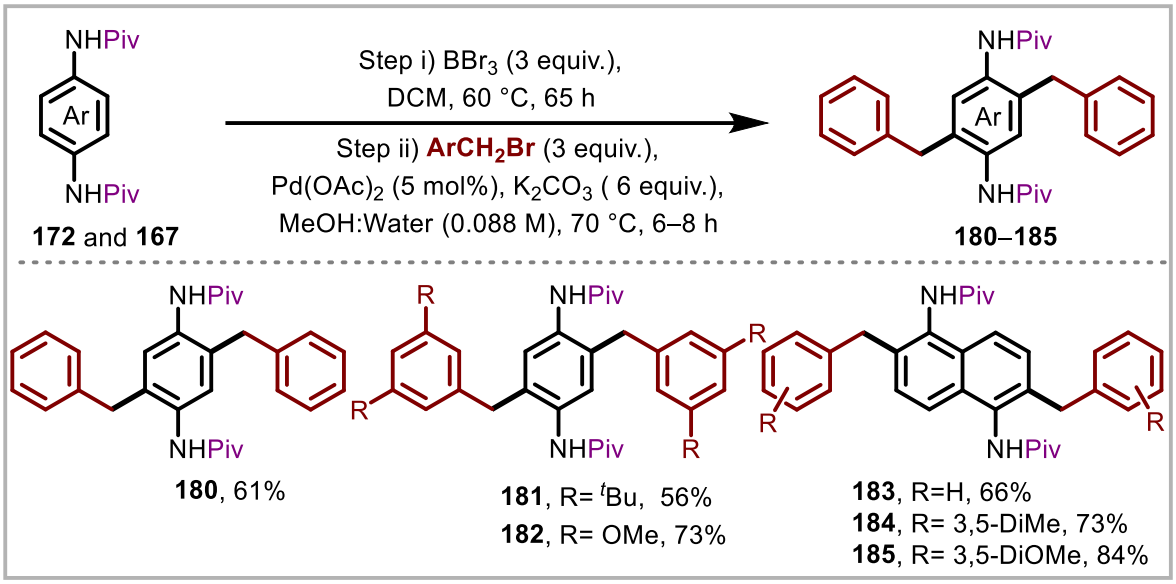


Scheme 8. Aplications: a) Scalable synthesis of diagonal diphenyldianilides. b) Synthesis of isoquinolino-phenanthridine derivative; Condition: P_2O_5 (21 equiv.), $POCl_3$ (1.2 mL), 110 °C, 24 h. c) Pivaloyl deprotection; Condition: H_2SO_4 (70%, 0.1M), 125 °C 20 h. d) Synthesis of diagonal tetraaryldianilides; Condition: step ii) 4-F-PhI (3 equiv.), MeOH:Water (3:2), 18 h. f) Synthesis of phenanthridine derivatives.

Building on our diarylation strategy, we extended this approach to achieve one-pot dibenzylation of dianilides (**Scheme 9**). The development of a diagonal dibenzylation strategy is particularly significant, as these compounds can serve as key intermediates for the synthesis of diagonal azepines[142] through subsequent cyclization.

Notably, the reaction proved to be both general and highly selective, efficiently converting dianilides **172** and **167** into the corresponding dibenzylated products upon treatment with various benzyl bromides (**Scheme 9**, **180**–**185**). Disubstituted benzyl bromides bearing *tert*–butyl and methoxy groups were well tolerated, affording **181** and **182** in 56% and 73% yield, respectively, with complete selectivity for the diagonal product. Furthermore, a naphthalene-

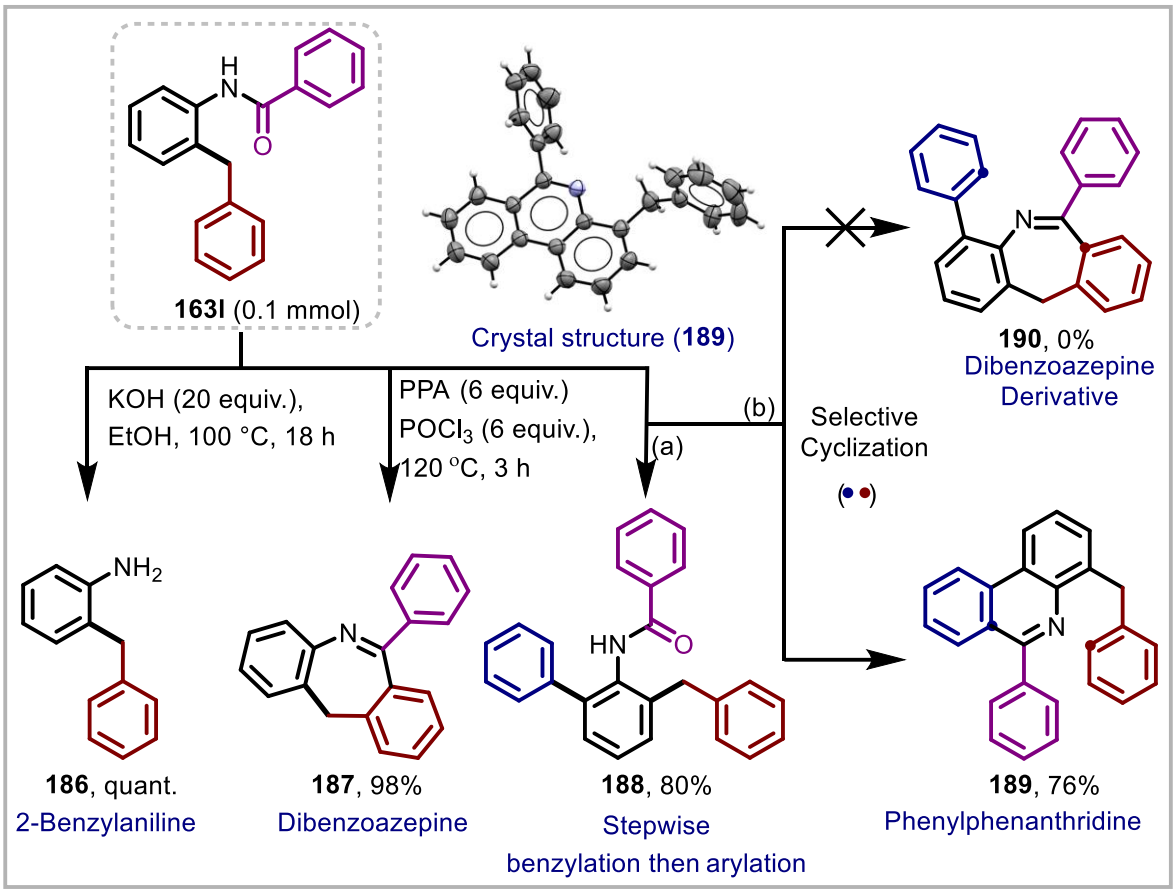
derived dianilide (**167**) underwent efficient conversion, yielding diagonal dibenzylation products (**183–185**) in 66–84% yield.



Scheme 9. Reaction scope: Diagonal dibenzylation of dianilides

To highlight the synthetic potential of benzylation protocol, we explored a series of transformations using **163l**, demonstrating its applicability in constructing core structures found in biologically active compounds (**Scheme 10**).

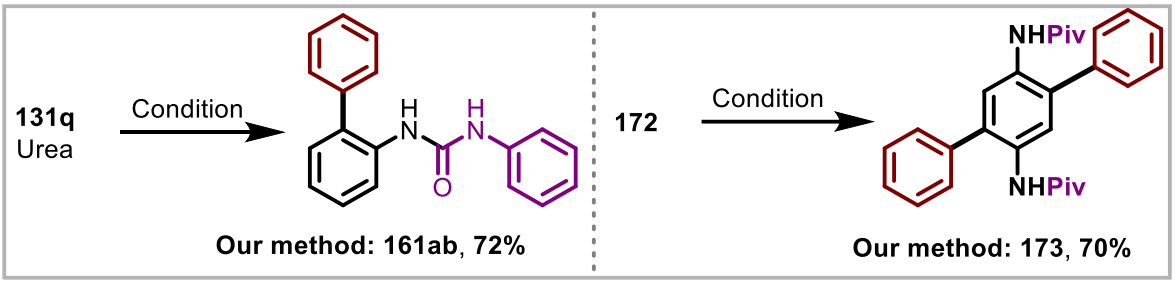
For instance, under basic conditions, **163l** was smoothly converted into the corresponding 2–benzylaniline (**186**) in quantitative yield. Furthermore, the benzyl group underwent an acid-catalyzed intramolecular cyclization, furnishing the pharmaceutically relevant dibenzoazepine[142] (**187**) in 98% yield. Expanding this approach, we synthesized a difunctional benzanilide (**188**) in 80% yield using sequential benzylation and arylation of a dibromoboracycle. This transformation is particularly noteworthy, as **188** serves as a direct precursor to selective phenanthridine derivatives. Interestingly, under acidic conditions, the cyclization pathway selectively led to the formation of **189**, a phenanthridine derivative, rather than the dibenzoazepine (**190**), emphasizing the chemoselectivity of the reaction. This selectivity can be explained by the preference for six-membered ring formation over seven-membered ring.



Scheme 10. Applications. Condition (a): **163l** (0.3 mmol), BBr_3 (1.2 equiv.), DCM, 40 °C, 24 h, then Iodobenzene (1.2 equiv.), $Pd(OAC)_2$ (2 mol%), K_2CO_3 (3 equiv.), methanol, 70 °C, 4 h. Condition (b): PPA (10 equiv.), $POCl_3$ (10 equiv.), 120 °C, 3.5 h.

To evaluate the effectiveness of our protocol compared to other established methods for directed C–H arylation, we subjected urea derivative **131q** to several reaction conditions typically used in such reactions (**Table 3**, entries 1–4). Our findings demonstrated that, among the tested conditions, only one methodology resulted in the formation of the desired product **161ab**, but with a relatively low yield (**Table 3**, entry 2). Building on these results, we demonstrated reported protocols to the diagonal diarylation of substrate **172** under similar conditions (**Table 3**, entries 5–8). Interestingly, only the conditions involving a Ru-catalyzed process[133] were able to produce the desired product **173**, though with a modest isolated yield of 7% and several unidentified side products (**Table 3**, entry 6). The failure of selected reported methods could be due to competition from two directing groups or the involvement of four C–H bonds. In contrast, our borylation protocol focuses on the electronic factors of the aromatic ring rather than relying on C–H bond activation. This allowed for precise diborylation at a diagonal position, overcoming the challenges faced by other methods

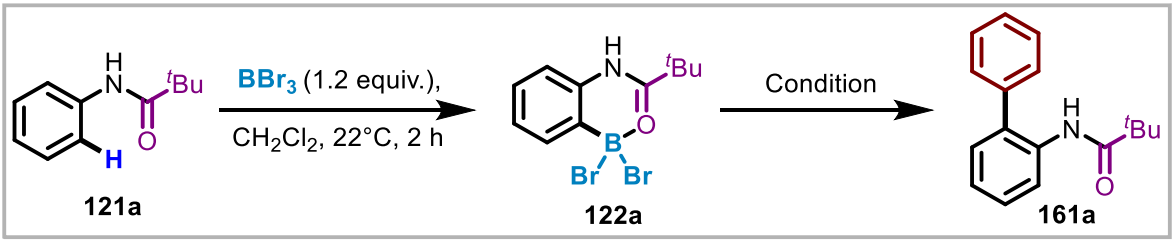
Table 3. Comparison study with reported methods



Entry	Condition	Yield (161ab)	Entry	Condition	Yield (173)
1	Rh (*ref. 134*)	0%	5	Rh (*ref. 134*)	0%
2	Ru (*ref. 133*)	19%	6	Ru (*ref. 133*)	7%
3	Pd (*ref. 136*)	0%	7	Pd (*ref. 136*)	0%
4	Pd (*ref. 139*)	0%	8	Pd (*ref. 139*)	0%

To gain deeper insights into the mechanism of the reaction, control experiments were conducted, revealing that all components of the reaction protocol such as catalyst, base, and methanol are essential for optimal performance (**Table 4**, entry 1 vs entries 2–3).

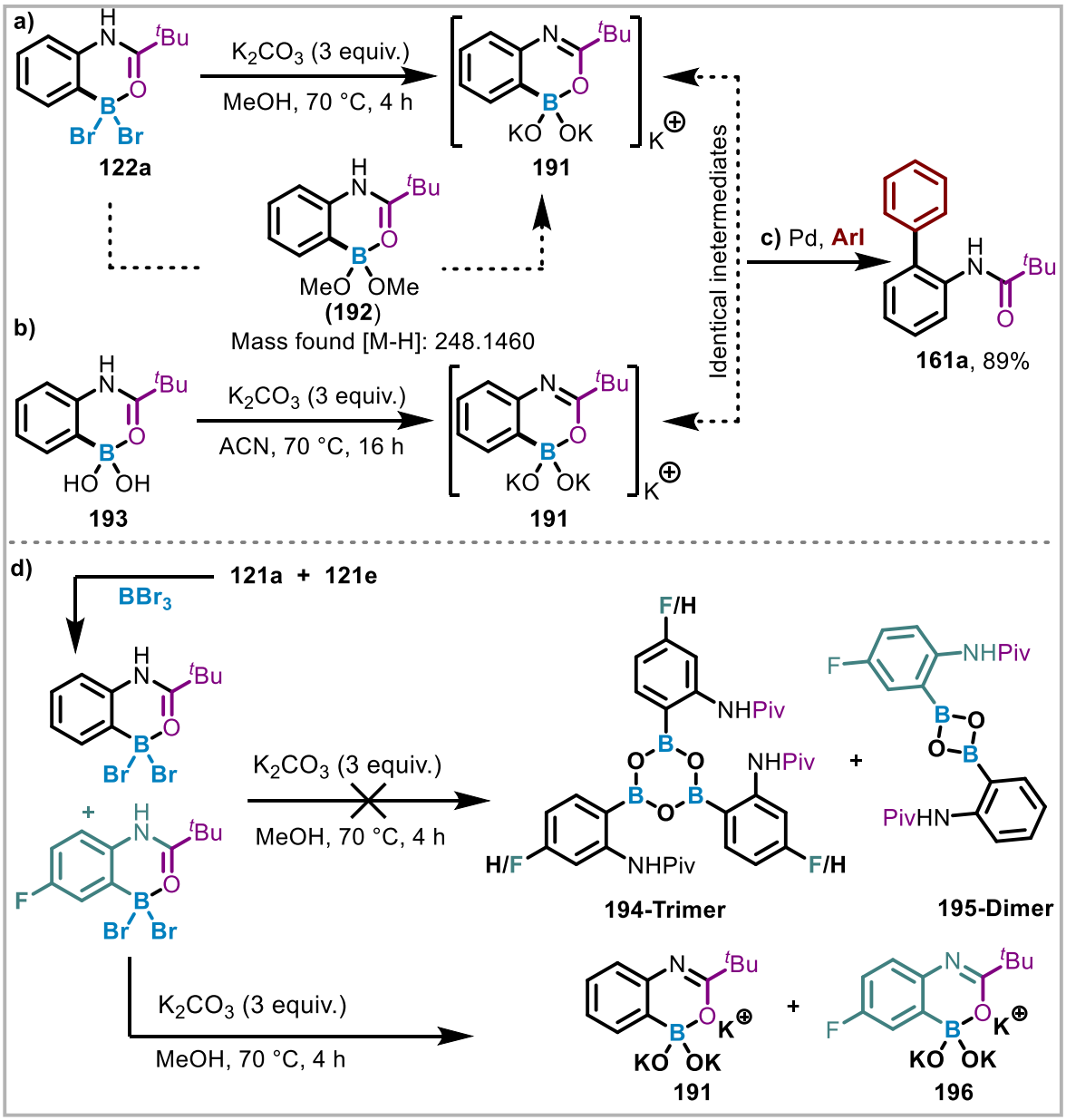
Table 4: Control experiments



Entry	Deviation	Yield
1	None[a]	**161a**, 89%[b]
2	No base	**161a**, 0%[c]
3	No BBr_3	**161a**, 0%[c]
4	Step ii) ACN instead of methanol, 20 h	**161a**, 0%[c]
5	ACN and 4 equiv. of methanol, 20 h	**161a**, 82%[c]
6	Step ii) Only K_2CO_3, methanol, 70 °C for 4 h	**191**
7	**191**, $Pd(OAc)_2$, PhI, ACN, 70 °C, 4 h	**161a**, 89%[b]

[a]**Reaction conditions:** Step i) **121a** (0.15 mmol), BBr_3 (0.18 mmol), in 0.5 mL anhydrous DCM at 22 °C, 2 h; Step ii) Iodobenzene (0.18 mmol), K_2CO_3 (0.45 mmol), $Pd(OAc)_2$ (1 mol%), in 1.5 mL MeOH at 22 °C to 70 °C for 4 h. [b]Isolated yield. [c]GC yield, *o*-xylene as an internal standard.

To further assess the reactivity of complex (**122a**) and evaluate the role of methanol, experiments were carried out using various solvents, as outlined in **Table 4** (entry 4) and **Table 1** (solvents screening). Interestingly, none of the solvents tested were suitable for this transformation, indicating that methanol plays a crucial role in the reaction. However, when the reaction was performed in ACN with as little as 4 equiv. of methanol under similar conditions, the product was obtained in 82 % yield (**Table 4**, entry 5 vs entry 4). These results suggest that the reaction likely proceeds through ligand exchange on boron facilitated by methanol.[143]



Scheme 11. a) Reaction of dibromo intermediate (**122a**) under basic condition. b) Reaction of boronic acid (**193**) under basic condition. c) *Ortho*-arylation of intermediate (**191**). d) Confirmation of intermediate.

Furthermore, stirring the reaction in the absence of both Pd and iodobenzene led to the formation of a new compound, as indicated by the NMR analysis (**Figure 2**) of the crude reaction mixture (**Scheme 11a**, entry 6, **Table 4**). Initially, we hypothesized that this species

could be a boronic dimer or trimer. However, cross-reaction control experiments demonstrated that no evidence for dimer or trimer formation was observed under the reaction conditions (**Scheme 11d**). The NMR analysis revealed two distinct patterns corresponding to different products (**Figure 2**). This observation further supports the absence of dimer or trimer formation and suggests the presence of a new intermediate beyond these possibilities. These results suggest that an anionic form of the boronic acid (**191**) is likely formed in the reaction mixture, potentially through a dimethoxy intermediate (**192**) (**Scheme 11a**). To further probe this hypothesis, **191** was subjected to the standard reaction conditions, yielding **161a** in 89%, thereby providing strong evidence for its involvement in the reaction mechanism (**Table 4**, entry 7, **Scheme 11c**).

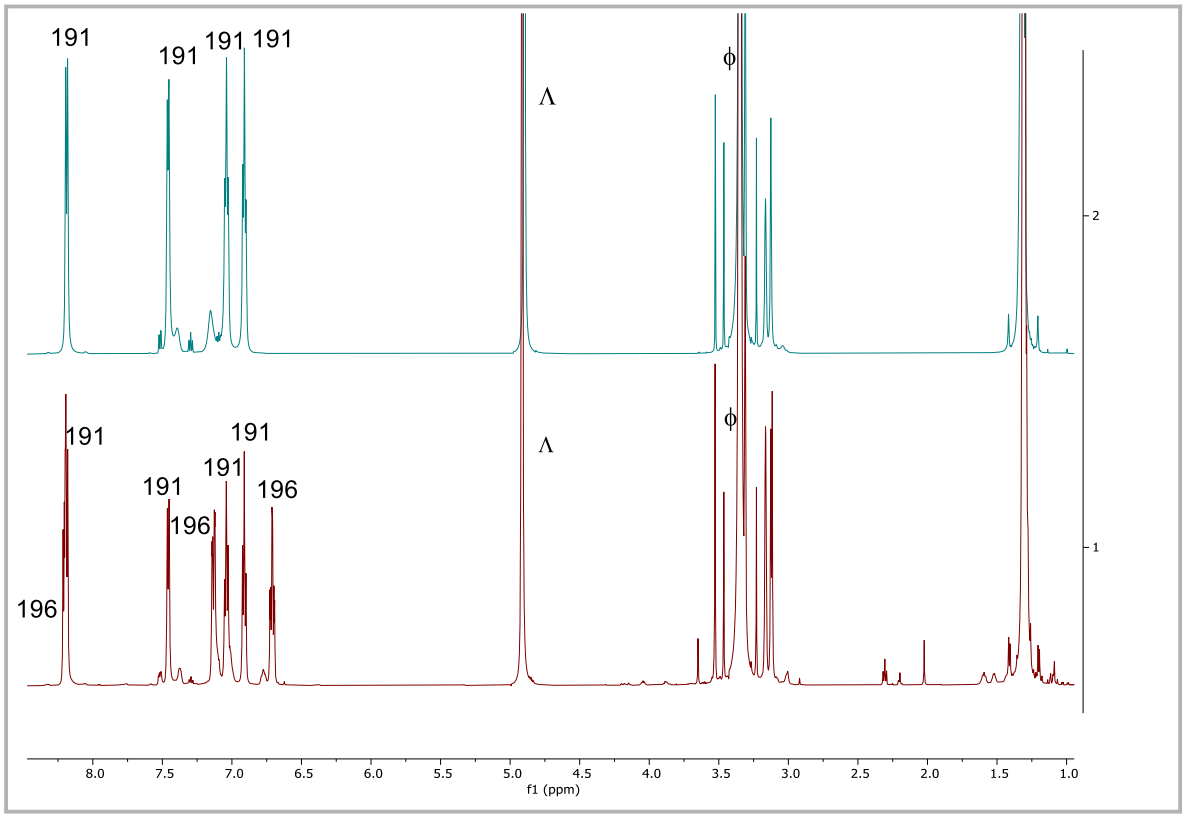
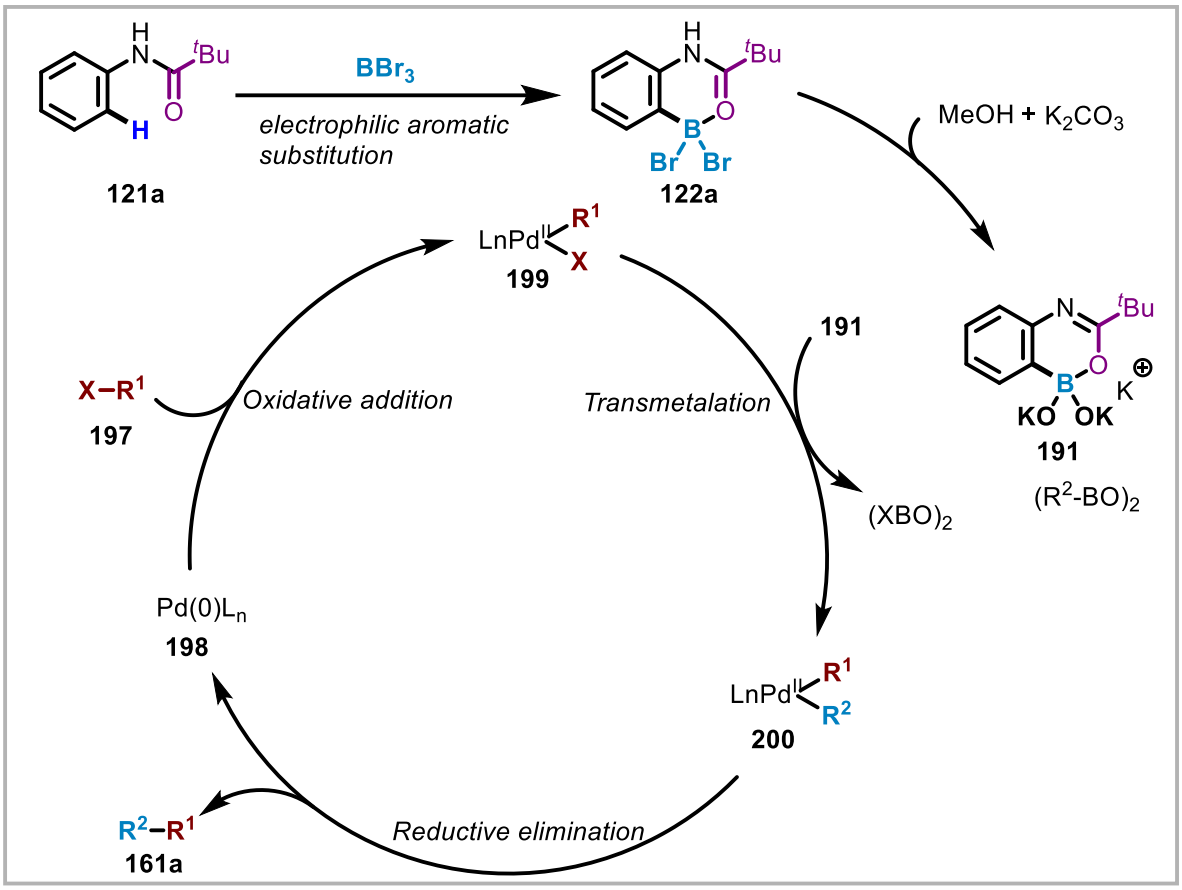


Figure 2: Stacked NMR of products **191** and **196**, CD_3OD (Λ= Water, ϕ= Methanol).

Based on control experiments, we propose a reaction mechanism that begins with the carbonyl-directed borylation of **121a**, generating the dibromoboracycle **122a** (**Scheme 12**). Under basic conditions, ligand exchange converts **122a** into its dimethoxy analogue **196** (**Scheme 11a**), which subsequently transforms into the anionic species **191**. Notably, **191** exhibits greater susceptibility to transmetalation compared to its dibromo counterpart, as evidenced by the absence of product formation in reactions performed without alcohol or water (**Table 4**, entry 4, **Table 1** solvent studies).

The catalytic cycle initiates with the oxidative addition of the aryl halide (**197**) to Pd(0), forming intermediate **199**. Transmetalation between **199** and boron species **191** subsequently generates intermediate **200**. Finally, reductive elimination from **200** furnishes the desired cross-coupling product **161a**, completing the catalytic cycle.



Scheme 12. Proposed mechanism.

3. Conclusion

In this study, we developed an efficient and versatile dibromoboracycle system as a readily accessible boron reagent for SM cross-coupling. This work significantly broadens the scope of BBr_3-mediated borylation by enabling both C(sp^2)–C(sp^2) and C(sp^2)–C(sp^3) bond formation, providing a unified strategy for selective functionalization. Unlike conventional methods, which often struggle with challenging substrates, our approach successfully facilitates the arylation of urea-derived substrates, diagonal diarylation of benzene diamides, and benzylation of anilides, showcasing the unique reactivity of our boracycle system.

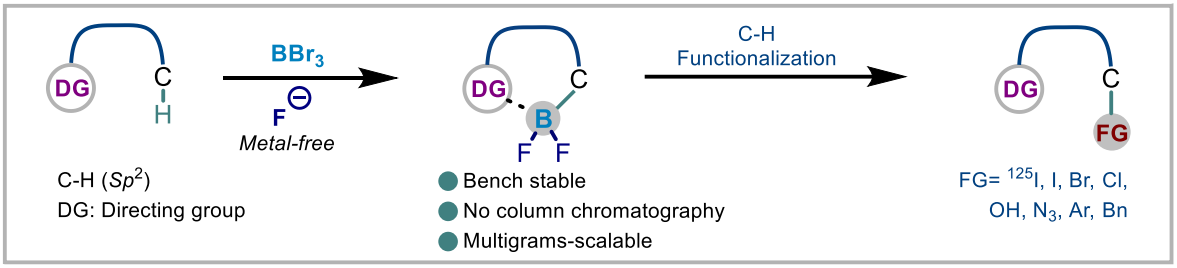
A major strength of this methodology lies in its broad substrate scope and functional group tolerance, accommodating sterically hindered, electronically varied, and heteroaromatic systems. This enables the synthesis of complex molecules, including diagonal tetraarylbenzenediamines, *N*–doped fulminenes, and dibenzoazepines, which are valuable in pharmaceutical and materials science applications. Additionally, the development of a one-pot diagonal dibenzylation strategy further extends the applicability of this approach, opening new opportunities for the streamlined synthesis of advanced organic frameworks.

Beyond its synthetic utility, this study demonstrates the potential of dibromoboracycles as an alternative for directed *ortho*-functionalization strategies in cross-coupling reactions. The mild reaction conditions, low catalyst loading, and operational simplicity make this methodology highly practical and scalable. Furthermore, the distinct reactivity patterns enabled by BBr_3-

mediated activation open new avenues for late-stage diversification, functionalization of complex molecular architectures, and pharmaceutical scaffold development. These findings demonstrate the broad applicability of boron-based chemistry in modern synthesis, offering innovative solutions for C–H activation and cross-coupling.

Chapter 5

Introducing Aryl-Difluoroborane: A Versatile Building for the Late Stage Diversification



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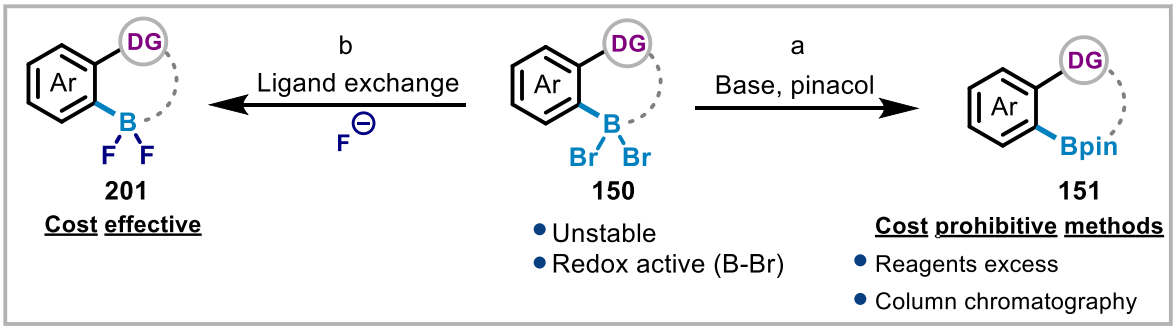
Shinde, G. H.; Babiker, J.; Prigent, A.; Foucras, G.; Amombo Noa, F. M.; Öhrström, L.; Cailly, T.*; and Sundén, H*. Introducing Aryl–Difluoroborane: A Versatile Building Block for Selective *Ortho*-Functionalization, Radioiodination, and Cross-Coupling Reactions.
Manuscript. **2025**.

Author Contributions: H. S. supervised the overall project. G. H. S. designed the study. Experimental work for BF_2 was carried out by G. H. S. and J.B.
Experimental work for radioiodination was carried out by P.A, F.G. and C.T.
F. M. A. N. and L. O. contributed to the crystal structure analysis.
H. S. and G. H. S. co-wrote the manuscript.

1. Introduction

Selective C–H borylation has emerged as a powerful strategy in modern organic synthesis, enabling the construction of valuable organoboron compounds for cross-coupling reactions and functionalization processes.[59-61] Traditional methods, such as directed *ortho*-metalation and transition-metal-catalyzed C–H activation, have proven effective for regioselective borylation (refer **chapter 1**, section 4). However, these approaches often rely on strong bases or precious metal catalysts, limiting their applicability in pharmaceutical and large-scale synthesis due to functional group incompatibilities, cost, and sustainability concerns.

As an alternative, BBr_3-directed *ortho*-borylation[63] has emerged as a metal-free, selective approach for C–H borylation, efficiently generating dibromoboracycles (**150**) (**Scheme 1**). This method leverages donor atoms such as nitrogen,[63] oxygen,[63] phosphorus,[81] and sulfur[82] to direct boron installation at the *ortho*-position, providing a practical alternative to transition-metal catalysis. Dibromoboracycles (**150**), however, are prone to oxidative ligand exchange or nucleophilic substitution due to the lability of the boron–bromine bond. To enhance their stability and synthetic utility, they are typically converted into boronic acid pinacol esters (**151**).



Scheme 1. a) State-of-the-art for BBr_2 to Bpin. b) Research question.

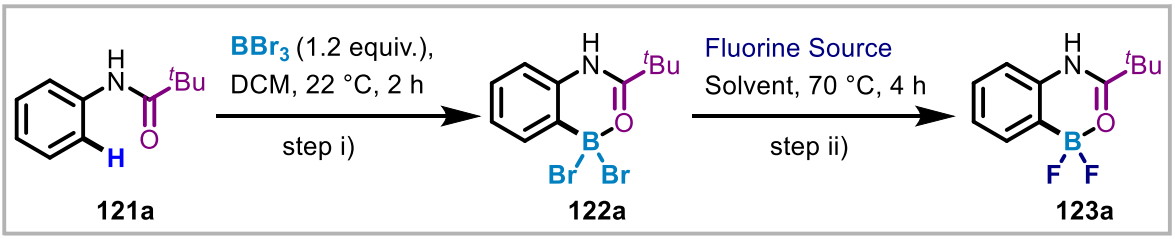
While Bpins provide a practical solution to boron instability, their synthesis often requires excess reagents and additional purification steps, such as column chromatography. To develop a more versatile and practical synthesis, we hypothesized that BF_2-containing compounds (**201**) could serve as an alternative to BPins, offering enhanced stability while maintaining reactivity. Our previous work (**Chapters 2** and **3**) demonstrated that BF_2 species exhibit unique properties, including high polarity, which facilitates easy purification without the need for chromatography, providing an important advantage in large-scale synthesis

In this work, we present a metal-free, chromatography-free, and scalable synthetic route to Ar–BF_2 compounds, demonstrating their versatility in late-stage functionalization and cross-coupling applications. This strategy represents a significant advancement in organoboron chemistry, expanding the utility of BBr_3-mediated borylation and introducing a new class of stable boron intermediates for modern organic synthesis.

2. Results and Discussion

The primary objective of this study shifted towards identifying the appropriate fluorine source and solvent to facilitate the formation of Ar–BF_2 (**123a**). Building on our previous work, where we discovered that tetrafluoroborates are effective fluorine sources, we focused on exploring tetrafluoroborates as a key source for fluorine in this study.

Table 1. Selected Reaction Optimization (0.6 mmol Scale)[a]

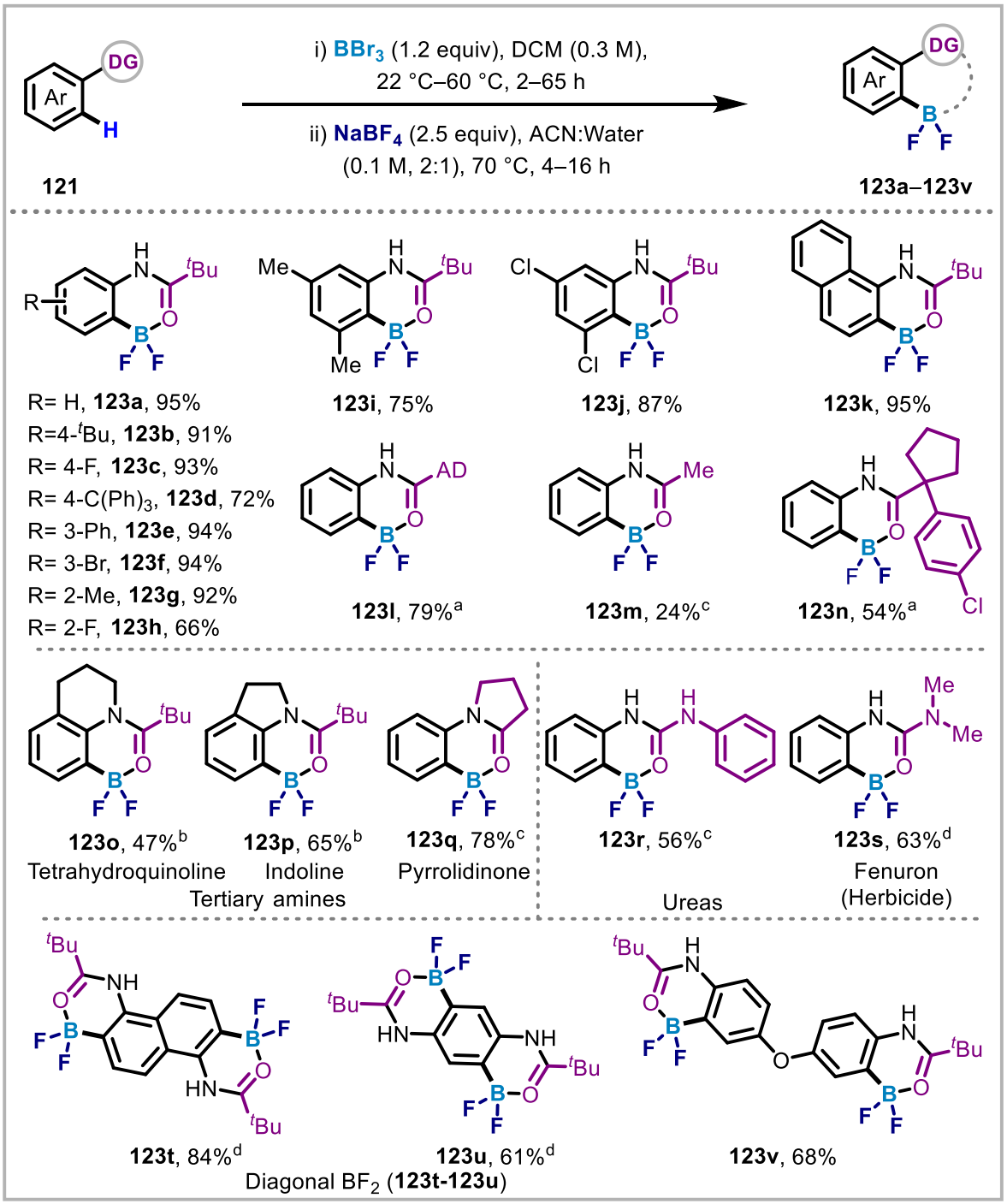


Entry	Fluorine Source (equiv.)	Solvent (ratio)	Yield[(c)] (123a)
1	$NaBF_4$ (2.5)	MeOH	80%
2	$NaBF_4$ (2.5)	MeOH:Water (2:1)	91%
3	**$NaBF_4$ (2.5)**	**ACN:Water (2:1)**	**95%**
4	$NaBF_4$ (2.2)	ACN:Water (2:1)	89%
5	KBF_4 (2.5)	ACN:Water (2:1)	94%
6	$LiBF_4$ (2.5)	ACN:Water (2:1)	93%
7[(b)]	KF (2.5)	ACN:Water (2:1)	89%
8[(b)]	CsF (2.5)	ACN:Water (2:1)	86%
9	KHF_2 (2.5)	ACN:Water (2:1)	85%

[a]**Reaction conditions:** Step i) **121a** (0.6 mmol), BBr_3 (0.72 mmol), in 2 mL anhydrous DCM at 22 °C, 2 h; Step ii) $NaBF_4$ (1.5 mmol) in 4 mL ACN and 2 mL distilled water, at 70 °C for 4 h; [b]step ii) time 6 h; [c]Isolated yields.

We began with sodium tetrafluoroborate as a fluoride source and selected methanol as the solvent due to solubility considerations, obtaining the desired product in 80% (**Table 1**, entry 1). Introducing water improved solubility and increased the yield to 91% (**Table 1**, entry 2). Further switching to ACN enhanced the yield to 95%, outperforming the methanol system (**Table 1**, entry 3 vs entry 2). Reducing the fluoride source loading slightly decreased the yield to 89% (**Table 1**, entry 4 vs entry 3). Testing other tetrafluoroborate salts showed similar yields (**Table 1**, entries 5–6), and considering availability and cost, $NaBF_4$ was selected as the preferred fluoride source. Alkaline fluoride sources were effective but resulted in slower reactions with yields ranging from 85% to 89% (**Table 1**, entries 7–9).

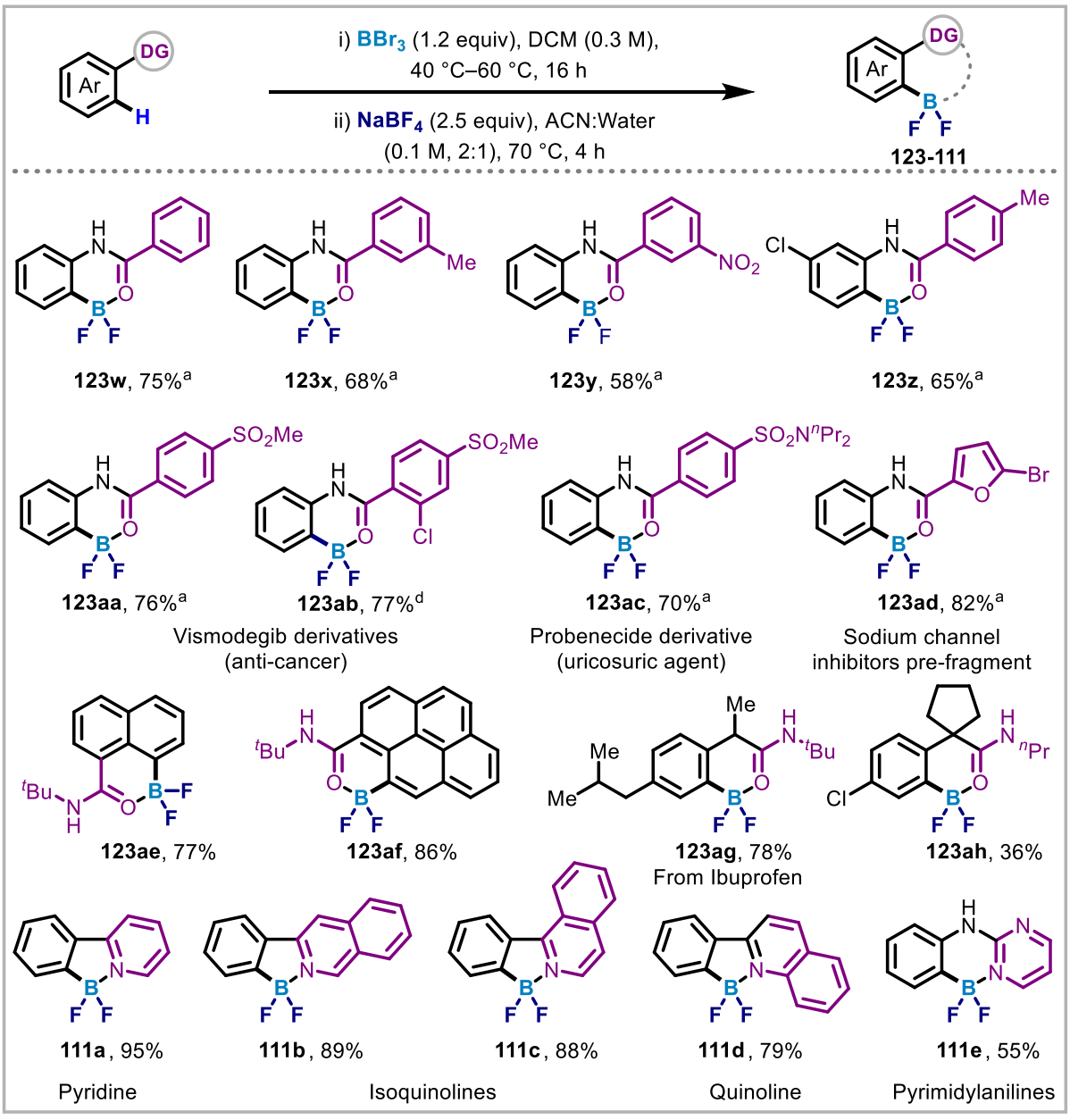
Following the identification of the optimal fluorine source for difluoroboron formation, the reaction was tested across a broad range of directing groups. Initially, a set of pivalamides (**Scheme 2a**, **121**) was assessed, demonstrating robust tolerance for various functional groups. Both electron-donating and electron-withdrawing substituents at *ortho*, *meta*, and *para* positions gave high yields, ranging from 66% to 95% (**Scheme 2a**, **123a**–**123h**).



Scheme 2a. Reaction scope, Condition (**123a**–**123k**, **123o**, **123q**): Step i) Amide (0.6 mmol, 1 equiv.), BBr_3 (0.72 mmol, 1.2 equiv.), in 2 mL anhydrous DCM at 22 °C, 2 h; Step ii) $NaBF_4$ (1.5 mmol, 2.5 equiv.) in 4 mL ACN and 2 mL distilled water, at 70 °C for 4 h. [a]Step i) at 40 °C, 16 h. [b]Step i) time 1 h. [c]Step i) at 60 °C, 24 h. For product **123t**–**123u**: Step i) Amide (0.6 mmol, 1 equiv.), BBr_3 (1.8 mmol, 3 equiv.), in 2.5 mL anhydrous DCM at 60 °C, 65 h; Step ii) $NaBF_4$ (3 mmol, 5 equiv.). [d]Step i) at 60 °C, 65 h.

Substrates with disubstitution (**123i**–**123j**) and extended aromatic rings (**123k**) were also compatible, yielding products between 75% and 95%. Further investigation with alternative acyl groups (**123l**–**123n**), including adamantyl and other acyl derivatives, afforded yields ranging from 24% to 79%. Tertiary amine-containing substrates (**123o**–**123q**) were similarly tested, with yields ranging from 47% to 78%. For derivatives of tetrahydroquinoline (**123o**)

and indoline (**123p**), the reaction time was reduced to avoid hydrolysis of the amide bond, ensuring its integrity. Substrates with urea directing groups (**123r**–**123s**) provided the desired products in 56% to 63%, which is noteworthy given the potential of urea–BF_2 derivatives in biologically active compounds.



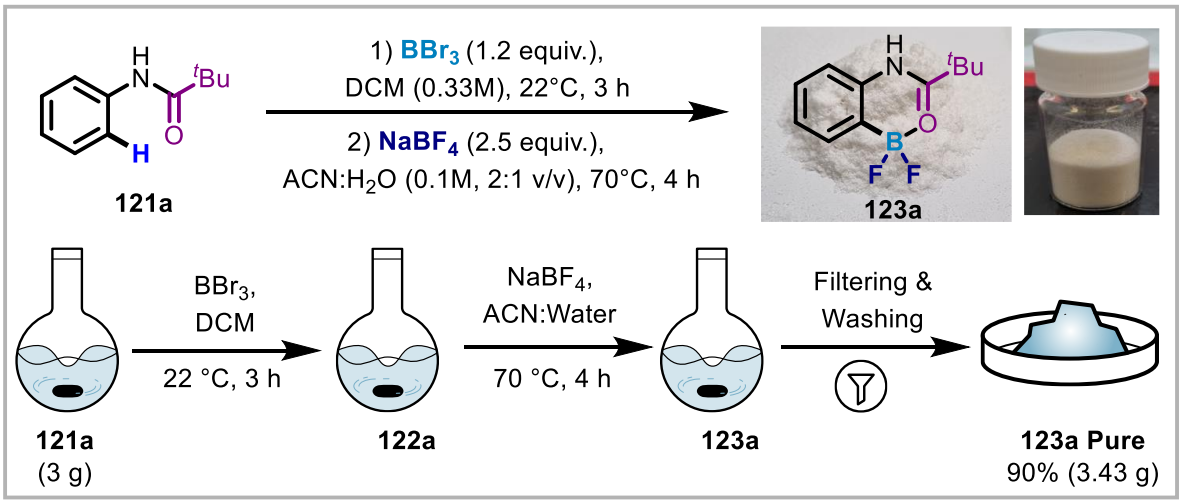
Scheme 2b. Reaction scope, [a]Step i) at 40 °C, 16 h. [d]Step i) at 60 °C, 65 h. For **123ae–123ah**: Step i) Amide (0.6 mmol, 1 equiv.), BBr_3 (1.05 mmol, 1.75 equiv.), in 2.5 mL anhydrous DCM, at 60 °C, 16 h. For **111a–111d**: Reactant (0.6 mmol, 1 equiv.), BBr_3 (1.8 mmol, 3 equiv.), 2,6-lutidine (1.2 mmol, 2 equiv.) in 2 mL anhydrous DCM at 40 °C, 16 h. For **111e**: Reactant (0.6 mmol, 1 equiv.), BBr_3 (1.8 mmol, 3 equiv.), 2,3,5,6-Tetramethylpyrazine (0.72 mmol, 1.2 equiv.) in 2 mL anhydrous CH_2Cl_2 at 22 °C, 16 h.

Functionalizing urea derivatives with directed *ortho*-metallation approaches is challenging due to the strong metal binding of ureas, which can interfere with catalytic processes. Additionally, successful diagonal double borylation was achieved on substrates **123t**–**123u**,

resulting in yields of 84% and 61%, respectively, which are valuable for materials chemistry. Finally, double borylation resulted in a yield of 68% (**Scheme 2a**, **123v**).

Building on the success with pivalamides and extended aromatic substrates, we turned our attention to benzanilides to investigate site-selective borylation on the aniline portion of the ring (**Scheme 2b**, **123w**–**123ad**). Under the optimized conditions, a range of substituents on the phenyl ring, including methyl, nitro, and compounds with modifications on both the aniline and benzoyl portions, were tolerated, yielding the desired products (**123w**–**123z**) in 58% to 75%. Considering the prevalence of the amide functional group in biologically active molecules, we extended the study to substrates of pharmaceutical interest, which exhibited varying molecular complexities. Notably, these complex substrates also underwent successful borylation, yielding products (**123aa**–**123ad**) in 70% to 82%, further illustrating the wide applicability of the method for drug-like molecules.

After successfully incorporating the BF_2 group onto various anilides, we expanded our scope to substrates with diverse directing groups. We focused on carbonyl-directed substrates,[79] such as naphthyl, pyrene, ibuprofen, and other acyl-containing compounds, which were subjected to the optimized conditions (**Scheme 2b**). These substrates showed broad compatibility, delivering the corresponding aryl-BF_2 products in yields from 36% to 86% (**123ae**–**123ah**). Next, we explored nitrogen-containing directing groups. Substrates such as pyridine, isoquinoline, quinoline, and pyrimidylaniline yielded the desired Ar–BF_2 (**111a**–**111e**) in excellent yields, ranging from 55% to 95%. This comprehensive study highlights the broad applicability of our method, which is effective not only with carbonyl-directed substrates but also with nitrogen-based directing groups. The ability to apply this approach to both pharmaceutically relevant compounds and heteroaromatic systems opens exciting possibilities for the synthesis of BF_2-functionalized molecules.

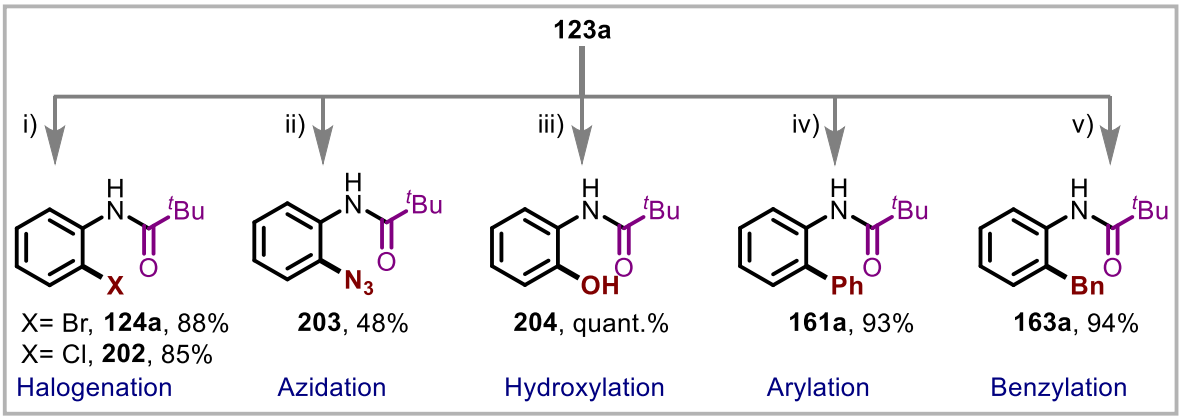


Scheme 3. Multigram-scale synthesis

Following the successful exploration of the substrate scope, we evaluated the scalability of our methodology. The Ar–BF_2 compound (**123a**) was synthesized on both a 1-gram (93%) and multigram scale (3 g), maintaining excellent yields (**Scheme 3**). The robustness and mild nature

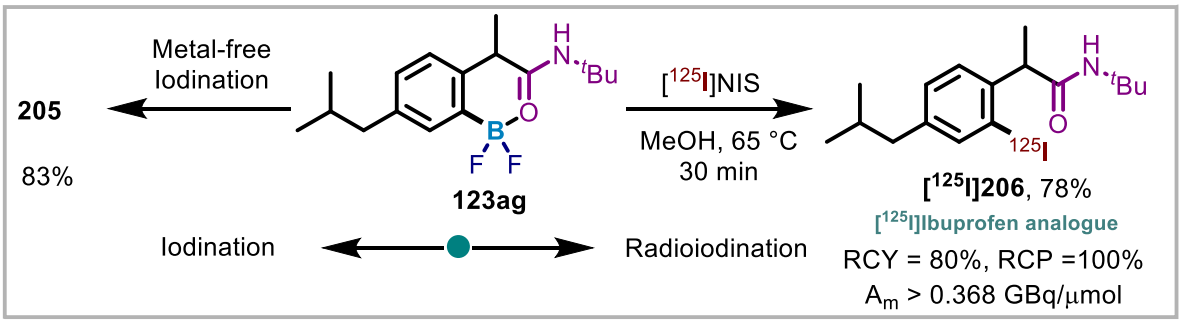
of this protocol allowed for efficient purification by simple pentane washing, yielding pure **123a** without requiring extensive chromatographic separation.

To assess the synthetic utility of **123a**, we explored its post-functionalization under both metal-free and transition-metal-catalyzed conditions (**Schemes 4**). Under Cu-catalysis, we successfully introduced halogens (**124a** and **202**) and an azide (**203**) at the *ortho*-position of *N*–phenyl pivalamide (**121a**). The ability to undergo both metal-free transformations and transition-metal-mediated modifications underscores the synthetic versatility of the Ar–BF_2 scaffold. Additionally, oxidation of **123a** resulted in the formation of the corresponding hydroxylated product (**204**) in quantitative yield. Furthermore, the applicability of **123a** in SM cross-coupling reactions was evaluated. The Ar–BF_2 moiety efficiently participated in C(sp^2)–C(sp^2) (**161a**) and C(sp^2)–C(sp^3) (**163a**) cross-coupling reactions, further demonstrating its synthetic utility in Pd-catalyzed transformations (**Scheme 4**).



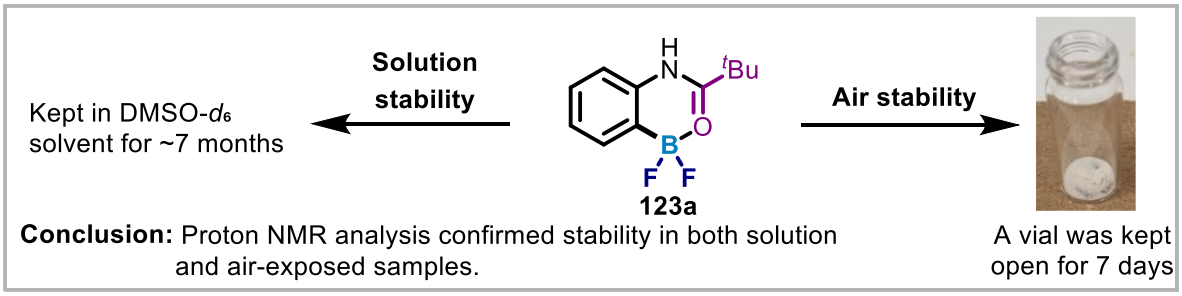
Scheme 4. *Ortho*-functionalizatio of Ar–BF_2 (**123a**). Condition for bromination and chlorination: **123a** (0.2 mmol), $CuBr_2$/$CuCl_2$ (3-3.5 equiv.), MeOH, 85 °C, 22 h. For azidation: **123a** (0.2 mmol), NaN_3 (2 equiv.), $Cu(OAc)_2.H_2O$ (20 mol%), MeOH, 80 °C, 5 h. For hydroxylation: **123a** (0.2 mmol), $NaBO_3.4H_2O$ (3 equiv.), THF:Water, rt, 2 h. For arylation: **123a** (0.2 mmol), Iodobenzene (1.2 equiv.), $Pd(OAc)_2$ (2.5 mol%), K_2CO_3 (3 equiv.), MeOH, 70 °C, 4 h. For benzylation: **123a** (0.2 mmol), Benzyl bromide (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (3 equiv.), MeOH:Water, 70 °C, 5 h.

To extend this approach to late-stage functionalization, we applied the methodology to an ibuprofen analogue (**123ag**) (**Scheme 5**). This study revealed highly efficient metal-free iodination (**205**, 83%) and radioiodination (**206**) (^{125}I) with an 80% radiochemical yield and 100% radiochemical purity. These results highlight the exceptional stability and reactivity of Ar–BF_2 compounds, reinforcing their potential for use in synthetic modifications, radiolabeling, and advanced chemical applications.



Scheme 5. Late-stage functionalization of Ibuprofen analogue. For radioiodination: [^{125}I]NIS solution was prepared by mixing NaI^{125} (2-4 MBq) and NCS (0.5 equiv.) in MeOH at 25 °C for 15 min. Condition for iodination: Selectfluor (1 equiv.), and KI (1.2 equiv.), in ACN (1 mL) and water (0.5 mL) at 22 °C for 2 h then **123ag** (0.1 mmol), at 60 °C, 5 h.

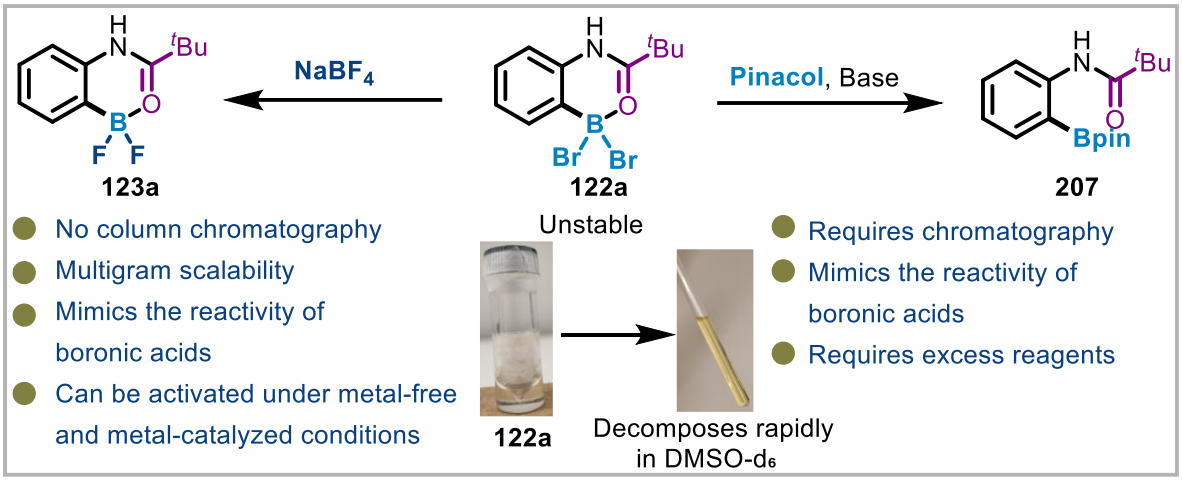
The stability of the newly synthesized Ar–BF_2 compound **123a** was assessed under both solution and solid-state conditions (**Scheme 6**). In solution, **123a** was dissolved in DMSO-d_6 and stored at ambient temperature for approximately seven months. Periodic analysis using ^{1}H NMR spectroscopy showed no detectable decomposition or the emergence of new peaks, indicating the compound's excellent stability in solution.



Scheme 6. Stability evaluation of **123a** in solution and air.

The importance of Ar–BF_2 compounds was further highlighted through a comparison with related boron species, specifically **122a** (BBr_2) and **207** (Bpin) (**Scheme 7**). While Ar–BF_2 **123a** displayed remarkable stability in both solution and solid states, compound **122a**, containing a BBr_2 group, proved significantly less robust. Compound **122a** showed rapid decomposition in DMSO–d_6, as confirmed by NMR studies, and proved even less stable in nucleophilic conditions, where oxidative ligand exchange reactions commonly occurred (**Chapter 2** and **3**). This instability highlights the limitations of BBr_2-functionalized compounds, as their poor stability and difficulty in storage further limit their practicality for broader synthetic applications. A comparison between **123a** and Bpin derivative **207** further illus-trates the advantages of BF_2-compounds. Unlike Bpin derivatives,[63bc] the synthesis of BF_2 arenes does not require column chromatography, simplifying their preparation and making the process more practical. Additionally, BF_2 arenes can be readily synthesized on a multigram scale, demonstrating their scalability and suitability for industrial and academic research. Furthermore, BF_2 arenes closely mimic the reactivity of boronic acids (**Scheme 4**), offering broad utility in cross-coupling and *ipso*-functionalization reactions. Importantly, these compounds can be activated under both metal-free and metal-catalyzed conditions, and due

to their robust synthesis and versatile reactivity, BF_2-arenes present a compelling alternative to Bpin derivatives for future applications.



Scheme 7. Functional and practical properties of BBr_2 (**122a**), Ar–BF_2 (**123a**), and Bpin (**207**) compounds.

3. Conclusion

In conclusion, the development of aryl difluoroborane (Ar–BF_2) compounds represents a major advancement in boron chemistry, providing significant advantages over conventional directed *ortho*-boron reagents. The scalable and chromatography-free synthesis of BF_2-arenes enhances their practicality, particularly for large-scale applications. These compounds exhibit exceptional stability in both solution and solid states, making them highly reliable intermediates for diverse synthetic transformations. Their efficient *ipso*-functionalization and high reactivity in SM cross-coupling reactions establish them as a compelling alternative to Bpin derivatives. Additionally, the ability to activate Ar–BF_2 species under both metal-free and metal-catalyzed conditions expands their synthetic utility, particularly in late-stage functionalizations, including radiolabeling for imaging and therapeutic applications. Overall, this work underscores the potential of Ar–BF_2 compounds in late-stage diversification strategies and highlights their broader applicability in modern organic synthesis.

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