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Development of Transition Metal Catalyzed
Alkyl C–H Functionalization Reactions

遷移金属触媒によるアルキル C–H 官能基化反応の開発

Ryo Murakami
2017
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General Introduction

Functionalization of carbon-hydrogen (C–H) bonds has become a useful and powerful method in modern organic synthesis\(^1\). This strategy enables the straightforward and step-economical synthesis of target compounds. Transition metal-catalyzed C–H bond functionalization reactions proceed under mild conditions with high site-selectivity, as compared to classical routes such as radical reactions\(^2\). Despite significant progress in this area, the direct functionalization of C(sp\(^3\))–H bonds compared to C(sp\(^2\))–H bonds still remains challenging because C(sp\(^3\))–H bonds do not have \(\pi\)-orbitals to interact with orbitals of transition metals. Therefore, C(sp\(^3\))–H functionalization often requires harsh reaction conditions such as high temperature, UV irradiation, and/or the use of strong oxidants, resulting in limited substrate scope and poor site selectivity. Furthermore, this molecular transformation introduces a new challenge of stereoselectivity owing to the tetrahedral geometry of the C(sp\(^3\)) atom. Thus, the author aimed at developing catalytic, site- and stereoselective C(sp\(^3\))–H functionalizations for efficient organic synthesis.

1. Transition Metal-catalyzed C(sp\(^3\))–H Functionalization\(^3\)

1.1. Types of C(sp\(^3\))–H Activation. The main types of C(sp\(^3\))–H activation with transition metal catalysts can be categorized as follows: 1) concerted metalation-deprotonation (CMD) of C(sp\(^3\))–H bonds; 2) oxidative addition of C(sp\(^3\))–H bonds; and 3) metal-carbene insertion into C(sp\(^3\))–H bonds. These reaction pathways are dependent on the properties of the transition metals. For instance, high-valent late transition metals such as Pd(II), Rh(III), Ir(III) and Ru(II) are favored to promote the CMD process. In contrast, low-valent and electron-rich transition metals such as Rh(I) and Ir(I) promote the oxidative addition process. To increase the electron density of the metal center, the use of electron-donating ligands such as trialkylphosphines and N-heterocyclic carbenes is preferred. Thus, modification of ligand properties provides a handle for tuning the reactivity. Metal carbenoid species, which have a divalent carbon atom coordinated to a metal complex, can react with C(sp\(^3\))–H bonds to form C–C bonds. Lewis acidic transition metal complexes, like Rh(II), Pd(II) and Cu, are effective catalysts for the C(sp\(^3\))–H insertion reaction.
Scheme 1. Types of Mechanisms in Transition Metal-Catalyzed C(sp$^3$)–H Activation

1.2 Control of Reaction Sites. Transition metal-catalyzed site-selective C(sp$^3$)–H bond functionalizations are challenging tasks because many C–H bonds exist in various positions of organic molecules. In general, transition metal-catalyzed C–H activation occurs preferentially at the least substituted and electronically activated C–H bonds. Therefore, functionalization of internal C(sp$^3$)–H bonds is a bigger challenge than that of terminal C(sp$^3$)–H bonds. In addition, the site-selective activation of C(sp$^3$)–H bonds over potentially more reactive C–H bonds such as C(sp$^2$)–H bonds is difficult. To solve these problems, substrate-based control of the site-selectivity in the C(sp$^3$)–H functionalization has been reported. According to the type of reaction, they are classified into two groups. The first is reactions that occur with the assistance of heteroatom-based metal-coordinating directing groups. Murai and co-workers’ ortho-selective C–H alkylation of aromatic ketones with a low-valent Ru-phosphine complex is a pioneering work. The second is the reactions of electronically activated substrates. For instance, benzylic C(sp$^3$)–H bonds and heteroatom-adjacent C(sp$^3$)–H bonds are preferred sites for cleavage by transition metal catalysts. Functionalization of less acidic C(sp$^3$)–H bonds far from a metal-coordinating functional group is generally more difficult.
1.3. Site-selective and Stereoselective C(sp$^3$)–H Functionalization

1.3.1. Chiral substrate-controlled stereoselective C(sp$^3$)–H functionalization. In early work, the stereoselective C(sp$^3$)–H functionalization reaction was achieved by using substrates bearing a chiral auxiliary$^6$. In 2001, Sames and co-worker reported the Pt-catalyzed intramolecular lactonization of α-amino acids via cleavage of C(sp$^3$)–H bonds$^7$. The yields of the products were not satisfactory, but stereoselectivity was induced at the metal center by the chiral center of the substrate (Scheme 3). In 2005, Yu and co-workers reported the Pd(OAc)$_2$-catalyzed C(sp$^3$)–H iodonation$^8$ and acetoxylation$^9$ of alkanes bearing optically pure oxazoline auxiliaries. This catalytic system was also applicable to cyclopropyl C–H bonds under mild conditions with high diastereoselectivity (Scheme 4). The asymmetric induction model is shown in Scheme 5. When the $R_L$ group is larger than the methyl group, the anti arrangement between $R_L$ and the tert-butyl group on the chiral oxazoline group is favored in the transition state of the C(sp$^3$)–H bond cleavage, to provide stereocontrolled products. In 2005, Shi and co-workers developed Pd-catalyzed diastereoselective C(sp$^3$)–H fluorination of chiral α-amino acid derivatives bearing bidentate chelating groups (Scheme 6)$^{10}$. Later, arylation and alkenylation of C(sp$^3$)–H bonds in a similar manner were reported by Chen and co-workers (Scheme 7)$^{11}$. This strategy was applied to the synthesis of natural products such as celogentin.
Scheme 3. Chiral Substrate-controlled Diastereoselective Reaction: The First Report

\[
\text{L-Valine} \quad \xrightarrow{\text{K}_2\text{PtCl}_4 (5 \text{ mol\%})} \quad \xrightarrow{\text{CuCl}_2 (7 \text{ eq})} \quad \text{H}_2\text{O, 160 °C, 10 h} \quad \xrightarrow{\text{Boc}_2\text{O}} \quad \xrightarrow{\text{AcOH}} \quad \text{NHBoc}
\]

27%, d.r. = 3:1

Scheme 4. Auxiliaries-controlled Diastereoselective C(sp^3)–H Functionalization

Scheme 5. Asymmetric Induction Model: Yu’s work

Scheme 6. Stereoselective C(sp^3)–H Fluorination
1.3.2. Stereoselective C(sp$^3$)–H functionalization. Stereoselective C(sp$^3$)–H functionalization controlled by chiral directing groups has been a mainstay of organic chemistry. The transition metal-catalyzed stereoselective C(sp$^3$)–H functionalization of achiral substrates offers an alternative strategy for the application of C(sp$^3$)–H activation to stereoselective bond-forming reactions$^{12}$. In the first report, Sames and co-worker described Ru-catalyzed stereoselective α-arylation of racemic 2-phenylpyrrolidines with arylboronic esters, however the stereoselectivity was low (Scheme 8)$^{13}$. Recently, Yu and co-worker reported Pd-catalyzed diastereoselective C(sp$^3$)–H cross-coupling with aryl boronic acids with the aid of thioamide-based directing groups (Scheme 9)$^{14}$. Moreover, the Yu group described the stereoselective C(sp$^3$)–H arylation with the NHC-Pd catalyst system (Scheme 10)$^{15}$.

Scheme 8. Stereoselective C(sp$^3$)–H Arylation: First Report
Scheme 9. Pd-catalyzed Stereoselective C(sp$^3$)–H Arylation: Yu group

Scheme 10. Ligand-enabled Stereoselective C(sp$^3$)–H Arylation: Yu group

1.3.3. Enantioselective C(sp$^3$)–H functionalization. The enantioselective functionalization of prochiral C(sp$^3$)–H bonds could be a useful and direct method for the synthesis of chiral compounds$^{16}$. Recently, many groups have achieved enantioselective C(sp$^3$)–H functionalization reactions. Kundig’s group reported the Pd-catalyzed enantioselective intramolecular C(sp$^3$)–H arylation with the chiral NHC ligand (Scheme 11)$^{17}$. This strategy allowed synthesis of highly enantioenriched trans-fused indolines. Cramer’s group also developed a Pd-catalyzed enantioselective intramolecular cyclization reaction via C–H activation of a cyclopropane using monodentate TADDOL-derived phosphoramidites (Scheme 12)$^{18}$. These reactions required high temperature (130 °C), but high asymmetric recognition of enantiotopic C(sp$^3$)–H bonds was achieved.

Scheme 11. Enantioselective C(sp$^3$)–H Functionalization: Intramolecular Reaction
Scheme 12. Enantioselective Intramolecular C(sp³)–H Functionalization: Cramer group

Enantioselective intermolecular C(sp³)–H functionalization reactions are more challenging and still rare. Shibata and co-workers reported enantioselective nitrogen-adjacent C(sp³)–H alkylation and alkenylation of 2-(alkylamino)pyridines with a cationic chiral bispshpine-Ir complex (Scheme 13). Yu and co-worker described the enantioselective C–H functionalization of small-ring carbocycles such as cyclopropanes and cyclobutanes through systematic tuning of chiral Pd complexes (Scheme 14). Recently, the Yu group achieved enantioselective amine α-arylation in combination with palladium catalysts and chiral BINOL-derived phosphoric acid. This catalytic reaction revealed that the chiral anionic ligand was effective for the Pd-catalyzed enantioselective C(sp³)–H functionalization (Scheme 15). Additionally, the Yu group reported enantioselective unactivated C(sp³)–H arylation with palladium catalysts prepared from chiral acetyl-protected aminoethyl quinoline (APAQ) ligands (Scheme 16). These reports have broken the barrier to transition metal-catalyzed enantioselective unactivated C(sp³)–H functionalizations.

Scheme 13. Chiral Ir-catalyzed Enantioselective N-adjacent C(sp³)–H Functionalization
Scheme 14. Pd-catalyzed Enantioselective C(sp^3)–H Functionalization of Small-ring Carbocycles

Scheme 15. Pd-catalyzed Enantioselective Amine α-C(sp^3)–H Arylation

Scheme 16. Pd-catalyzed Enantioselective Unactivated C(sp^3)–H Arylation
1.4. Enantioselective Functionalization of Internal C(sp³)–H Bonds through Metal Carbenoid Insertion

The carbene C–H insertion is a powerful method for functionalization of unactivated C–H bonds. The metal carbenoid species are generally prepared from diazo compounds. The carbene-induced C(sp³)–H insertion can lead to high levels of site- and stereoselectivity. The rhodium-catalyzed C(sp³)–H insertion reaction was found to be particularly effective. The regioselectivity of this C(sp³)–H insertion chemistry is summarized in Scheme 17.\(^25\) The C(sp³)–H carbenoid reactions proceed with electronically activated C(sp³)–H bonds for stabilization of the polarization, and thus the C(sp³)–H insertion occurs with a partial positive charge build-up at the carbon atom.

**Scheme 17. Carbenoid Reactivity**

Davies and co-worker reported that rhodium carbenoids derived from methyl diazoacetates enabled the effective catalytic asymmetric internal C(sp³)–H functionalization (Scheme 18).\(^26\) This reaction occurred with high regio- and enantioselectivity. Recently, the same group reported that site-selective and stereoselective functionalization of unactivated internal C(sp³)–H bonds was allowed by designed dirhodium catalysts (Scheme 19).\(^27\) This reaction proceeded under mild conditions and showed good functional group compatibility.
**Scheme 18.** Rhodium-catalyzed Enantioselective Insertion Reaction with Relatively Activated C(sp³)–H Bonds

![Scheme 18]

**Scheme 19.** Rhodium-catalyzed Enantioselective Unactivated C(sp³)–H Insertion Reaction

![Scheme 19]

1.5. Site-selective C(sp³)–H Functionalization with Metal-oxo Insertion

Hydrogen atom transfer (HAT) reactions with radical species such as halogen radicals, hydroxyl radicals, amidyl radicals, oxoimidyl radicals and benzoyl radicals are widely recognized as classical C–H bond functionalizations in organic synthesis. The HAT reactivity toward the C–H functionalization is mainly dependent on bond strengths, resulting in unselective C–H bond cleavage. Tertiary C–H bonds over secondary and primary C–H bonds are prone to be activated by free radical processes.

The metal-oxo complexes-catalyzed C(sp³)–H functionalizations through generation of alkyl radical species have been well-studied for synthetic purposes. Recently, White and co-workers reported the iron-catalyzed stereoselective oxidation of unactivated C(sp³)–H bonds (Scheme 20). In this reaction, the oxo-iron complexes abstract a hydrogen atom from C–H bonds of alkanes to form an iron-bound hydroxo complex and an alkyl radical is generated. Next, the alkyl radical reacts rapidly with the hydroxo ligand to form the alcohol product site-selectively.
Scheme 20. Fe-catalyzed Stereoselective Unactivated C(sp$^3$)–H Oxidation

2. Transition Metal-catalyzed Site- and Stereoselective C(sp$^3$)–H Borylation

2.1. Utility of Alkylboronates in Organic Synthesis

Alkylboronates can be used as synthetic intermediates in carbon-carbon and carbon-heteroatom bond forming reactions owing to their air- and moisture stability and functional-group compatibility. This section illustrates the utility of alkylboronates in organic synthesis.

2.1.1. 1,2-Rearrangement$^{30}$. In 1963, Matteson reported that 1,2-rearrangement of an organic group on a boron atom to the $\alpha$-carbon occurred with organometallic reagents such as organolithium. Furthermore, the addition of $\alpha$-alkyl carbanions to alkylboronates leads to one-carbon homologation of alkylboronates by 1,2-metallate rearrangement (Scheme 21). Chiral alkylboronates can be used for stereocontrolled homologations to afford various chiral alkylboronates.

Scheme 21. 1,2-Rearrangement of Alkylboronates
2.1.2. Oxidation. Alkylboronates can be converted into alcohol products by treatment with alkaline hydrogen peroxide (Scheme 22)\(^\text{31}\). The oxidation of α-chiral alkylboronates proceeds with retention of the configuration to afford the chiral alcohol products. The oxidation reaction proceeds with a boron to oxygen migration of the ipso carbon.

**Scheme 22.** Oxidation of Alkylboronates

2.1.3. Amination. Recently, Morken and co-workers reported the stereospecific amination of alkyl pinacol boronates using amine reagents such as methoxyamine (Scheme 23)\(^\text{32}\). This amination occurred with retention of configuration, affording the chiral amine products.

**Scheme 23.** Amination of Alkylboronates

2.1.4. Transition metal-catalyzed cross-coupling with alkylboronates. In 1979, Suzuki and Miyaura reported the Pd-catalyzed cross-coupling reaction between aryl halides and alkenyl boranes\(^\text{33}\). This finding led to a breakthrough in organic synthesis. However, alkylboronates have been known to be unwilling substrates in the Suzuki-Miyaura cross-coupling reaction. Owing to the slow transmetalation with alkylboronates, harsh reaction conditions are required. Moreover, β-hydride elimination from the alkylpalladium intermediate may compete with
productive reductive elimination\textsuperscript{34}. To date, many groups have reported efficient Pd-catalyzed cross-coupling reactions between alkylboronates and aryl halides (Scheme 24)\textsuperscript{35}. Recently, Molander and co-workers reported a dual-catalyzed photoredox/cross-coupling between alkyltrifluoroborates and arylbromide. Alkyltrifluoroborates have documented ability to function as carbon radical sources upon photoredox catalysis and single electron transmetalation occurred with nickel catalysts (Scheme 25)\textsuperscript{36}.

Scheme 24. Suzuki-Miyaura Cross-coupling with Alkylboronates

![Scheme 24](image)

Scheme 25. Dual Catalyst: Photoredox / Cross-coupling

![Scheme 25](image)

2.1.5. Rh-catalyzed 1,2-addition of alkylboronates to aldehydes. The rhodium-catalyzed 1,2-addition of boronic acid to aldehydes was achieved by Miyaura and co-workers\textsuperscript{37}. However, the use of sp\textsuperscript{3}-carbon boron derivatives has been limited. Recently, Aggarwal and co-worker reported Rh-catalyzed stereoretention in the 1,2-addition of chiral alkyltrifluoroborates to aldehydes. This catalytic reaction could be applied to secondary and tertiary alkylboronates (Scheme 26)\textsuperscript{38}.

Scheme 26. Rh-catalyzed 1,2-Addition of Alkylboronates to Aldehydes: First Report

![Scheme 26](image)
2.1.6. **Ag-catalyzed fluorination of alkylboronates.** In 2014, Li and co-workers achieved AgNO₃-catalyzed radical fluorination of alkylboronates using Selectfluor as the fluoro reagent (Scheme 27)³⁹. This catalytic reaction enabled the fluorination of primary, secondary and tertiary alkylboronate substrates to afford the corresponding alkyl fluoride products.

**Scheme 27.** Ag-catalyzed Fluorination of Alkylboronates: Li Group

\[
R - B \quad \xrightarrow{\text{cat. AgNO}_3, \text{selectfluor}} \quad R - F
\]

\[
R = 1^\circ, 2^\circ, 3^\circ \\
B = \text{Bpin, B(OH)}_2
\]

**2.2. Synthesis of Alkylboronates**

2.2.1. **Classical approach**⁴⁰. Alkylboronates can be synthesized from trapping organometallic nucleophiles such as organomagnesium and organolithium with borates. Brown’s hydroboration of alkenes also has been known as a powerful method to synthesize alkylboranes. However, these methods have limitations of functional group tolerance and site- and chemo-selectivities.

**Scheme 28.** Classical Reaction

2.2.2. **Transition metal-catalyzed synthesis of alkylboronates.** Recently, many researchers have reported various methods for preparing alkylboronates-based transition metal catalysts. For instance, 1) transition metal-catalyzed hydroboration of alkenes to synthesize alkylboronates has been reported⁴¹. This method can be applied with various catalysts, such as platinum, iridium, rhodium, palladium, nickel, copper, iron, magnesium, and by asymmetric hydroboration. 2) Transition metal-catalyzed boryl substitution reaction of alkyl halides using bis(pinacolato)diboron as a boron source proceeds under mild conditions⁴². This method enables borylation of primary and secondary alkyl halides to afford the corresponding alkylboronates. 3) 1,4-Addition reaction of diboron to α,β-unsaturated carbonyl compounds with transition metal catalysts⁴³ or organocatalysts⁴⁴ has been developed. The asymmetric
catalysis gives the corresponding chiral alkylboronates. 4) Cu-catalyzed 1,2-addition of diboron to carbonyl compounds was reported\textsuperscript{45}. Recently, the Cu-catalyzed enantioselective addition reaction to give chiral $\alpha$-alkoxy alkylboronates was achieved\textsuperscript{46}.

Scheme 29. Synthesis of Alkylboronates: Transition Metal Catalysts

\[
\begin{align*}
R \equiv R' & \quad \xrightarrow{\text{cat. [M]}} \quad B \equiv R' \\
R - X & \quad \xrightarrow{\text{cat. [M]}} \quad R - \text{Bpin} \\
O \equiv R'' & \quad \xrightarrow{\text{cat. [M]} \text{ or cat. NHC}} \quad \text{O} \equiv R''
\end{align*}
\]

2.2.3. Transition metal-catalyzed C(sp$^3$)–H borylation. Transition metal-catalyzed C(sp$^3$)–H borylation reactions offer a useful and efficient strategy for the synthesis of alkylboronates. The transition metal-catalyzed direct C(sp$^3$)–H borylation reaction was achieved by Hartwig and co-workers in 1999\textsuperscript{47}. They described Re-catalyzed site-selective borylation of primary C(sp$^3$)–H bonds under UV irradiation using bis(pinacolato)diboron as a boron reagent. The primary C(sp$^3$)–H borylation at terminal sites on alkanes with various metal-boryl catalysts based on Rh, Ru, Ir complexes has been developed\textsuperscript{48}. The regioselectivity of these catalytic reactions is controlled by the steric properties of the substrate.

Scheme 30. Selective Borylation of Primary C(sp$^3$)–H Bonds

\[
\begin{align*}
R \equiv H & \quad \xrightarrow{\text{cat. [M]}} \quad R \equiv \text{Bpin} \\
[M] & = \text{Re, Rh, Ru, Ir}
\end{align*}
\]

Marder and co-workers reported Rh-catalyzed benzylic C–H borylation\textsuperscript{49}. However, this reaction competed with arene C–H borylation to give undesired products. Ishiyama, Miyaura
and co-workers described that a heterogeneous palladium-carbon catalyst was effective for benzylic C–H borylation of toluene\textsuperscript{50}. The Hartwig group also developed Ir-catalyzed site-selective benzylic C–H borylation using Et\textsubscript{3}SiBpin as a boron source\textsuperscript{51}.

**Scheme 31.** Benzylic C(sp\textsuperscript{3})–H Borylation

![Scheme 31](image)

Recently, Hartwig and co-worker reported that an Ir–phenanthroline catalytic system enabled secondary C(sp\textsuperscript{3})–H borylation within heterocyclic compounds such as cyclic ethers\textsuperscript{52}. The origin of selective β–C(sp\textsuperscript{3})–H borylation in cyclic ethers was proposed to be the formation of a six-membered transition state such as the coordination of an oxygen atom to the boryl ligand. Moreover, the Hartwig group demonstrated the trans-selective C–H borylation of substituted cyclopropanes with the same catalytic system\textsuperscript{53}. This stereoselectivity is due to avoidance of the substituent on the cyclopropane ring.

**Scheme 32.** Secondary C(sp\textsuperscript{3})–H Borylation

![Scheme 32](image)
2.2.4. Transition metal-catalyzed heteroatom-directed C(sp\(^3\))–H borylation. In general, the selectivity of transition metal-catalyzed C(sp\(^3\))–H borylation favors primary C(sp\(^3\))–H bonds, avoiding the steric hindrance of the substrate. Therefore, the scope of site-selective internal C(sp\(^3\))–H borylation has been limited. Recently, site-selective internal C(sp\(^3\))–H borylation has been reported where the use of a directing group in the substrate affords selective borylation of a specific C(sp\(^3\))–H bond (Scheme 33). The first report of heteroatom-directed internal C(sp\(^3\))–H borylation was reported by the Sawamura group in 2012. They described N-adjacent C(sp\(^3\))–H borylation of amides, ureas, and 2-aminopyridines using the silica-supported triarylphosphine Silica-TRIP–Rh catalyst\(^{54}\). They also reported Ir-Silica-SMAP-catalyzed site- and stereoselective unactivated secondary C(sp\(^3\))–H borylation of 2-alkylpyridine derivatives\(^{55}\). These reactions occurred with high site-selectivity at the position γ to the directing group under mild conditions. Moreover, other homogeneous ligands were not effective for these heteroatom-directed C(sp\(^3\))–H borylations.

The Hartwig group reported hydrosilane-directed internal benzylic C(sp\(^3\))–H borylation using the Ir-phenanthroline catalytic system (Scheme 34)\(^{56}\). Recently, they reported that the same catalytic system could be applied in site- and stereoselective borylation of unactivated internal C(sp\(^3\))–H bonds\(^{57}\). This directing group could be removed or used for further transformation. Amide-directed site- and stereoselective C(sp\(^3\))–H borylation with Pd catalyst was achieved by the Yu group\(^{58}\).
**Scheme 33.** Heteroatom-directed Secondary C(sp³)–H Borylation: Sawamura Group

![Scheme 33 Diagram]

**Scheme 34.** Heteroatom-directed Secondary C(sp³)–H Borylation: Other Groups

![Scheme 34 Diagram]
3. Overview of this Thesis

The author focused on the transition metal-catalyzed site- and stereoselective C(sp^3)–H functionalization under mild conditions. In chapter 1, the heteroatom-directed site- and stereoselective C–H borylation of small-ring carbocycles such as cyclopropanes and cyclobutanes with the silica-supported monophosphine Silica-SMAP–Ir catalytic system is described. In chapter 2, the author expands this strategy using the Silica-SMAP-Ir system to the C(sp^3)–H borylation of alkyl side chains of 1,3-azoles. In chapters 3 and 4, the author shows the development of the Pd-catalyzed allylation of 2-alkylaarenes. In chapter 3, the author describes the Pd-catalyzed linear selective allylation of 2-alkylaarenes without the use of external base. In chapter 4, Pd-catalyzed enantioselective allylation of 2-alkylpyridines using the newly synthesized chiral monophosphine ligand is described.

3.1. Stereoselective C–H Borylations of Cyclopropanes and Cyclobutanes with Silica-supported Monophosphine-Ir Catalysts (Chapter 1)

Chapter 1 describes the combination of a silica-supported monophosphine (Silica-SMAP) and [Ir(OMe)(cod)]_2 to produce a heterogeneous catalyst system that is effective for site- and stereoselective C–H borylation of small-ring carbocycles such as cyclopropanes and cyclobutanes in various N-containing heterocyclic compounds and carbonyl-related compounds and amides using bis(pinacolato)diboron. This borylation occurred with exceptional cis stereochemistry under mild conditions, affording the corresponding alkylboronates. The site- and stereoselectivity of this reaction suggested that C–H bond cleavage occurred with the assistance of a proximity effect due to N-to-Ir coordination.

Scheme 35. Silica-SMAP–Ir Catalyzed Stereoselective C–H Borylation
3.2. Site-selective and Stereoselective C(sp$^3$)–H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Ir Catalyst (Chapter 2)

Chapter 2 describes the heteroatom-directed site- and stereoselective unactivated secondary C(sp$^3$)–H borylation bearing N-heteroarenes catalyzed by Silica-SMAP–Ir catalytic systems. This borylation occurred $\gamma$ to N atoms on the directing groups. The ligand effects are summarized in Scheme 36. An immobilized catalytic system prepared from Silica-SMAP and [Ir(OMe)(cod)]$_2$ promoted C(sp$^3$)–H borylation to give the corresponding alkylboronates. On the other hand, homogeneous monophosphine ligands and other immobilized ligands produced no reaction. Notably, this catalytic system promoted the stereoselective C(sp$^3$)–H borylation of cyclic alkyl substituted substrates.

Scheme 36. Ligand Effect
3.3. Transition Metal-catalyzed Enantioselective C(sp\(^3\))–H Functionalization of Alkyl Azaarenes

The α-stereogenic substituted chiral alkyl azaarene moiety is well-known in biologically active compounds, agrochemicals and natural products. The development of enantioselective direct functionalization reactions within 2-alkylazaarenes is important in organic synthesis. Several catalytic approaches via α-deprotonation of the 2-alkylazaarene have been reported\(^{59}\). For instance, Trost and co-workers reported Pd-catalyzed enantioselective allylation of 2-alkylazaarenes. This reaction required the addition of a Lewis acid such as BF\(_3\)·OEt\(_2\) to increase the acidity of the benzylic C–H bonds\(^{60}\). The Walsh group also reported Ni-catalyzed enantioselective allylation of diarylmethane pronucleophiles with a pyridine moiety\(^{61}\). However, a stoichiometric amount of strong base was needed in these allylation reactions.

Recently, the α-deprotonation-functionalization of preactivated 2-alkylazaarenes with electron-withdrawing groups in the aromatic ring, such as \(p\)-nitroazaarenes and
polyheteroarenes, and N-oxide azaarenes or side chain C(α) benzylic positions such as ester, amide, or aryl groups have been reported. These strategies allowed formation of α-stereogenic 2-substituted azaarenes with high enantioselectivity under mild conditions. In 2012, Lam and co-workers described diastereo- and enantioselective Pd-catalyzed addition of 2-alkylazaarenes to N-Boc imines and nitroalkenes (Scheme 39). The introduction of an electron-withdrawing functional group into an aromatic ring of azaarene played a key role in the C–H bond deprotonation step with the palladium acetate complex. The Wang group developed enantioselective direct conjugate addition of aryl methane nucleophiles to enals with a chiral amine catalyst under mild conditions. Only methyl groups activated by the strongest electron-withdrawing groups were applicable in this addition reaction. Recently, Palomo and co-worker developed base-catalyzed enantioselective functionalization of 2-(cyanomethyl)azaarene N-oxides to construct quaternary stereocenters. However, these reactions required the use of preactivated 2-alkylpyridine substrates.

**Scheme 39.** Substrate-controlled Functionalization of 2-Alkylazaarenes

![Scheme 39](image-url)
3.4. Pd-catalyzed Side Chain C(α) Allylation of 2-Alkylaazaarenes without the Use of External Bases (Chapter 3)

Chapter 3 describes Pd-catalyzed side chain C(α) allylation of 2-alkylaazaarenes with allylic carbonates using a large bite-angle bisphosphine Pd-TRAP as a ligand. The reaction occurred under mild conditions without the use of external base and afforded the linear allylation products with high regioselectivity. Importantly, the (Ph-TRAP)-Pd system showed compatibility toward base-sensitive functional groups (Scheme 39).

Scheme 40. Ph-TRAP-Pd-catalytic System: Substrate Scope
3.5. Pd-catalyzed Enantioselective Allylation of 2-Alkylpyridines (Chapter 4)

Chapter 4 describes Pd-catalyzed enantioselective allylation of 2-alkylpyridine. The chiral palladium catalysts prepared from the newly synthesized chiral monophosphine ligand induced a highly enantioselective allylation reaction. The use of other ligands was ineffective.

**Scheme 41.** Enantioselective Allylation of 2-Alkylpyridines
4. References


Chapter 1

Stereoselective C–H Borylations of Cyclopropanes and Cyclobutanes with Silica-supported Monophosphane-Ir Catalysts

Heteroatom-directed C–H borylation of cyclopropanes and cyclobutanes was achieved with silica-supported monophosphine-Ir catalysts. Borylation occurred at the C–H bonds located γ to the directing N or O atoms with exceptional cis stereoselectivity relative to the directing groups. This protocol was applied to the borylation of a tertiary C–H bond of a ring-fused cyclopropane.
Introduction

Cyclopropanes and cyclobutanes, categorized as small-ring carbocycles, are common units in natural products, biologically active compounds, and synthetic building blocks.\textsuperscript{1,2} Recently, transition metal catalyzed C–H bond activation strategies were developed as direct methods for functionalizing small-ring frameworks such as cyclopropanes and cyclobutanes.\textsuperscript{3–6} Among these reactions, C–H borylation reactions are attractive because borylated small-ring compounds can act as "handles" for diverse molecular transformations.\textsuperscript{7–11} Recently, Hartwig and co-workers reported the trans-selective borylation of substituted cyclopropanes using Ir-phenanthroline catalyst systems.\textsuperscript{4} However, introduction of a boron atom with cis stereochemistry relative to a substituent existing in small-ring systems is still difficult. Furthermore, C–H borylation of cyclobutane derivatives has not yet been achieved.

A previous report from the Sawamura group described the directed borylation of primary and secondary C(sp\textsuperscript{3})–H bonds of N-alkylated amides, ureas, and aminopyridines\textsuperscript{10b} and 2-alkylpyridines\textsuperscript{10c} catalyzed by Ir- or Rh-catalyst systems based on immobilized monophosphine ligands such as Silica-SMAP\textsuperscript{12} and Silica-TRIP\textsuperscript{12} (Figure 1). This strategy allowed the borylation of a cyclohexane ring substituted with a pyridine directing group with trans stereoselectivity, but its applicability for small-ring systems was not demonstrated.

![Figure 1. Silica-supported Monophosphines.](image)

This chapter describes the heteroatom-directed C–H borylation reactions of cyclopropanes and cyclobutanes catalyzed by silica-supported monophosphine-Ir systems. The reactions proceeded under mild conditions with exceptional cis stereochemistry relative to the directing group, and thus complement Hartwig’s trans-selective C–H borylation of cyclopropanes.\textsuperscript{4,13} Applicability for borylation of a tertiary C–H bond and cyclobutane systems and the effectiveness of carbonyl-related directing groups are new features of this heterogeneous catalysis.
Results and Discussion

Initially, Ir and Rh catalyst systems based on various ligands \{[M(OMe)(cod)]_2 (M = Ir or Rh, 2 mol % M)\} were evaluated for catalytic activity toward borylation of 2-cyclopropylpyridine (1a, 0.4 mmol) with bis(pinacolato)diboron (2, 0.2 mmol) in THF. As a result, the Ir complex coordinated with the commercially available silica-supported caged trialkylphosphine Silica-SMAP showed the greatest turnover efficiency (25 °C, 15 h), giving cyclopropylboronate 3a (150% based on 2 by \(^1\)H NMR, Scheme 1) along with 2,3-bisborylation product 3a' (6%, \textit{vide infra} for details on this compound) in total yields over 100%, indicating that HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield based on B atom is 200%). The reaction using HBpin instead of 2 under otherwise identical reaction conditions gave 3a in 77% yield. The C–H borylation occurred with exclusive regio- and stereoselectivity at the three-membered ring C–H bond located \(\gamma\) to the pyridine N atom in favor of the \textit{cis} configuration, which indicates N-to-Ir coordination leading to a five-membered iridacyclic reaction pathway. The presence or absence of an N–B interaction of borylation products in solution were determined by \(^{11}\)B NMR analysis. The existence of an intramolecular N–B interaction in the product (3a) was indicated by \(^{11}\)B NMR spectroscopy in CDCl\(_3\). Aromatic C–H borylation on the pyridine ring, benzylic C–H borylation, and ring opening of the cyclopropane were not observed. No reaction occurred with the corresponding Rh catalyst under identical reaction conditions.

Scheme 1. Silica-SMAP-Ir catalyzed borylation of 1a.

When the Silica-SMAP-Ir-catalyzed reaction of 1a was conducted with 2.5 equiv of 2, a novel 1,2,3-trisubstituted cyclopropane derivative (3a') with all-\textit{cis} configuration was obtained selectively (Scheme 2). Single-crystal X-ray diffraction confirmed the stereochemistry and intramolecular N–B coordination.
Scheme 2. Silica-SMAP-Ir catalyzed bisborylation of 1a.

Crystal data for 3a' (CCDC 1005180; recrystallization from hot pentane; the single crystals of 3a' contained one molecule of pinacol). C_{23}H_{37}B_{2}NO_{5}, M = 429.17, monoclinic, space group P2_1/c (#14), a = 10.145(5) Å, b = 7.932(4) Å, c = 30.269(14) Å, β = 95.723(9)°, V = 2424(2) Å^3, Z = 4, density (calc.) = 1.176, total reflections collected = 14388, unique reflections = 4167 (R_{int} = 0.0804), GOF = 1.067, R_1 = 0.0963 (I > 2σ(I)), wR_2 = 0.2907.

Homogeneous Ir catalyst systems with Ph-SMAP,^{14} PPh_3, PMe_3, PCy_3 or PrBu_3 without exogenous ligands induced much lower borylation activity (0–54% yields of 3a, 2 mol % of Ir, at 25 °C in Table 1, or at 50 °C in Table 2, for 15 h) indicating the importance of immobilization. The phenanthroline-based ligand (2,9-Me_2phen), which was the optimal ligand in the Hartwig’s study for the trans-selective cyclopropane borylation,^{4} caused borylation of the pyridine ring (C4 and C5 positions, 78% and 59%, respectively, at 50 °C), but not at the cyclopropane ring (entry 13, Table 2).

Figure 1. Structures of Immobilized Monophosphanes and Soluble Ligands Used in Tables 1 and 2.
**Table 1.** Ligand Effects in the Ir-catalyzed Borylation of 1a at 25 °C.\(^a\)

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield of 3a (%)(^b)</th>
<th>Yield of 3a’ (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Silica-SMAP</td>
<td>150 (133)</td>
<td>6</td>
</tr>
<tr>
<td>2(^c)</td>
<td>Silica-SMAP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Silica-TRIP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Silica-3p-TPP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>PS-TPP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ph-SMAP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PMe(_3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>PCy(_3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>P’Bu(_3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>PPh(_3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>XPhos</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12(^d)</td>
<td>dtbpy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13(^d)</td>
<td>2,9-Me(_2)Phen</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14(^d)</td>
<td>3,4,7,8-Me(_4)Phen</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>none</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 1a (0.4 mmol), 2 (0.2 mmol), [Ir(OMe)(cod)]\(_2\) (0.004 mmol Ir), ligand (0.004 mmol), THF (1 mL), 25 °C, 15 h. \(^b\) Yields based on 2 were determined by \(^1\)H NMR spectroscopy. Yield in excess of 100% indicates that HBpin also worked as a borylating reagent (theoretical maximum yield is 200%). \(^c\) [Rh(OMe)(cod)]\(_2\) was used instead of [Ir(OMe)(cod)]\(_2\). \(^d\) Aromatic C–H borylation products were obtained (entry 12, 89% (C4) and 41% (C5); entry 13, 0% (C4) and 0% (C5); entry 14, 0% (C4) and 0% (C5)).
Table 2. Ligand Effects in the Ir-catalyzed Borylation of 1a at 50 °C. $^a$

![Chemical reaction image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield of 3a [%]$^b$</th>
<th>Yield of 3a' [%]$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Silica-SMAP</td>
<td>138</td>
<td>7</td>
</tr>
<tr>
<td>2 $^c$</td>
<td>Silica-SMAP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Silica-TRIP</td>
<td>121</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Silica-3p-TPP</td>
<td>102</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>PS-TPP</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ph-SMAP</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PMe$_3$</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>PCy$_3$</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>P'Bu$_3$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>PPh$_3$</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>XPhos</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12 $^d$</td>
<td>dtbpy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13 $^d$</td>
<td>2,9-Me$_2$Phen</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14 $^d$</td>
<td>3,4,7,8-Me$_4$Phen</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>none</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Conditions: 1a (0.4 mmol), 2 (0.2 mmol), [Ir(OMe)(cod)]$_2$ (0.004 mmol Ir), ligand (0.004 mmol), THF (1 mL), 50 °C, 15 h. $^b$Yields based on 2 were determined by $^1$H NMR spectroscopy. Yield in excess of 100% indicates that HBpin also worked as a borylating reagent (theoretical maximum yield is 200%). $^c$[Rh(OMe)(cod)]$_2$ was used instead of [Ir(OMe)(cod)]$_2$. $^d$Aromatic C–H borylation products were obtained (entry 12, 82% (C4) and 56% (C5); entry 13, 78% (C4) and 59% (C5); entry 14, 54% (C4) and 21% (C5)).
Substrate Scope with C–H Borylation of Cyclopropanes

Various heteroarenes functioned as a directing group (Table 3, entries 1–6). Electron-donating (1b,c) or electron-withdrawing (1d) substituents at the 5-position of 2-cyclopropylpyridine had little effect on the effectiveness of the cyclopropane C–H borylation (entries 1–3). Benzoannulated N-heteroaryls, such as benzoimidazole, benzoxazole, and benzothiazole, were suitable directing groups, showing exclusive diastereoselectivity (Table 3, entries 4–6). For instance, reaction of 2-cyclopropyl-N-methylbenzoimidazole (1e) proceeded smoothly at 25 °C to afford borylation product 3e in 133% isolated yield based on 2 (entry 4). Gram-scale borylation of 1e was possible by decreasing catalyst loading to 0.1 mol % Ir at 80 °C (Scheme 3). The crude reaction mixture contained a significant amount of a byproduct (2-cyclopropyl-1-methyl-2,3-dihydro-1H-benzoimidazole, 39%) resulting from C=N reduction of the starting material (1e); however, the borylation product 3e did not undergo C=N reduction. Therefore, 3e could be isolated easily by bulb-to-bulb distillation. Benzoxazole (in 1f) also functioned as a directing group, but C(sp^3)–H borylations were minor reaction paths (entry 5). 2-Cyclopropylbenzothiazole (1g) reacted cleanly at 70 °C to provide cyclopropylboronate 3g as a sole product (entry 6). The 11B NMR spectra of 3e–g indicated that their azole groups were not coordinated to the boron atom.15

Effects of alkyl substituents on the cyclopropane ring are shown in Table 3 (entries 7–9). Methyl group substitution with trans geometry in 1h and geminal dimethyl substitution in 1i had little effect on either reaction effectiveness or diastereoselectivity. Interestingly, a tertiary C–H bond on the cyclopropane ring of 2-(7-bicyclo[4.1.0]heptyl)-1-methyl-1H-benzoimidazole (1j) successfully participated in borylation under mild conditions (50 °C, entry 9). The structure of 3j was confirmed by single-crystal X-ray diffraction analysis (Figure 2). This is the first catalytic borylation of a tertiary C–H bond. These experimental results demonstrating good tolerance toward substituted cyclopropanes likely reflect the increased acidity of the small-ring C–H bonds with relatively high s-character, and are consistent with the report of Hartwig’s group describing successful non-directed cyclopropane borylation.4

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Table 3. Silica-SMAP-Ir catalyzed C–H borylation of cyclopropane derivatives (1) with diboron (2).a

<table>
<thead>
<tr>
<th>Enter</th>
<th>Substrate 1</th>
<th>Product 3</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /></td>
<td>25</td>
<td>168 (^{d}) (150)</td>
</tr>
<tr>
<td>2c</td>
<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /></td>
<td>25</td>
<td>108 (^{e,f}) (82)</td>
</tr>
<tr>
<td>3c</td>
<td><img src="image5" alt="Structure" /></td>
<td><img src="image6" alt="Structure" /></td>
<td>25</td>
<td>164 (^{e}) (158)</td>
</tr>
<tr>
<td>4</td>
<td>1e (X = NMe)</td>
<td>3e (X = NMe)</td>
<td>25</td>
<td>148 (^{e}) (133)</td>
</tr>
<tr>
<td>5</td>
<td>1f (X = O)</td>
<td>3f (X = O)</td>
<td>40</td>
<td>98 (87) (^{a})</td>
</tr>
<tr>
<td>6</td>
<td>1g (X = S)</td>
<td>3g (X = S)</td>
<td>70</td>
<td>156 (130)</td>
</tr>
<tr>
<td>7</td>
<td>1h</td>
<td>3h</td>
<td>30</td>
<td>137 (^{e}) (123) (^{\dagger})</td>
</tr>
<tr>
<td>8</td>
<td>1i</td>
<td>3i</td>
<td>40</td>
<td>86 (^{e}) (61)</td>
</tr>
<tr>
<td>9</td>
<td>1j</td>
<td>3j</td>
<td>50</td>
<td>91 (^{e}) (80)</td>
</tr>
</tbody>
</table>

\(^{a}\) Conditions: 1 (0.4 mmol), 2 (0.2 mmol), [Ir(OMe)(cod)]\(_2\) (0.004 mmol Ir), Silica-SMAP
(0.004 mmol P), THF (2 mL), 15 h. \(^b\) Yields based on 2 were determined by \(^1\)H NMR spectroscopy. Isolated yields are in parentheses. Yield in excess of 100% indicates that HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield is 200%). \(^c\) THF (1 mL). \(^d\) Bisborylation products 3’ were observed in the crude mixture (entry 1, 6%; entry 3, 11%). \(^e\) Diboron 2 remained in the crude mixture. \(^f\) A partial N–B interaction was indicated by \(^11\)B NMR spectroscopy. \(^g\) The C=N reduction product of 1 was observed in the crude mixture (entry 4, 39%; entry 7, 48%; entry 8, 17%; entry 9, 26%). \(^h\) Isolated product was contaminated with arylboronates (10%). \(^i\) Isolated product was contaminated with regioisomers (8%).

**Figure 2.** Molecular structure of the tertiary alkylboronate 3j.

Crystal data for 3j (CCDC 1005181; recrystallization from CH\(_2\)Cl\(_2\)/hexane): C\(_{21}\)H\(_{29}\)BN\(_2\)O\(_2\), \(M = 352.28\), monoclinic, space group \(P2_1/c\) (#14), \(a = 6.667(3)\) Å, \(b = 19.503(8)\) Å, \(c = 14.595(6)\) Å, \(\beta = 95.519(7)^\circ\), \(V = 1889.9(14)\) Å\(^3\), \(Z = 4\), density (calc.) = 1.239, total reflections collected = 15682, unique reflections = 4302 (\(R_{int} = 0.1056\)), GOF = 1.062, \(R_1 = 0.0927\) (\(I > 2\sigma(I)\)), \(wR_2 = 0.2012\).

**Scheme 3.** Gram-scale borylation of 1e.

 ![Scheme 3](image)

Carbonyl-related functional groups also acted as directing groups for cyclopropane C–H borylation as shown in Table 4. \(N\)-Methoxyimine derived from dicyclopropyl ketone (1k) reacted at 25 °C to give monoborylation product 3k selectively (entries 1 and 2). For
N-methoxyimine (II) derived from an unsymmetrical ketone, only the E isomer was converted to the corresponding cyclopropylboronate (3l) while the Z isomers remained intact (entries 3 and 4, respectively). N-Mesitylimine 1m was more efficiently borylated using Silica-TRIP than using Silica-SMAP (entries 5 and 6, respectively). Again, only the E isomers participated in the transformation. N,N-Diisopropylamide 1n reacted at 80 °C using Silica-SMAP with exceptional cis selectivity to afford cyclopropylboronate 3n (entries 7 and 8). Coordination of the carbonyl oxygen atom to the Ir atom is thought to be responsible for the regio- and stereoselectivities.

Table 4. Ir-catalyzed C–H borylation of cyclopropanes (1) with carbonyl-related functional groups

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>Product 3</th>
<th>Ligand</th>
<th>Temp. (°C)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO N</td>
<td>MeO N Bpin</td>
<td>Silica-SMAP</td>
<td>25</td>
<td>107 (66)</td>
</tr>
<tr>
<td>2</td>
<td>MeO N</td>
<td>MeO N Bpin</td>
<td>Silica-TRIP</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>MeO N Bu</td>
<td>MeO N Bpin</td>
<td>Silica-SMAP</td>
<td>25</td>
<td>115c (64)</td>
</tr>
<tr>
<td>4</td>
<td>MeO N Bu</td>
<td>MeO N Bpin</td>
<td>Silica-TRIP</td>
<td>25</td>
<td>104c</td>
</tr>
<tr>
<td>5d</td>
<td>MeO N Mes</td>
<td>MeO N Bpin</td>
<td>Silica-SMAP</td>
<td>100</td>
<td>85c,ek</td>
</tr>
<tr>
<td>6d</td>
<td>MeO N Mes</td>
<td>MeO N Bpin</td>
<td>Silica-TRIP</td>
<td>100</td>
<td>113c,ek (98)</td>
</tr>
<tr>
<td>7f</td>
<td>MeO N iPr</td>
<td>MeO N Bpin</td>
<td>Silica-SMAP</td>
<td>80</td>
<td>77 (75)</td>
</tr>
<tr>
<td>8f</td>
<td>MeO N iPr</td>
<td>MeO N Bpin</td>
<td>Silica-TRIP</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

a Conditions: 1 (0.4 mmol), 2 (0.2 mmol), [Ir(OMe)(cod)]2 (0.004 mmol Ir), ligand (0.004 mmol P), THF (1 mL), 24 h. b Yields based on 2 were determined by 1H NMR spectroscopy. Isolated yield is in parentheses. Yield in excess of 100% indicates that HBpin also worked as a borylating reagent (theoretical maximum yield is 200%). c The Z isomers of substrates remained intact in the crude mixture. d In THF (2 mL), for 15 h. e The C=N reduction product of 3 was observed in the crude mixture (entry 5, 9%; entry 6, 4%). f In hexane (1 mL).

Substrate Scope with C–H Borylation of Cyclobutanes

Next, the Silica-SMAP-Ir system was applied to C–H borylation of cyclobutanes, which had not been reported previously. Results are summarized in Table 5. Reaction of
2-cyclobutylpyridine (4a) occurred at 25 °C to give cyclobutylboronate 5a as the sole product (entry 1). The borylation showed exceptional cis selectivity, and no ring opening was detected. N-Methylbenzoimidazole and benzooxazole also were suitable directing groups (entries 2–4). The structure of 5b was confirmed by single-crystal X-ray diffraction analysis (Figure 3). Gram-scale borylation of 4b with a reduced catalyst loading (0.1 mol % Ir, at 80 °C) proceeded efficiently to give 5b in 94% isolated yield (Scheme 4).

**Table 5.** Silica-SMAP-Ir catalyzed C–H borylation of cyclobutane derivatives (4) with diboron (2).a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Temp. (°C)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td><img src="image" alt="4a" /></td>
<td><img src="image" alt="5a" /></td>
<td>25</td>
<td>105 (85)c</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="4b" /></td>
<td><img src="image" alt="5b" /></td>
<td>40</td>
<td>109c1 (99)c</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="4c" /></td>
<td><img src="image" alt="5c" /></td>
<td>50</td>
<td>99 (94)c</td>
</tr>
</tbody>
</table>

*a Conditions: 4 (0.4 mmol), 2 (0.2 mmol), [Ir(OMe)(cod)]2 (0.004 mmol Ir), ligand (0.004 mmol P), THF (2 mL), 15 h. b Yields based on 2 were determined by 1H NMR spectroscopy. Isolated yield is in parentheses. Yield in excess of 100% indicates that HBpin also worked as a borylating reagent (theoretical maximum yield is 200%). c In THF (1 mL). d Isolated 5a was contaminated with traces of impurities. e The C=N reduction products of 4 were observed in the crude mixture (entry 2, 39%). f Isolated products were contaminated with arylboronates (entry 2, 6%; entry 3, 20%).
Figure 3. Molecular structure of the alkylboronate 5b.

Crystal data for 5b (CCDC 1005182; recrystallization from CH₂Cl₂/hexane). C₁₈H₂₅BN₂O₂, M = 312.22, orthorhombic, space group Pna₂₁ (#33), a = 20.315(10) Å, b = 9.222(5) Å, c = 9.401(5) Å, V = 1761.2(16) Å³, Z = 4, density (calc.) = 1.177, total reflections collected = 10688, unique reflections = 2907 (R_int = 0.0685), GOF = 0.987, R₁ = 0.0515 (I>2σ(I)), wR₂ = 0.1310.

Scheme 4. Gram-scale borylation of 4b.

Transformation of Cyclopropyl and cyclobutyl boronates

The cyclopropyl and cyclobutyl boronates (3e and 5b, respectively) obtained through C–H borylation were used for transformations as shown in Scheme 5. Cyclopropylboronate 3e underwent transformation to a trifluoroborate salt,\textsuperscript{11a} one-carbon-homologation/oxidation sequence,\textsuperscript{17} and Pd-catalyzed Suzuki–Miyaura coupling with aryl or alkenyl bromides.\textsuperscript{11a,18} The structure of 8a was confirmed by single-crystal X-ray diffraction analysis (Figure 4). The alkenylated cyclopropane 8d is structurally related to chrysanthemic acid derivatives, which is a class of pyrethroids insecticides.\textsuperscript{19} Cyclobutylboronate 5b was converted to primary alcohol 9 through the one-carbon-homologation/oxidation sequence. These transformations occurred with retention of configurations to give the corresponding 1,2-cis-disubstituted small-ring compounds.
Scheme 5. Transformations of borylation products.

Scheme 5.

Figure 4. Molecular structure of the cross-coupling product 8a.

Crystal data for 8a (CCDC 1005183; recrystallization from CH$_2$Cl$_2$/hexane). C$_{17}$H$_{16}$N$_2$, $M = 248.33$, triclinic, space group $P1$ (#2), $a = 6.418(4)$ Å, $b = 9.102(5)$ Å, $c = 12.253(6)$ Å, $\alpha = 94.716(7)$, $\beta = 103.510(6)$, $\gamma = 104.835(7)$, $V = 665.0(7)$ Å$^3$, $Z = 2$, density (calc.) = 1.240, total reflections collected = 5433, unique reflections = 2862 ($R_{int} = 0.0280$), GOF = 1.081, $R_1 = 0.0568$ ($I>2\sigma(I)$), $wR_2 = 0.1802$. 

42
Conclusion

The author found that silica-supported monophosphine-Ir catalyst systems enabled N- or O-atom-directed C–H borylation of cyclopropanes and cyclobutanes. Borylation occurred with exceptional regio- and stereoselectivities with the assistance of various directing groups, including N-heteroarenes, an oxime, imine, and amide, resulting in formation of cis-substituted cyclopropyl- and cyclobutylboronates. The successful borylation of sterically congested C–H bonds of substituted cyclopropanes, including a tertiary C–H bond, demonstrates the potential of this heterogeneous borylation strategy toward functionalization of small-ring systems.

Experimental Section

Instrumentation and Chemicals.

$^1$H (400 MHz), $^{13}$C (100 MHz) and $^{11}$B (128 MHz) NMR spectra were recorded on a JEOL JNM-ECX400 spectrometer. Chemical shift values for $^1$H, $^{13}$C and $^{11}$B NMR spectra are referenced to Me$_4$Si, the residual solvent resonances and BF$_3$•OEt$_2$, respectively. Chemical shifts are reported in δ ppm. High-resolution mass spectra were recorded on a Thermo Fisher Scientific Exactive, JEOL JMS-T100LP mass spectrometer or JEOL JMS-T100GCV mass spectrometer at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. IR spectra were measured with a Perkin-Elmer Spectrum One. Melting points were measured on a Yanaco MP-500D apparatus. GLC analyses were conducted on a Shimadzu GC-14B equipped with a flame ionization detector. Gel permeation chromatography (GPC) was performed by LC-908 (Japan Analytical Industry Ltd., two in-line JAIGEL-2H, CHCl$_3$, 3.5 mL/min, UV and RI detectors). Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F$_{254}$.

All reactions were carried out under a nitrogen atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. [Ir(OMe)(cod)]$_2$,[20] Ph-SMAP[14a] and PS-TPP[21] were prepared according to the literatures. Silica-SMAP,[22] Silica-TRIP[10b] and Silica-3p-TPP[23] were prepared with CARiACT Q-10 according to the reported procedures. CARiACT Q-10 (Catalyst grade, 75–150 µm) was purchased from Fuji Silysia Chemical Ltd. and dehydrated by heating at 150 °C for 10 h and
stored in a glove box before use. All solvents for catalytic reactions were degassed via three freeze-pump-thaw cycles before use. All substrates for catalytic reactions were purified by distillation under vacuum or recrystallization before use. Bis(pinacolato)diboron (2) was purchased from AllyChem Co., Ltd., and purified as follows: The diboron 2 was dissolved into hexane at room temperature, and traces of insoluble solids were removed by filtration. The filtrate was concentrated under vacuum, and the residue was recrystallized from pentane before use. The use of freshly prepared [Ir(OMe)(cod)]₂ (stored in a glove box) and purified materials are important for good yields of the products.

Experimental Procedures

Procedure for the Borylation of 2-Cyclopropylpyridine (1a) with Silica-SMAP-Ir Catalyst (Scheme 1). In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.004 mmol, 2 mol %), bis(pinacolato)diboron (2) (50.8 mg, 0.2 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]₂ (1.3 mg, 0.002 mmol, 1 mol %) in THF (0.7 mL) and 2-cyclopropylpyridine (1a) (47.7 mg, 0.4 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 25 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yields of the products 3a and 3a’ were determined by ¹H NMR (150% and 6% based on 2, respectively). The crude material was then purified by Kugelrohr distillation (1 mmHg, 75 °C), to give the corresponding product 3a (65.4 mg, 0.27 mmol, 133% yield). Yield in excess of 100% indicates that HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield is 200%).

Procedure for the Borylation of 2-Cyclopropylpyridine (1a) with HBpin (Note [15]). In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.004 mmol, 2 mol %), HBpin (25.6 mg, 0.2 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]₂ (1.3 mg, 0.002 mmol, 1 mol %) in THF (0.7 mL) and 2-cyclopropylpyridine (1a) (47.7 mg, 0.4 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 25 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3a was
determined by $^1$H NMR (77%).

Procedure for the Double Borylation of 2-Cyclopropylpyridine (1a) (Scheme 2). In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.004 mmol, 2 mol %), bis(pinacolato)diboron (2) (127 mg, 0.5 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]$_2$ (1.3 mg, 0.002 mmol, 1 mol %) in THF (0.7 mL) and 2-cyclopropylpyridine (1a) (23.8 mg, 0.2 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 50 °C for 48 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yields of the products 3a' were determined by $^1$H NMR (91%). The crude material was then purified by Kugelrohr distillation (1 mmHg, 125 °C), to give the corresponding product 3a' (44.4 mg, 0.12 mmol, 60% yield).

Typical Procedure for the Borylation of 2-Cyclopropylpyridine (1a) with Immobilized Ligands (Tables 1 and 2). In a nitrogen-filled glove box, an immobilized ligand (0.004 mmol, 2 mol %), bis(pinacolato)diboron (2) (50.8 mg, 0.2 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]$_2$ (1.3 mg, 0.002 mmol, 1 mol %) in THF (0.7 mL) and 2-cyclopropylpyridine (1a) (47.7 mg, 0.4 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 25 or 50 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yields of the products 3a and 3a' (based on 2) was determined by $^1$H NMR. Yield in excess of 100% indicates that HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield is 200%).

Typical Procedure for the Borylation of 2-Cyclopropylpyridine (1a) with Soluble Ligands. In a nitrogen-filled glove box, bis(pinacolato)diboron (2) (50.8 mg, 0.2 mmol) was placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of Ph-SMAP (0.9 mg, 0.004 mmol, 2 mol %) in anhydrous, degassed THF (0.3 mL), a solution of [Ir(OMe)(cod)]$_2$ (1.3 mg, 0.002 mmol, 1 mol %) in THF (0.7 mL) and 2-cyclopropylpyridine (1a) (47.7 mg, 0.4 mmol) were added successively. The tube was sealed with a screw cap and
removed from the glove box. The reaction mixture was stirred at 25 or 50 °C for 15 h. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3a (based on 2) was determined by 1H NMR.

**Typical Procedure for the Borylation of Cyclopropane Derivatives (Table 3).** In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.004 mmol, 2 mol %), bis(pinacolato)diboron (2) (50.8 mg, 0.2 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]_2 (1.3 mg, 0.002 mmol, 1 mol %) in THF (0.7 mL) and 2-cyclopropyl-5-methylpyridine (1b) (53.3 mg, 0.4 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 25 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3b was determined by 1H NMR (168%). The crude material was then purified by Kugelrohr distillation (1 mmHg, 90 °C), to give the corresponding product 3b (77.8 mg, 0.30 mmol, 150% yield).

**Procedure for the Borylation of 1e at a Gram Scale (Scheme 3).** In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g, 71.4 mg, 0.005 mmol, 0.1 mol %), bis(pinacolato)diboron (2) (1.27 g, 5 mmol), and anhydrous, degassed THF (1 mL) were placed in a 50-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]_2 (1.7 mg, 0.0025 mmol, 0.05 mol %) in THF (4 mL) and 2-cyclopropyl-1-methyl-1H-benzo[d]imidazole (1e) (1.72 g, 10 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 80 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3e was determined by 1H NMR (82%). The crude material was then purified by Kugelrohr distillation (1 mmHg, 90 °C), to give the corresponding product 3e (1.16 g, 3.9 mmol, 78% yield).

**Typical Procedure for the Borylation of Cyclopropanes with Carbonyl-related Functional Groups (Tables 4).** In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g,
Typical Procedure for the Borylation of Cyclobutane Derivatives (Tables 5). In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.004 mmol, 2 mol %), bis(pinacolato)diboron (2) (50.8 mg, 0.2 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]2 (1.3 mg, 0.002 mmol, 1 mol %) in THF (0.7 mL) and dicyclopentylmethane O-methyl oxime (1k) (55.7 mg, 0.4 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 25 °C for 24 h, and filtered through a glass pipette equipped with a cotton filter. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3k was determined by 1H NMR (107%). The crude material was then purified by Kugelrohr distillation (1 mmHg, 80 °C), to give the corresponding product 3k (35.0 mg, 0.13 mmol, 66% yield).

Procedure for the Borylation of 4b at a Gram Scale (Scheme 4). In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol/g, 71.4 mg, 0.005 mmol, 0.1 mol %), bis(pinacolato)diboron (2) (1.27 g, 5 mmol), and anhydrous, degassed THF (1 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]2 (1.7 mg, 0.0025 mmol, 0.05 mol %) in THF (4 mL) and 2-cyclobutyl-1-methyl-1H-benzo[d]imidazole (4b) (1.86 g, 10 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 80 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the
product 4b was determined by $^1\text{H}$ NMR (96%). The crude material was then purified by Kugelrohr distillation (1 mmHg, 150 °C), to give the corresponding product 5b contaminated with C(sp$^2$)–H borylation products (6%) (1.47 g, 4.7 mmol, 94% yield).

**Procedure for the Conversion of 3e to Trifluoroborate salt 6 (Scheme 5).** The boronate pinacol ester 3e (29.8 mg, 0.1 mmol) was dissolved in MeOH (1 mL) in a 10-mL vial containing a magnetic stirring bar. An aqueous solution of KHF$_2$ (4.5 M, 0.8 mmol, 8 equiv) was added to the vial. The mixture was stirred at 25 °C for 2 h. After the volatiles were evaporated under reduced pressure, the residue was washed with aqueous methanol (1:1). The resulting solid was dissolved in acetone and filtered through a Celite pad. The filtrate was evaporated to give the trifluoroborate salt 6 (25.6 mg, 0.092 mmol, 92% yield).

**Procedure for the One-Carbon Homologation/Oxidation Sequence of 3e (Scheme 5).** Under Ar atmosphere, the boronate 3e (29.8 mg, 0.1 mmol), bromochloromethane (32.3 mg, 0.25 mmol), and anhydrous THF (1 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. The tube was sealed with a screw cap with a Teflon-coated silicon rubber septum. After the mixture was cooled to –78 °C, $^n$BuLi in hexane (1.6 M, 125 µL, 0.2 mmol) was added. The mixture was stirred at –78 °C for 5 min, and stirred at room temperature for 4 h. The volatiles were evaporated under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue, and the yield of 1-methyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclopropyl-1H-benzo[d]imidazole was determined by $^1\text{H}$ NMR (78%) in the crude mixture. The resulting product was used to next reaction without further purification. The crude product, THF (0.5 mL), water (0.5 mL) and NaBO$_3$•4H$_2$O (46.1 mg, 0.3 mmol) were placed in a round bottom flask containing a magnetic stirring bar, and the reaction mixture was stirred vigorously at room temperature for 2 h under air. The volatiles were evaporated under reduced pressure. The residue was suspended in CHCl$_3$, filtered through a pipette equipped with a cotton plug. The filtrate was concentrated under reduced pressure, and the crude mixture was then purified by silica gel chromatography (CHCl$_3$/MeOH 90:10) to give the alcohol 7 (13.1 mg, 0.065 mmol, 65% yield in two steps).

**Typical Procedure for the Suzuki–Miyaura Coupling of 3e (Scheme 5, for 8a–c).** In a nitrogen-filled glove box, 3e (29.8 mg, 0.1 mmol), 4-bromoanisole (28.1 mg, 0.15 mmol, 1.5 eq), Pd(dba)$_2$ (2.9 mg, 0.005 mmol, 5 mol %), RuPhos (4.7 mg, 0.01 mmol, 10 mol %) and
Cs₂CO₃ (97.8 mg, 0.3 mmol, 3 eq) were placed in a 4-mL glass tube containing a magnetic stirring bar. 1,4-Dioxane (0.3 mL) was added, and the tube was sealed with a screw cap and removed from the glove box. The reaction mixture was heated at 110 °C for 24 h. After cooling to room temperature, water was added to the tube and the mixture was extracted with Et₂O. The organic layer was washed with water, dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (CHCl₃/MeOH 95:5) to give the arylcyclopropane 8b (26.1 mg, 0.094 mmol, 94% yield).

Procedure for the Suzuki–Miyaura Coupling of 3e (Scheme 5, for 8d). In a nitrogen-filled glove box, 3e (29.8 mg, 0.1 mmol), 1-bromo-2-methyl-1-propene (16.2 mg, 0.12 mmol, 1.2 eq), Pd(dba)₂ (2.9 mg, 0.005 mmol, 5 mol %), RuPhos (4.7 mg, 0.01 mmol, 10 mol %) and Cs₂CO₃ (97.8 mg, 0.3 mmol, 3 eq) were placed in a 10-mL glass tube containing a magnetic stirring bar. Toluene (0.8 mL) was added, and the tube was sealed with a screw cap and removed from the glove box. The reaction mixture was heated at 120 °C for 24 h. After cooling to room temperature, water was added to the tube and the mixture was extracted with Et₂O. The organic layer was washed with water, dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (CHCl₃/EtOAc 80:20) followed by Kugelrohr distillation (1 mmHg, 125–135 °C) to give the alkenylcyclopropane 8d contaminated with traces of impurities (13.7 mg, 0.061 mmol, 61% yield).

Procedure for the One-Carbon Homologation Following Oxidation of 5b (Scheme 5). Under Ar atmosphere, the boronate 5b (31.2 mg, 0.1 mmol), bromochloromethane (32.3 mg, 0.25 mmol), and anhydrous THF (1 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. The tube was sealed with a screw cap with a Teflon-coated silicon rubber septum. After the mixture was cooled to –78 °C, n-BuLi in hexane (1.6 M, 125 µL, 0.2 mmol) was added. The mixture was stirred at –78 °C for 5 min, and stirred at room temperature for 4 h. The volatiles were evaporated under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue, and the yield of desired 1-methyl-2-(2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclobutyl)-1H-benzo[d]imidazole was determined by ¹H NMR (57%) in the crude mixture. The resulting product was used to next reaction without further purification. The crude product, THF (0.5 mL), water (0.5 mL) and NaBO₃·4H₂O (46.1 mg, 0.3 mmol) were placed in a round bottom flask containing a magnetic stirring bar, and the reaction mixture was stirred vigorously at room temperature for 2 h under air. The volatiles were evaporated under reduced pressure. The residue was suspended in CHCl₃, filtered through a pipette equipped with a cotton plug. The
filtrate was concentrated under reduced pressure, and the crude mixture was then purified by silica gel chromatography (CHCl₃/MeOH 90:10) to give the alcohol 9 (10.3 mg, 0.048 mmol, 48% yield in two steps).

**Preparation of Substrates.**

The substrates for borylation 1a, 1f, 1g, 1h and 4c are reported in the literatures.

**Preparation of 2-Cyclopropyl-5-methylpyridine (1b).** The title compound (1b) was synthesized via the reaction of 2-chloro-5-methylpyridine and cyclopropyl magnesium bromide with a ZnBr₂/PEPPSI catalyst system (22%).

\[
\begin{align*}
\text{Me} & \\
\text{N} & & \text{N}
\end{align*}
\]

1b

Isolated by silica gel chromatography (hexane/EtOAc 80:20) followed by Kugelrohr distillation (10 mmHg, 75 °C). Colorless oil. \(^1\text{H NMR}\) (CDCl₃) δ 0.91–0.99 (m, 4H), 1.95–2.04 (m, 1H), 2.56 (d, J = 2.8 Hz, 3H), 7.00 (dd, J = 8.0, 2.8 Hz, 1H), 7.31–7.33 (m, 1H), 8.26 (s, 1H). \(^13\text{C NMR}\) (CDCl₃) δ 9.32 (2C), 15.86, 17.87, 120.51, 129.36, 136.39, 149.40, 159.65. \(\text{IR (ATR): 3004, 1604, 1489, 1213, 1022, 818, 803 cm}^{-1}\). \(\text{HRMS–ESI (m/z): [M+H]}^+\) Calcd for C₉H₁₂N, 134.09643; found, 134.09661.

**Preparation of 2-Cyclopropyl-5-(methoxymethoxy)pyridine (1c).** The title compound (1c) was synthesized via the reaction of 2-chloro-5-(methoxymethoxy)pyridine and cyclopropyl magnesium bromide with a Fe(acac)₃ catalyst system (50%).

\[
\begin{align*}
\text{MOMO} & \\
\text{N} & & \text{N}
\end{align*}
\]

1c

Isolated by silica gel chromatography (hexane/EtOAc 80:20) followed by GPC. Pale yellow oil. \(^1\text{H NMR}\) (CDCl₃) δ 0.94 (d, J = 6.0 Hz, 4H), 1.93–2.02 (m, 1H), 3.47 (s, 3H), 5.14 (s, 2H), 7.06 (br-s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 8.26 (br-s, 1H). \(^13\text{C NMR}\) (CDCl₃) δ 9.13 (2C), 16.31, 55.96, 94.90, 121.17, 123.57, 138.81, 151.27, 156.03. \(\text{IR (ATR): 3003, 2957, 2902, 1570, 1485, 1200, 1152, 1080, 986, 903, 825 cm}^{-1}\). \(\text{HRMS–ESI (m/z): [M+H]}^+\) Calcd for C₁₀H₁₄N, 180.10191; found, 180.10204.
Preparation of 2-Cyclopropyl-5-(trifluoromethyl)pyridine (1d). The title compound (1d) was synthesized via the reaction of 2-chloro-5-(trifluoromethyl)pyridine and cyclopropyl magnesium bromide with a Fe(acac)$_3$ catalyst system (42%).

\[
\text{Fe(acac)$_3$ catalyst system (42%)}
\]

Isolated by silica gel chromatography (hexane/EtOAc 80:20) followed by Kugelrohr distillation (10 mmHg, 70 °C). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.04–1.13 (m, 4H), 2.04–2.12 (m, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 8.68 (s, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 10.89 (2C), 17.32, 120.99, 123.21 (q, $J = 32.4$ Hz), 123.88 (q, $J = 269.8$ Hz), 132.63 (q, $J = 3.8$ Hz), 146.19 (q, $J = 3.8$ Hz), 167.17. IR (ATR): 3011, 1605, 1325, 1121, 1082, 1013, 902, 830, 733 cm$^{-1}$. HRMS–APCI (m/z): [M+H]$^+$ Calcd for C$_9$H$_9$F$_3$, 188.06816; found, 188.06861.

Preparation of 2-Cyclopropyl-1-methyl-1H-benzo[d]imidazole (1e). The title compound (1e) was synthesized via the reaction of 2-cyclopropyl-1H-benzo[d]imidazole and MeI with NaH (95%).

\[
\text{Me}
\]

Isolated by silica gel chromatography (CHCl$_3$/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 100 °C). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.08–1.13 (m, 2H), 1.21–1.25 (m, 2H), 1.96–2.03 (m, 1H), 3.82 (s, 3H), 7.18–7.24 (m, 2H), 7.26–7.28 (m, 1H), 7.63–7.69 (m, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 7.46, 7.94 (2C), 29.54, 108.56, 118.81, 121.69, 121.74, 135.91, 142.20, 156.60. IR (ATR): 2971, 1622, 1485, 1406, 1145, 1077 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for, C$_{11}$H$_{13}$N$_2$, 173.10732; found, 173.10761.

Preparation of 1-Methyl-2-(2-methylcyclopropyl)-1H-benzo[d]imidazole (1h). The title compound (1h) was synthesized via the reaction of 1-methyl-2-(2-methylcyclopropyl)-1H-benzo[d]imidazole and MeI with NaH (99%).

\[
\text{Me}
\]
Isolated by silica gel chromatography (CHCl₃/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 110 °C). Colorless oil. ¹H NMR (CDCl₃) δ 0.87–0.94 (m, 1H), 1.27 (d, J = 6.0 Hz, 3H), 1.38–1.43 (m, 1H), 1.54–1.62 (m, 1H), 1.66 (td, J = 8.8, 4.4 Hz, 1H), 3.80 (s, 3H), 7.19–7.26 (m, 3H), 7.63–7.67 (m, 1H). ¹³C NMR (CDCl₃) δ 15.80, 16.39, 16.68, 18.57, 29.54, 108.49, 118.78, 121.57, 121.64, 135.90, 142.32, 156.58. IR (ATR): 2952, 2926, 1616, 1515, 1460, 1278, 1076, 739 cm⁻¹. HRMS–ESI (m/z): [M+H]⁺ Calcd for, C₁₂H₁₅N₂, 187.12298; found, 187.12321.

Preparation of 2-(2,2-Dimethylcyclopropyl)-1-methyl-1H-benzo[d]imidazole (1i). The title compound (1i) was synthesized via the reaction of 2-(2,2-dimethylcyclopropyl)-1H-benzo[d]imidazole³³ and MeI with NaH (68%).

Isolated by silica gel chromatography (CHCl₃/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 115 ºC). White solids. M.p. 63.3–64.7 ºC. ¹H NMR (CDCl₃) δ 0.90 (s, 3H), 1.07 (dd, J = 8.0, 5.2 Hz, 1H), 1.34 (s, 3H), 1.54 (t, J = 5.2 Hz, 1H), 1.85 (dd, J = 8.0, 5.2 Hz, 1H), 3.78 (s, 3H), 7.20–7.29 (m, 3H), 7.67–7.74 (m, 1H). ¹³C NMR (CDCl₃) δ 19.17, 19.87, 20.97, 21.87, 26.51, 29.60, 108.56, 119.17, 121.57, 121.79, 136.04, 142.36, 154.69. IR (ATR): 2949, 1615, 1521, 1468, 1442, 1324, 1122, 735 cm⁻¹. HRMS–ESI (m/z): [M+H]⁺ Calcd for, C₁₃H₁₇N₂, 201.13863; found, 201.13892.

Preparation of 2-(Bicyclo[4.1.0]heptan-7-yl)-1-methyl-1H-benzo[d]imidazole (1j). The title compound (1j) was synthesized via the reaction of bicyclo[4.1.0]heptan-7-carboxylic acid³⁴ and o-phenylenediamine, followed by the methylation with MeI and NaH (82%).

Isolated by silica gel chromatography (CHCl₃/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 115 ºC). Colorless oil. ¹H NMR (CDCl₃) δ 0.87–0.94 (m, 1H), 1.27–1.45 (m, 4H), 1.69 (t, J = 4.8 Hz, 1H), 1.78–1.88 (m, 4H), 1.99–2.09 (m, 2H), 3.80 (s, 3H), 7.18–7.26 (m, 3H), 7.62–7.66 (m, 1H). ¹³C NMR (CDCl₃) δ 20.09, 21.20 (2C), 21.34 (2C), 23.23 (2C), 52

**Preparation of Dicyclopropylmethanone O-Methyl Oxime (1k).** The title compound (1k) was synthesized via the reaction of dicyclopropylmethanone and MeONH₂·HCl with pyridine (90%).

![1k](image)

Isolated by silica gel chromatography (hexane/EtOAc 95:5) followed by Kugelrohr distillation (10 mmHg, 75 °C). Colorless oil. ¹H NMR (CDCl₃) δ 0.57–0.62 (m, 2H), 0.69–0.73 (m, 2H), 0.82–0.87 (m, 2H), 0.90–0.97 (m, 3H), 2.30–2.37 (m, 1H), 3.82 (s, 3H). ¹³C NMR (CDCl₃) δ 4.83 (2C), 5.32 (2C), 8.64, 9.41, 61.15, 160.90. IR (ATR): 3010, 2939, 2899, 1613, 1399, 1054, 1028, 1012, 899, 725 cm⁻¹. HRMS–APCI (m/z): [M+H]⁺ Calcd for C₈H₁₄O₂N, 140.10699; found, 140.10757.

**Preparation of 1-Cyclopropylpentan-1-one O-Methyl Oxime (1l).** The title compound (1l, E/Z 2.3:1) was synthesized via the reaction of 1-cyclopropylpentan-1-one and MeONH₂·HCl with pyridine (86%).

![1l](image)

Isolated by silica gel chromatography (hexane/EtOAc 99:1) followed by Kugelrohr distillation (10 mmHg, 80 °C). Colorless oil. ¹H NMR (CDCl₃) δ 0.68–0.71 (m, 3.4H), 0.80–0.85 (m, 0.6H), 0.88–0.93 (m, 3H), 1.27–1.52 (m, 5H), 1.75–1.79 (m, 0.6H), 2.13–2.23 (m, 1.4H), 3.78 (s, 2.1H), 3.86 (s, 0.9H). ¹³C NMR (CDCl₃) major: δ 5.00 (2C), 8.62, 13.82, 22.99, 27.14, 28.42, 61.89, 161.89. minor: δ 5.03 (2C), 8.62, 13.96, 22.59, 28.68, 29.70, 61.20, 161.03. IR (ATR): 2958, 2935, 1622, 1466, 1054, 916, 868 cm⁻¹. HRMS–ESI (m/z): [M+H]⁺ Calcd for C₉H₁₈O₂N, 156.13829; found, 156.13857.

**Preparation of N-(1-Cyclopropylethylidene)-2,4,6-trimethylaniline (1m).** The title compound (1m, E/Z 2.7:1) was synthesized via the reaction of 1-cyclopropylethanone and 2,4,6-trimethylaniline (34%).
Isolated by Kugelrohr distillation (1 mmHg, 115 °C). Colorless oil. $^1$H NMR (CDCl$_3$) δ 0.66–0.71 (m, 0.3H), 0.83–0.89 (m, 2H), 1.02–1.06 (m, 1.7H), 1.35–1.41 (m, 0.3H), 1.63 (s, 2.1H), 1.72–1.79 (m, 0.7H), 1.84 (s, 0.9H), 1.92 (s, 4.2H), 2.02 (s, 1.8 H), 2.23 (s, 2.1H), 2.25 (s, 0.9H), 6.79 (s, 1.4H), 6.82 (s, 0.6H). $^{13}$C NMR (CDCl$_3$) major: δ 8.35 (2C), 17.71 (2C), 18.93, 19.33, 20.67, 125.92 (2C), 128.35 (2C), 131.36, 146.00, 171.90. minor: 5.91 (2C), 14.43, 17.91 (2C), 19.40, 20.67, 126.33 (2C), 128.30 (2C), 131.46, 145.89, 171.49. IR (ATR): 3004, 2913, 1656, 1479, 1387, 1202, 853 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{14}$H$_{20}$N, 202.15903; found, 202.15929.

**Preparation of 2-Cyclobutylpyridine (4a).** The title compound (4a) was synthesized via the reaction of 2-bromopyridine and cyclopropyl magnesium bromide with a ZnBr$_2$/Pd(OAc)$_2$/P$^t$Bu$_3$ catalyst system (60%).

![4a](image)

Isolated by silica gel chromatography (hexane/EtOAc 80:20) followed by Kugelrohr distillation (10 mmHg, 85 °C). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.84–1.93 (m, 1H), 2.01–2.12 (m, 1H), 2.27–2.40 (m, 4H), 3.66 (quint, $J$ = 8.8 Hz, 1H), 7.05–7.11 (m, 1H), 7.14 (d, $J$ = 8.0 Hz, 1H), 7.58 (td, $J$ = 8.0, 2.0 Hz, 1H), 8.55 (d, $J$ = 4.0 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 18.15, 28.33 (2C), 41.95, 120.81, 120.86, 136.06, 149.12, 164.61. IR (ATR): 2978, 2938, 1589, 1473, 1433, 1148, 745 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_9$H$_{12}$N, 134.09643; found, 134.09665.

**Preparation of 2-Cyclobutyl-1-methyl-1H-benzo[d]imidazole (4b).** The title compound (4b) was synthesized via the reaction of 2-cyclobutyl-1H-benzo[d]imidazole and MeI with NaH (89%).

![4b](image)

Isolated by silica gel chromatography (CHCl$_3$/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 110 °C). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.98–2.07 (m, 1H), 2.09–
2.21 (m, 1H), 2.42–2.50 (m, 2H), 2.56–2.66 (m, 2H), 3.64 (s, 3H), 3.75 (quint, $J = 8.4$ Hz, 1H), 7.22–7.28 (m, 3H), 7.44–7.79 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ 18.71, 27.00 (2C), 29.43, 32.33, 108.68, 119.21, 121.60, 121.92, 135.97, 142.47, 157.77. IR (ATR): 2942, 1616, 1512, 1463, 1438, 1398, 1309, 1279, 1232, 739 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{12}$H$_{15}$N$_2$, 187.12298; found, 187.12321.

5. Characterization of Products

2-[(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyridine (3a)

Isolated by Kugelrohr distillation (1 mmHg, 75 °C, 65.4 mg, 133% yield). Colorless oil. $^1$H NMR (CDCl$_3$) δ 0.68–0.76 (m, 2H), 1.14–1.18 (m, 1H), 1.27 (s, 6H), 1.28 (s, 6H), 2.40 (td, $J = 7.2$, 3.2 Hz, 1H), 7.21 (ddd, $J = 7.2$, 5.6, 1.2 Hz, 1H), 7.39 (d, $J = 7.2$ Hz, 1H), 7.74 (td, $J = 7.2$, 1.2 Hz, 1H), 8.40 (d, $J = 5.6$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 9.0 (br), 18.86, 21.11, 25.76 (2C), 25.97 (2C), 80.24 (2C), 121.42, 122.26, 139.56, 143.71, 164.04. $^{11}$B NMR (CDCl$_3$) δ 16.2. IR (ATR): 2975, 1519, 1481, 1255, 1144, 1082, 1030, 867, 746 cm$^{-1}$. HRMS–APCI (m/z): [M+H]$^+$ Calcd for C$_{14}$H$_{21}$O$_2$N$^{10}$B, 245.16962; found, 245.17007.

2-[(2,3-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyridine (3a')

Isolated by Kugelrohr distillation (1 mmHg, 125 °C, 44.4 mg, 60% yield, contaminated with traces of impurities). White solids. M.p. 97.7–104.4 °C $^1$H NMR (CDCl$_3$) δ 0.81 (d, $J = 6.8$ Hz, 2H), 1.12 (s, 12H), 1.14 (s, 12H), 2.61 (t, $J = 6.8$ Hz, 1H), 7.23 (ddd, $J = 8.0$, 6.0, 1.6 Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.75 (td, $J = 8.0$, 1.6 Hz, 1H), 8.29 (d, $J = 6.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 14.7 (br, 2C), 25.16, 25.45 (4C), 25.56 (4C), 80.84 (4C), 121.20, 123.06, 139.55, 141.97, 163.91. $^{11}$B NMR (CDCl$_3$) δ 21.6. IR (ATR): 2971, 1622, 1485, 1406, 1145, 1077, 968, 791, 782 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{20}$H$_{32}$O$_2$N$^{10}$B$_2$, 370.25846; found, 370.25868.

5-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyridine (3b)
Isolated by Kugelrohr distillation (1 mmHg, 90 °C, 77.8 mg, 150% yield). Colorless oil.

$^1$H NMR (CDCl$_3$) δ 0.57–0.61 (m, 1H), 0.64 (td, $J = 9.6, 6.4$, 1H), 1.09–1.14 (m, 1H), 1.28 (s, 6H), 1.30 (s, 6H), 2.32 (s, 3H), 2.34–2.38 (m, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 8.19 (s, 1H). $^{13}$C NMR (CDCl$_3$) δ 9.2 (br), 18.09, 19.00, 20.44, 25.87 (2C), 26.12 (2C), 79.92 (2C), 121.65, 131.47, 140.89, 142.89, 161.39. $^{11}$B NMR (CDCl$_3$) δ 14.4. IR (ATR): 2976, 1627, 1501, 1145, 1082, 1041, 980, 728 cm$^{-1}$. HRMS–APCI (m/z): [M+H]$^+$ Calcd for C$_{15}$H$_{23}$O$_2$N$_{10}$B, 259.18527; found, 259.18576.

5-(Methoxymethoxy)-2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyridine (3c)

Isolated by Kugelrohr distillation (1 mmHg, 100 °C, 50.0 mg, 82% yield). Colorless oil.

$^1$H NMR (CDCl$_3$) δ 0.60–0.66 (m, 1H), 0.74–0.78 (m, 1H), 1.08–1.13 (m, 1H), 1.23 (s, 6H), 1.24 (s, 6H), 2.35 (td, $J = 8.0, 4.0$ Hz, 1H), 3.45 (s, 3H), 5.13 (d, $J = 6.8$ Hz, 1H), 5.16 (d, $J = 6.8$ Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 7.40 (dd, $J = 8.4, 2.4$ Hz, 1H), 8.23 (d, $J = 2.4$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 7.6 (br), 16.44, 20.77, 25.55 (2C), 25.60 (2C), 56.06, 80.83 (2C), 94.95, 122.40, 126.98, 133.90, 152.21, 156.50. $^{11}$B NMR (CDCl$_3$) δ 19.9. IR (ATR): 2999, 1607, 1404, 1327, 1300, 1134, 1120, 1086, 1018, 847 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{16}$H$_{25}$O$_4$N$_{10}$B, 305.19075; found, 305.19094.

2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-5-(trifluoromethyl)pyridine (3d)

Isolated by Kugelrohr distillation (1 mmHg, 85 °C, 98.9 mg, 158% yield). White solids. M.p. 76.0–77.0 °C. $^1$H NMR (CDCl$_3$) δ 0.64 (td, $J = 9.6, 8.0$ Hz, 1H), 1.16 (s, 6H), 1.17 (s,
$^1$H NMR (CDCl$_3$) $\delta$ 0.65 (td, $J = 9.6, 8.0$ Hz, 1H), 0.88 (s, 6H), 1.03 (s, 6H), 1.33 (td, $J = 8.0, 4.0$ Hz, 1H), 1.58–1.63 (m, 1H), 2.24–2.31 (m, 1H), 3.80 (s, 3H), 7.18–7.29 (m, 2H), 7.38–7.43 (m, 1H), 7.61–7.63 (m, 1H).

$^{13}$C NMR (CDCl$_3$) $\delta$ 2.2 (br), 9.71, 13.28, 24.22 (2C), 24.77 (2C), 29.58, 83.00 (2C), 108.35, 119.16, 121.44, 121.74, 136.05, 142.08, 154.73. $^{11}$B NMR (CDCl$_3$) $\delta$ 31.1. IR (ATR): 2976, 1617, 1571, 1411, 1328, 1141, 1223, 857, 742 cm$^{-1}$. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{17}$H$_{23}$BN$_2$O$_2$, 298.18526; found, 298.18498.

2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]benzo[d]oxazole (3f)

Isolated by Kugelrohr distillation (1 mmHg, 95 °C, 49.6 mg, 87% yield, contaminated with arylboronates (10%)). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 0.69 (td, $J = 9.6, 8.0$ Hz, 1H), 1.02 (s, 6H), 1.10 (s, 6H), 1.33–1.40 (m, 1H), 1.57 (ddd, $J = 8.0, 5.2, 4.6$ Hz, 1H), 2.47 (ddd, $J = 9.6, 7.6, 5.2$ Hz, 1H), 7.23–7.29 (m, 2H), 7.38–7.43 (m, 1H), 7.61–7.63 (m, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 3.5 (br), 10.71, 14.21, 24.36 (2C), 24.77 (2C), 83.39 (2C), 109.97, 119.21, 123.89, 124.07, 141.46, 150.52, 167.05. $^{11}$B NMR (CDCl$_3$) $\delta$ 31.2. IR (ATR): 2978, 1617, 1571, 1411, 1328, 1141, 1223, 857, 742 cm$^{-1}$. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{16}$H$_{21}$O$_3$N$_{10}$B, 285.16453; found, 285.16530.
2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)benzo[d]thiazole (3g)

Isolated by Kugelrohr distillation (1 mmHg, 120 °C, 78.2 mg, 130% yield). Colorless oil. 

$^{1}$H NMR (CDCl$_3$) $\delta$ 0.71 (td, $J = 10.0, 8.0$ Hz, 1H), 1.00 (s, 6H), 1.10 (s, 6H), 1.39 (ddd, $J = 10.0, 8.0, 4.4$ Hz, 1H), 1.54–1.59 (m, 1H), 2.65 (ddd, $J = 10.0, 7.6, 5.2$ Hz, 1H), 7.31 (td, $J = 7.6, 1.2$ Hz, 1H), 7.39 (td, $J = 7.6, 1.2$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.90 (d, $J = 7.6$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 5.1 (br), 12.43, 19.86, 24.50 (2C), 24.85 (2C), 83.31 (2C), 121.22, 122.30, 124.29, 125.65, 135.18, 153.05, 171.94. $^{11}$B NMR (CDCl$_3$) $\delta$ 31.2.

IR (ATR): 2977, 1522, 1408, 1326, 1224, 1142, 853, 757 cm$^{-1}$. HRMS–APCI (m/z): [M+H]$^+$ Calcd for C$_{16}$H$_{21}$O$_2$N$_1$B, 301.14169; found, 301.14163.

1-Methyl-2-[2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-1H-benzo[d]imidazole (3h)

Isolated by Kugelrohr distillation (1 mmHg, 150 °C, 76.8 mg, 123% yield, contaminated with regioisomers (8%)). White solids. M.p. 125.1–126.6 °C. $^{1}$H NMR (CDCl$_3$) $\delta$ 0.42 (t, $J = 7.6$ Hz, 1H), 0.87 (s, 6H), 1.03 (s, 6H), 1.27–1.34 (m, 4H), 1.95–1.99 (m, 1H), 3.77 (s, 3H), 7.17–7.23 (m, 3H), 7.63–7.68 (m, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 20.23, 23.9 (br), 24.58 (2C), 24.65 (2C), 25.10, 29.61, 33.72, 82.83 (2C), 108.50, 119.05, 121.28, 121.65, 136.28, 142.13, 157.66. $^{11}$B NMR (CDCl$_3$) $\delta$ 30.6 (br). IR (ATR): 2980, 2942, 1616, 1469, 1372, 1315, 1141, 853, 757 cm$^{-1}$. HRMS–EI (m/z): [M$^+$] Calcd for C$_{18}$H$_{25}$O$_2$N$_2$$^{11}$B, 312.20081; found, 312.20080.

2-[2,2-Dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-1-methyl-1H-benzo[d]imidazole (3i)

58
Isolated by Kugelrohr distillation (1 mmHg, 155 °C) followed by washing with a small amount of hexane (40.1 mg, 61% yield). White solids. **M.p.** 139.9–141.8 °C. **1H NMR** (CDCl₃) δ 0.56 (d, J = 10.0 Hz, 1H), 1.14 (s, 3H), 1.27 (s, 6H), 1.30 (s, 6H), 1.36 (s, 3H), 2.08 (d, J = 10.0 Hz, 1H), 3.74 (s, 3H), 7.17–7.24 (m, 3H), 7.62 (d, J = 8.4 Hz, 1H). **13C NMR** (CDCl₃) δ 15.3 (br), 18.69, 24.76, 24.86 (2C), 25.18 (2C), 26.36, 29.02, 29.73, 82.66 (2C), 108.50, 118.90, 121.23, 121.52, 136.11, 142.12, 154.19. **11B NMR** (CDCl₃) δ 30.1. **IR** (ATR): 2975, 1616, 1523, 1397, 1317, 1143, 862, 741 cm⁻¹. **HRMS–EI** (m/z): [M]+ Calcd for C₁₉H₂₇O₂N₂B, 326.21656; found, 326.21612.

1-Methyl-2-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[4.1.0]heptan-7-yl]-1H-benzo[d]imidazole (3j)

Isolated by Kugelrohr distillation (1 mmHg, 200 °C) followed by recrystallization from hexane. (56.3 mg, 80% yield). White solids. **M.p.** 161.9–163.0 °C. **1H NMR** (CDCl₃) δ 0.80 (s, 6H), 0.99 (s, 6H), 1.22–1.47 (m, 4H), 1.81–1.90 (m, 1H), 1.94 (d, J = 5.6 Hz, 1H), 2.04–2.10 (m, 2H), 2.14–2.19 (m, 2H), 3.76 (s, 3H), 7.16–7.22 (m, 3H), 7.66 (dd, J = 8.8, 3.2 Hz, 1H). **13C NMR** (CDCl₃) δ 20.69, 21.59, 22.56, 22.65, 24.20 (2C), 24.79 (2C), 25.80, 25.96, 29.74, 82.78 (2C), 108.28, 119.06, 121.37, 121.61, 135.97, 142.09, 155.37. A signal for the carbon directly attached to the boron atom was not observed. **11B NMR** (CDCl₃) δ 30.8. **IR** (ATR): 2926, 1615, 1466, 1394, 1318, 1141, 856, 741 cm⁻¹. **HRMS–EI** (m/z): [M]+ Calcd for C₂₁H₂₉O₂N₂B, 352.23221; found, 352.23151.

(E)-Cyclopropyl[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]methanone O-Methyl Oxime (3k)
Isolated by Kugelrohr distillation (1 mmHg, 90 °C, 35.0 mg, 66% yield). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta 0.20\) (td, \(J = 9.2, 7.2\) Hz, 1H), 0.74–0.87 (m, 4H), 1.04–1.11 (m, 1H), 1.18–1.31 (m, 2H), 1.20 (s, 6H), 1.24 (s, 6H), 2.27–2.36 (m, 1H), 3.86 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta 1.1\) (br), 5.50, 5.67, 6.81, 9.90, 15.07, 24.55 (2C), 25.06 (2C), 61.24, 83.04 (2C), 158.85. \(^{11}\)B NMR (CDCl\(_3\)) \(\delta 31.3\). IR (ATR): 2979, 1614, 1409, 1324, 1221, 1144, 1055, 857, 736 cm\(^{-1}\). HRMS–ESI (m/z): [M+H]\(^+\) Calcd for C\(_{14}\)H\(_{25}\)O\(_3\)N\(^{10}\)B, 265.19583; found, 265.19586.

\((E)-1-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pentan-1-one\)

\(O\)-Methyl Oxime (3l)

\begin{center}
\begin{tikzpicture}
\draw (0,0) -- (1,1) -- (0.5,1.5) -- cycle;
\draw (0,0) -- (1,0);
\draw (0.5,1.5) -- (1,1);
\draw (0,0) -- (0.5,1.5);
\node at (0.5,1.5) {Bu};
\node at (0,0) {MeO};
\node at (1,1) {N};
\node at (1.5,0) {Bpin};
\node at (0.5,-0.5) {3l};
\end{tikzpicture}
\end{center}

Isolated by Kugelrohr distillation (1 mmHg, 100 °C, 36.0 mg, 64% yield). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta 0.25\) (td, \(J = 9.2, 7.6\) Hz, 1H), 0.86–0.93 (m, 1H), 0.89 (t, \(J = 6.8\) Hz, 3H), 1.16–1.23 (m, 1H), 1.17 (s, 6H), 1.20 (s, 6H), 1.36 (sext, \(J = 7.2\) Hz, 2H), 1.48–1.56 (m, 2H), 1.73–1.79 (m, 1H), 2.18–2.26 (m, 1H), 2.40–2.47 (m, 1H), 3.80 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta 1.0\) (br), 8.01, 13.88, 19.87, 22.98, 24.64 (2C), 25.02 (2C), 28.00, 29.18, 61.04, 83.05 (2C), 159.92. \(^{11}\)B NMR (CDCl\(_3\)) \(\delta 31.6\). IR (ATR): 2978, 2959, 2933, 1627, 1409, 1323, 1222, 1144, 1053, 858 cm\(^{-1}\). HRMS–ESI (m/z): [M+H]\(^+\) Calcd for C\(_{15}\)H\(_{29}\)O\(_3\)N\(^{10}\)B, 281.22713; found, 281.22720.

\((E)-2,4,6-Trimethyl-N-[1-{2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]ethylidene}aniline (3m)

\begin{center}
\begin{tikzpicture}
\draw (0,0) -- (1,1) -- (0.5,1.5) -- cycle;
\draw (0,0) -- (1,0);
\draw (0.5,1.5) -- (1,1);
\draw (0,0) -- (0.5,1.5);
\node at (0.5,1.5) {Mes};
\node at (0,0) {Me};
\node at (1,1) {N};
\node at (1.5,0) {Bpin};
\node at (0.5,-0.5) {3m};
\end{tikzpicture}
\end{center}

Isolated by Kugelrohr distillation (1 mmHg, 100 °C) followed by recrystallization from hexane. (64.1 mg, 98% yield). White solids. M.p. 152.5–154.2 °C. \(^1\)H NMR (CDCl\(_3\)) \(\delta 0.71\) (td, \(J = 9.2, 6.4\) Hz, 1H), 0.83 (s, 6H), 0.92–0.96 (m, 1H), 0.97 (s, 6H), 1.23 (td, \(J = 8.6, 2.8\) Hz, 1H), 1.91 (s, 3H), 2.04 (s, 3H), 2.10–2.16 (m, 1H), 2.19 (s, 3H), 2.26 (s, 3H), 6.80 (s, 1H), 6.85 (s, 1H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta 10.9\) (br), 18.12, 18.33, 19.17, 20.85, 21.41, 25.14 (2C), 25.28, 25.54 (2C), 79.57 (2C), 128.71, 128.75, 131.54, 132.52, 135.94, 137.34, 188.00. \(^{11}\)B NMR (CDCl\(_3\)) \(\delta 14.5\). IR (ATR): 2964, 1632, 1381, 1359, 1293, 1165, 1084, 877, 774 cm\(^{-1}\). HRMS–APCI (m/z): [M+H]\(^+\) Calcd for C\(_{20}\)H\(_{31}\)O\(_2\)N\(^{10}\)B, 327.24787; found, 327.24795.
$N,N$-Diisopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropanecarboxamide (3n)

Isolated by Kugelrohr distillation (1 mmHg, 85 °C, 44.3 mg, 75% yield, contaminated with traces of impurities). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 0.56 (td, $J = 9.6, 6.8$ Hz, 1H), 0.84–0.87 (m, 1H), 1.02–1.07 (m, 1H), 1.23 (s, 12H), 1.28 (d, $J = 6.4$ Hz, 6H), 1.33–1.37 (m, 6H), 1.95 (td, $J = 6.8, 2.8$ Hz, 1H), 3.71 (septet, $J = 6.8$ Hz, 1H), 4.32 (septet, $J = 6.8$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 8.4 (br), 14.72, 19.16, 20.11, 20.49, 20.79 (2C), 25.12 (2C), 25.19 (2C), 47.42, 49.92, 80.03 (2C), 177.54. $^{11}$B NMR (CDCl$_3$) $\delta$ 16.1. IR (ATR): 2971, 1595, 1371, 1312, 1143, 1110, 751, 730 cm$^{-1}$. HRMS–APCI (m/z): [M+H]$^+$ Calcd for C$_{16}$H$_{31}$O$_3$N$_{10}$B, 295.24728; found, 295.24364.

2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl]pyridine (5a)

Isolated by Kugelrohr distillation (1 mmHg, 85 °C, 43.8 mg, 85% yield, contaminated with traces of impurities). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.21 (s, 6H), 1.24 (s, 6H), 1.85–2.00 (m, 2H), 2.01–2.14 (m, 2H), 2.60–2.68 (m, 1H), 3.75–3.81 (m, 1H), 7.31–7.37 (m, 2H), 7.85 (td, $J = 8.0, 1.2$ Hz, 1H), 8.64 (d, $J = 5.6$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 19.11, 25.74 (2C), 25.12 (2C), 25.74 (2C), 26.04 (2C), 28.03, 42.05, 79.98 (2C), 122.30, 122.70, 140.10, 143.18, 166.54. A signal for the carbon directly attached to the boron atom was not observed. $^{11}$B NMR (CDCl$_3$) $\delta$ 16.9. IR (ATR): 2973, 2931, 1617, 1476, 1379, 1134, 1080, 772 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{16}$H$_{23}$O$_2$N$_{10}$B, 259.18527; found, 259.18549.

1-Methyl-2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl]-1H-benzo[d]imidazole (5b)

61
Isolated by Kugelrohr distillation (1 mmHg, 150 °C, 66.8 mg, 99% yield, contaminated with arylboronates (6%).) White solids. M.p. 121.8–122.4 °C. $^1$H NMR (CDCl$_3$) δ 0.86 (s, 6H), 1.00 (s, 6H), 2.16–2.29 (m, 2H), 2.42–2.52 (m, 2H), 2.90 (quint, $J = 8.8$ Hz, 1H), 3.63 (s, 3H), 3.93 (q, $J = 8.8$ Hz, 1H), 7.18–7.24 (m, 3H), 7.70–7.73 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ 20.23, 23.7 (br), 24.58 (2C), 24.64 (2C), 25.10, 29.61, 33.72, 82.83 (2C), 108.50, 119.05, 121.65, 121.94, 136.28, 142.13, 157.66. $^{11}$B NMR (CDCl$_3$) δ 33.1. IR (ATR): 2979, 2943, 1616, 1470, 1372, 1314, 1140, 852, 750 cm$^{-1}$. HRMS–EI (m/z): [M]$^+$ Calcd for C$_{18}$H$_{25}$O$_2$N$_2$B, 312.20028; found, 312.20028.

2-[(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl]benzo[d]oxazole (5c)

Isolated by Kugelrohr distillation (1 mmHg, 120 °C, 56.2 mg, 94% yield, contaminated with arylboronates (20%)). Colorless oil. $^1$H NMR (CDCl$_3$) δ 0.98 (s, 6H), 1.05 (s, 6H), 2.21–2.30 (m, 2H), 2.49–2.58 (m, 2H), 2.69–2.76 (m, 1H), 3.96 (td, $J = 9.2$, 7.6 Hz, 1H), 7.26–7.30 (m, 2H), 7.45–7.48 (m, 1H), 7.65–7.68 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ 20.49, 23.0 (br), 24.56 (2C), 24.65 (2C), 25.47, 34.54, 83.18 (2C), 110.18, 119.44, 123.80, 124.13, 141.45, 150.74, 169.51. $^{11}$B NMR (CDCl$_3$) δ 32.6. IR (ATR): 2978, 1614, 1576, 1456, 1370, 1319, 1141, 853, 742 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{17}$H$_{23}$O$_3$N$_2$B, 299.18018; found, 299.18110.

Pottasium Trifluoro[2-(1-methyl-1H-benzo[d]imidazol-2-yl)cyclopropyl]borate (6)

Isolated by recrystallization from acetone. (25.6 mg, 92% yield). White solids. M.p. >300 °C. $^1$H NMR (DMSO-$d_6$) δ −0.05 (br-m, 1H), 0.70 (br-t, $J = 8.0$ Hz, 1H), 0.97 (br-m, 1H), 1.69 (br-m, 1H), 3.75 (s, 3H), 7.02–7.10 (m, 2H), 7.34 (d, $J = 7.2$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H). $^{13}$C NMR (DMSO-$d_6$) δ 6.57, 11.09, 29.35, 108.75, 117.93, 120.01, 120.23, 136.17, 142.40, 157.84. A signal for the carbon directly attached to the boron atom was not observed. $^{11}$B NMR (DMSO-$d_6$) δ 2.4. IR (ATR): 2976, 1514, 1472, 1320, 1284, 1008, 918,
738 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{11}$H$_{12}$N$_2$BF$_3$K, 278.07135; found, 278.07198.

[2-(1-Methyl-1$H$-benzo[d]imidazol-2-yl)cyclopropyl]methanol (7)

![Image of 7]

Isolated by silica gel chromatography (CHCl$_3$/MeOH 90:10, 13.1 mg, 65% yield). White solids. **M.p.** 118.8–119.4 °C. $^1$H NMR (CDCl$_3$) $\delta$ 0.87 (q, $J$ = 5.2 Hz, 1H), 1.32 (td, $J$ = 8.4, 5.2 Hz, 1H), 1.78–1.87 (m, 1H), 2.09 (td, $J$ = 8.4, 6.4 Hz, 1H), 3.32 (dd, $J$ = 12.0, 9.6 Hz, 1H), 3.85 (s, 3H), 4.13 (dd, $J$ = 12.0, 4.4 Hz, 1H), 6.07 (br, 1H), 7.22–7.32 (m, 3H), 7.64 (d, $J$ = 8.4 Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 10.72, 12.42, 20.78, 29.87, 62.55, 108.87, 119.11, 122.15, 123.37, 135.53, 141.27, 153.51. IR (ATR): 3190, 2845, 1617, 1520, 1456, 1318, 1042, 746 cm$^{-1}$.

HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{12}$H$_{15}$ON$_2$, 203.11789; found, 203.11830.

1-Methyl-2-(2-phenylcyclopropyl)-1$H$-benzo[d]imidazole (8a)

![Image of 8a]

Isolated by silica gel chromatography (CHCl$_3$/MeOH 97:3, 21.1 mg, 85% yield). White solids. **M.p.** 101.9–102.3 °C. $^1$H NMR (CDCl$_3$) $\delta$ 1.71 (td, $J$ = 8.4, 6.4 Hz, 1H), 2.16 (q, $J$ = 6.4 Hz, 1H), 2.53 (td, $J$ = 8.4, 6.4 Hz, 1H), 2.62 (td, $J$ = 8.4, 6.4 Hz, 1H), 3.49 (s, 3H), 6.95–7.03 (m, 5H), 7.09–7.12 (m, 1H), 7.14–7.21 (m, 2H), 7.68–7.72 (m, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 11.23, 18.45, 23.95, 29.37, 108.63, 119.25, 121.54, 121.91, 126.07, 126.81 (2C), 127.95 (2C), 135.86, 137.32, 142.20, 151.88. IR (ATR): 3015, 2927, 1615, 1514, 1457, 1440, 1405, 1314, 1280, 1233, 1079 cm$^{-1}$. HRMS–APCI (m/z): [M+H]$^+$ Calcd for C$_{17}$H$_{15}$N$_2$, 249.13863; found, 249.13866.

2-[2-(4-Methoxyphenyl)cyclopropyl]-1-methyl-1$H$-benzo[d]imidazole (8b)

![Image of 8b]
Isolated by silica gel chromatography (CHCl₃/MeOH 95:5, 26.1 mg, 94% yield). White solids. **M.p.** 126.7–127.6 °C. **¹H NMR** (CDCl₃) δ 1.66 (td, J = 8.4, 6.0 Hz, 1H), 2.10 (q, J = 6.0 Hz, 1H), 2.47 (td, J = 8.4, 6.0 Hz, 1H), 2.57 (q, J = 8.4 Hz, 1H), 3.52 (s, 3H), 3.63 (s, 3H), 6.56 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.10–7.21 (m, 3H), 7.68–7.71 (m, 1H). **¹³C NMR** (CDCl₃) δ 10.94, 18.03, 23.32, 29.38, 55.01, 108.66, 113.40 (2C), 119.17, 121.49, 121.85, 127.86 (2C), 129.15, 135.87, 142.17, 152.10, 157.86. **IR** (ATR): 2954, 1608, 1510, 1249, 1035, 832, 734 cm⁻¹. **HRMS–ESI** (m/z): [M+H]⁺ Calcd for C₁₈H₁₉O₂N₂, 279.14919; found, 279.14977.

**Methyl 4-[2-(1-Methyl-1H-benzo[d]imidazol-2-yl)cyclopropyl]benzoate (8c)**

Isolated by silica gel chromatography (CHCl₃/MeOH 95:5, 27.3 mg, 89% yield). White solids. **M.p.** 175.1–176.5 °C. **¹H NMR** (CDCl₃) δ 1.77 (td, J = 8.4, 6.0 Hz, 1H), 2.24 (q, J = 6.0 Hz, 1H), 2.58–2.69 (m, 2H), 3.47 (s, 3H), 3.79 (s, 3H), 7.04 (d, J = 8.0 Hz, 2H), 7.07–7.11 (m, 1H), 7.14–7.21 (m, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.66–7.71 (m, 1H). **¹³C NMR** (CDCl₃) δ 11.87, 19.16, 24.06, 29.31, 51.86, 108.68, 119.26, 121.70, 122.11, 126.73 (2C), 127.87, 129.17 (2C), 135.77, 142.00, 143.10, 151.11, 166.84. **IR** (ATR): 3053, 2950, 1716, 1610, 1523, 1434, 1277, 1183, 1103, 753 cm⁻¹. **HRMS–ESI** (m/z): [M+H]⁺ Calcd for C₁₉H₁₉O₂N₂, 307.14410; found, 307.14445.

**1-Methyl-2-(2-(2-methylprop-1-en-1-yl)cyclopropyl)-1H-benzo[d]imidazole (8d)**

Isolated by silica gel chromatography (CHCl₃/EtOAc 80:20) followed by Kugelrohr distillation (1 mmHg, 125–135 °C, 13.7 mg, 61% yield, contaminated with traces of impurities). White solids. **M.p.** 81.2–82.5 °C. **¹H NMR** (CDCl₃) δ 1.46 (td, J = 8.0, 4.8 Hz, 1H), 1.50 (d, J = 1.2 Hz, 3H), 1.58–1.66 (m, 1H), 1.75 (d, J = 1.2 Hz, 3H), 2.11–2.20 (m, 1H), 2.28 (td, J = 8.0, 6.0 Hz, 1H), 3.75 (s, 3H), 4.46 (dt, J = 5.2, 1.6 Hz, 1H), 7.23–7.29 (m, 3H), 7.71–7.75 (m, 1H). **¹³C NMR** (CDCl₃) δ 12.06, 15.27, 18.24, 18.87, 25.62, 29.48, 108.66,
119.22, 121.57, 121.83, 121.93, 133.61, 136.11, 142.35, 153.71. **IR** (ATR): 3043, 3018, 2997, 2930, 1675, 1614, 1510, 1444, 1410, 1281, 1235, 1008, 741 cm\(^{-1}\). **HRMS–APCI** (m/z): [M+H]\(^+\) Calcd for C\(_{13}\)H\(_{19}\)N\(_2\), 227.15428; found, 227.15444.

[2-(1-Methyl-1\(H\)-benzo[d]imidazol-2-yl)cyclobutyl]methanol (9)

Isolated by silica gel chromatography (CHCl\(_3/\)MeOH 90:10, 10.3 mg, 48% yield). White solids. **M.p.** 144.4–144.6 °C. **\(^1\)H NMR** (CDCl\(_3\)) \(\delta\) 1.79–1.86 (m, 1H), 2.30 (quint, \(J = 8.8\) Hz, 1H), 2.44–2.51 (m, 2H), 2.96–3.03 (m, 1H), 3.68 (s, 3H), 3.68–3.72 (m, 1H), 3.94–4.05 (m, 2H), 6.86 (br, 1H), 7.23–7.29 (m, 3H), 7.69–7.71 (m, 1H). **\(^{13}\)C NMR** (CDCl\(_3\)) \(\delta\) 21.07, 26.44, 29.88, 34.33, 41.40, 62.95, 108.90, 119.05, 122.09, 122.39, 135.38, 141.26, 155.83. **IR** (ATR): 3233, 2934, 2862, 1616, 1509, 1472, 1444, 1402, 1283, 1058, 729 cm\(^{-1}\). **HRMS–ESI** (m/z): [M+H]\(^+\) Calcd for C\(_{13}\)H\(_{17}\)ON\(_2\), 217.13354; found, 217.13379.

**X-ray Crystallographic Analysis**

Data were collected on a Rigaku Mercury CCD diffractometer with graphite monochromated Mo-K\(\alpha\) radiation (\(\lambda = 0.71075\) Å) at 150 K, and processed using the CrystalClear software.\(^{35}\) Structures were solved by a direct method using SIR2004,\(^{36}\) and refined by full-matrix least-square method using SHELXL-97.\(^{37}\) Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located on the calculated positions and refined using a riding model. All calculations were performed using the CrystalStructure software package.\(^{38}\) The supplementary crystallographic data for this paper can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**References**


(12) Silica-SMAP and Silica-TRIP can be purchased from Wako Pure Chemical Industries, Ltd. For their applications, see refs 10b,c.


(37) Sheldrick, G. M. SHELX97, University of Göttingen, Germany, 1997.

Chapter 2

Site-selective and Stereoselective C(sp³)–H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Ir Catalyst

Site-selective and stereoselective C(sp³)–H borylation of alkyl side chains of 1,3-azoles with bis(pinacolato)diboron was effectively catalyzed by a silica-supported monophosphine-Ir catalyst. The borylation occurred under relatively mild conditions (2 mol% Ir, 50–90 °C), affording the corresponding primary and secondary alkylboronates. This system was applicable to a variety of 1,3-(benzo)azoles such as thiazoles, oxazoles, and imidazoles.
Introduction

1,3-Azoles are common structures in many biologically active natural compounds, pharmaceuticals and organic functional materials, and many of these molecules have an alkyl substituent at the 2-position (Figure 1).\(^1\) Therefore, functionalization of the alkyl side chain of 1,3-azoles is of great importance for construction of complex molecules containing 1,3-azole scaffolds.\(^2\) Among the methods for functionalization of alkyl groups, C(sp\(^3\))–H borylation is attractive because alkylboron compounds are versatile synthetic intermediates with broad functional group compatibility, and air- and moisture stability.\(^3,4\) Despite recent significant progress in this area, the site-selective borylation of unactivated C(sp\(^3\))–H bonds over potentially more reactive C–H bonds such as C(sp\(^2\))–H bonds remains challenging.\(^5-10\)

Moreover, the stereoselective borylation of C(sp\(^3\))–H bonds is underdeveloped.\(^5e,5g,5h,7,10a\)

Figure 1. Representative Compounds Containing the 2-Alkyl-1,3-azole Scaffold.

Recently, the Sawamura group reported the heteroatom-directed borylation of C(sp\(^3\))–H bonds bearing N-heteroarenes or carbonyl-based functional groups catalyzed by Rh- or Ir systems based on solid-supported monophosphines with mono-P-ligating features (Figure 2).\(^10\) This strategy allowed site-selective borylation of the N-adjacent\(^{10b}\) or unactivated\(^{7b,10a,c,d}\) C(sp\(^3\))–H bonds located \(\gamma\) to N or O atoms on the directing groups. The regioselectivity was due to the proximity effect by the heteroatom-to-metal coordination. In fact, cyclic and acyclic alkyl substituents at the 2-position of pyridines underwent the C(sp\(^3\))–H borylation with excellent site- and stereoselectivities.\(^{10a}\) Chapter 1 of this thesis described that 1,3-azoles...
also worked as suitable directing groups for the C(sp³)–H borylation of small-ring carbocycles such as cyclopropanes and cyclobutanes. However, its applicability for linear alkyl groups and normal-sized (five-to-seven membered) carbocycles has not been explored.

Figure 2. Solid-Supported Monophosphine.

This chapter describes the heteroatom-directed C(sp³)–H borylation of alkyl side chains of 1,3-azoles with a silica-supported monophosphine-Ir catalyst. Owing to the proximity effect by N-to-Ir coordination, the borylation occurred under relatively mild reaction conditions with high site- and stereoselectivities. This catalytic system was applicable for the reaction of primary and secondary C(sp³)–H bonds of linear and cyclic alkyl substituents in 1,3-azoles, including thiazoles, oxazoles, and imidazoles.

Results and Discussion

Optimization of reaction conditions. Initially, the borylation reaction between 2-ethylbenzothiazole (1a, 0.6 mmol) and bis(pinacolato)diboron (B₂pin₂) (2, 0.2 mmol) in THF at 60 °C for 15 h in the presence of various Ir catalysts (2 mol% Ir), which were prepared in situ from [Ir(OMe)(cod)]₂ and different ligands. The results are summarized in Table 1.

In contrast to the C(sp³)–H borylation of 2-alkylpyridines reported previously, for which all solid-supported monophosphines shown in Figure 1 were effective ligands (Silica-SMAP, Silica-TRIP, Silica-TPP and PS-TPP), the borylation of 1a was
specifically promoted by commercially available Silica-SMAP, affording the terminal C(sp³)–H borylation product 3a and the geminal bisborylation product 4a in 82% and 32% NMR yields, respectively (Table 1, entry 1). The reactivity of the alkyl side chain in 1a seems to be lower than that in the pyridine analogue. Indeed, 2-ethylpyridine underwent efficient C(sp³)–H borylation with the Silica-SMAP-Ir system at 25 °C, while 1a was intact under identical conditions.

The ligand specificity of Silica-SMAP in the present borylation reaction may suggest a requirement for the high electron density of the metal and/or sparse nature of the catalytic environment provided by the compact ligand. The total borylation yields over 100% based on B₂pin₂ (2) indicated that pinacolborane (HBpin), which was a byproduct of the reaction with B₂pin₂, also served as a borylating reagent, although it was less reactive than 2. The C(sp²)–H bonds of the benzothiazole ring and the C(sp³)–H bonds at the position α to the azole group were intact. Table 1 also shows the inefficiency of homogeneous catalytic systems. The use of monophosphines such as Ph-SMAP (Figure 2) and PPh₃ did not promote the C(sp³)–H borylation (entries 5 and 6). Bipyridine-based ligands such as Dtbpy and Me₄Phen (Figure 2) resulted in only aromatic C–H borylation with lower efficiencies (<4% yields of arylboronates, entries 7 and 8). No reaction occurred without an exogenous ligand (entry 9). A larger-scale reaction (5 mmol for 2) at 0.5 mol% Ir loading proceeded efficiently at 90 °C to give 3a in 54% isolated yield (Scheme 1). The geminal diborylation product 4a could be obtained as a major product in 89% isolated yield by the reaction with 2 equiv of 2 (2 mol% Ir, 60 °C) (Scheme 2).

Table 1. Ligand Effects in Ir-catalyzed Borylation of 2-Ethylbenzothiazole (1a) with Bis(pinacolato)diboron (2)a

<table>
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<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield of 3a (%)b</th>
<th>Yield of 4a (%)b</th>
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<td>1</td>
<td>Silica-SMAP</td>
<td>82c (75)d</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Silica-TRIP</td>
<td>0</td>
<td>0</td>
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</tbody>
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a. The experiments were conducted at 60 °C with 0.5 mol% Ir loading.
b. Based on NMR yields.
c. Calculated from the NMR spectrum.
d. Include the yield of the byproduct HBpin.

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<th>Ligand</th>
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<th>Y</th>
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<td>0</td>
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<tr>
<td>4</td>
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</table>

$^a$ Conditions: 1a (0.6 mmol), 2 (0.2 mmol), [Ir(OMe)(cod)]$_2$ (2 mol% Ir), ligand (2 mol%), THF (1 mL), 60 °C, 15 h. $^b$ $^1$H NMR yield based on 2. Isolated yields shown in parentheses. $^c$ The C=N reduction product of 1a (4%) was formed. $^d$ The isolated product 3a was contaminated with 4a (<1%) and traces of impurities. $^e$ Arylboronates were formed in entries 7 and 8 (4% and 3%, respectively).

**Figure 3.** Homogeneous Ligands Used in Table 1.

![Homogeneous Ligands](image)

**Scheme 1.** Gram-scale borylation of 1a.

![Scheme 1](image)

**Scheme 2.** Geminal diborylation of 1a.

![Scheme 2](image)
Scope of 1,3-azoles. The Silica-SMAP-Ir system was applicable to various 1,3-(benzo)azoles 1, including thiazoles, oxazoles, and imidazoles (Table 2). Some of the borylation products 3 obtained in this manner were converted into the corresponding alcohols 5 through subsequent oxidation for facile product isolation (Table 3). In some cases, significant amounts of C=N reduction products of starting materials 1 also formed during the borylation reactions. The desired products 3 or 5 could be isolated by bulb-to-bulb distillation or silica gel column chromatography. The results are summarized in Tables 2 and 3. The reaction with 2-ethylbenzoxazole (1b) proceeded smoothly at 60 °C to give the monoborylation product 3b and the geminal diborylation product 4b in 78% and 26% yields, respectively, with the formation of small amounts of C(sp²)–H borylation products (5%) (Table 2, entry 1). 2-Ethylbenzimidazole (1c) was borylated at 50 ºC, affording the monoborylation product 3c and the diborylation product 4c in 38% and 19% yields, respectively (entry 2). However, the formation of a significant amount of a C=N reduction product of 3c (structure not determined, ca. 20%) was observed in the ¹H NMR spectrum of the crude reaction mixture. The use of cyclooctene as an additive effectively suppressed the C=N reduction of 3c, resulting in an increase in yields of 3c and 4c to 60% and 31%, respectively (entry 3). Cyclooctene should be a scavenger of HBpin. A significant amount of hydroborylation product (2-cyclooctyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 35%) was contained in the crude reaction mixture. Benzimidazoles bearing bulky alkyl groups, such as isopropyl (1d) and tert-butyl (1e) groups, at their 2-positions were successfully borylated at the terminal C(sp³)–H bonds (entries 4 and 5). The methyl C(sp³)–H borylation of polycyclic compound 1f gave primary alkylboronate 3f as a sole product (entry 6). Monocyclic 1,3-thiazole 1g was also a suitable substrate for the terminal C(sp³)–H borylation (entry 7). Internal C(sp³)–H bonds in 2-alkyl-1,3-azoles successfully participated in the borylation with the Silica-SMAP-Ir system under relatively mild conditions (2 mol% Ir, 70–90 ºC), affording the corresponding secondary alkylboronates (Table 2, entries 8–13). For example, the reactions of 1h or 1i containing a phenyl substituent proceeded with excellent site-selectivity at the C(sp³)–H bonds located γ to the directing sp²-hybridized N atoms (entries 8 and 9). The site-selective borylation occurred efficiently with 2-pentylbenzimidazole (1j) to provide alkylboronate 3j (entry 10). As was the case for the small-sized carbocycles, normal-sized ring compounds were also borylated site- and stereoselectively. Specifically, the reaction of 2-cyclopentyl-N-methylbenzimidazole (1k) at 90 ºC afforded the borylation product 3k as a mixture of cis and trans isomers in a 4:1 ratio (Table 2, entry 11). The cyclohexyl and cycloheptyl groups in 1l and 1m, respectively, reacted at 70–80 ºC with exceptional trans
selectivity (entries 12 and 13).

**Table 2.** Silica-SMAP–Ir Catalyzed C(sp\(^3\))–H Borylation of 2-Alkyl-1,3-azoles 1 with Diboron 2.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>Borylation Product 3</th>
<th>Temp ( (°C) )</th>
<th>Yield of 3 ( (%)^{b} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>3b</td>
<td>60</td>
<td>78(^{c,d,e}) (48)(^f)</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>3c</td>
<td>50</td>
<td>38(^{c,d,g})</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>3c</td>
<td>50</td>
<td>60(^{c,d}(54))^f</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>3d</td>
<td>80</td>
<td>83(^d)</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>3e</td>
<td>80</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>3f</td>
<td>70</td>
<td>86</td>
</tr>
</tbody>
</table>
Conditions for C–H borylation: 1a (0.6 mmol), 2 (0.2 mmol), [Ir(OMe)(cod)]₂ (2 mol% Ir), Silica-SMAP (2 mol% P), THF (1 mL), 15 h. Conditions for oxidation: NaBO₃·4H₂O (1 mmol), THF (1 mL), H₂O (1 mL), rt, 5 h. ¹H NMR yield based on 2. Isolated yields shown in parentheses. Geminal diborylation products 4 were formed in entries 1, 2, 3 and 7 (26%, 19%, 31%, and 34%, respectively). The C=N reduction products of 1 were formed in entries 1, 2, 3, 4, 8, 9, 10, 11, 12 and 13 (30%, 64%, 42%, 85%, 40%, 59%, 84%, 35%, 83%, and 41%, respectively). Arylboronates were formed in entries 1, 8, 9, 10, 11, 12 and 13 (5%, 7%,...
6%, 11%, 4%, 8%, and 2%, respectively. Isolated product was contaminated with arylboronates (9%) and the diborylation product (1%). The C=N reduction product of 3e (structure not determined, ca. 20%) was formed. Cyclooctene (0.2 mmol) was used as an additive. Isolated product was contaminated with the diborylation product (<1%).

Table 3. Oxidation of borylated 2-Alkyl-1,3-azoles 3:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Borylated compound 3</th>
<th>Alcohol product 5</th>
<th>Yield of 5 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="3d" /></td>
<td><img src="image" alt="5d" /></td>
<td>59</td>
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<td>2</td>
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<tr>
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<td><img src="image" alt="3h" /></td>
<td><img src="image" alt="5h" /></td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="3i" /></td>
<td><img src="image" alt="5i" /></td>
<td>70</td>
</tr>
</tbody>
</table>
Conditions: NaBO$_3$·4H$_2$O (1 mmol), THF (1 mL), H$_2$O (1 mL), rt, 5 h. $^b$ Isolated yields. $^c$ Isolated products in entries 7, 8, and 9 were contaminated with phenol derivatives (1%, 5%, and 2%, respectively), which were derived from the corresponding arylboronates.

**Transformation of alkylboronates.** To demonstrate the synthetic utility of the present borylation reaction, transformations of alkylboronate 3a were performed as shown in Scheme 3. The boronate 3a was converted into tertiary amine 6 through a Cu-catalyzed reaction with N-methylaniline in the presence of Ag$_2$CO$_3$ as an oxidant.$^{13}$ The Suzuki–Miyaura cross-coupling of 4-chloroanisole with a RuPhos-ligated palladacycle precatalyst provided the sp$^3$–sp$^2$ coupling product 7.$^{14-15}$ The one-carbon-homologation-oxidation sequence afforded the corresponding primary alcohol 8.$^{16}$
Scheme 3. Transformation of 3a.

Conclusion

The author developed that a heterogeneous Ir catalyst system with silica-supported cage-type trialkylphosphine Silica-SMAP enabled C(sp^3)–H borylation of alkyl side chains of 1,3-azoles, including thiazoles, oxazoles, and imidazoles, under relatively mild conditions with high site- and stereoselectivities. The borylation occurred not only at terminal C(sp^3)–H bonds but also at internal secondary C(sp^3)–H bonds in linear alkyl groups or carbocyclic rings. The obtained alkylboronates serve as precursors for C–N and C–C bond formation reactions. Thus, this heterogeneous Ir catalysis offers a useful method for rapid access to functionalized molecules with 1,3-azole scaffolds.

Experimental Section

Instrumentation and Chemicals.

^1H (400 MHz), ^13C (100 MHz) and ^11B (128 MHz) NMR spectra were recorded on a
JEOL JNM-ECX spectrometer. Chemical shift values for $^1$H, $^{13}$C and $^{11}$B NMR spectra are referenced to Me$_4$Si (0 ppm) and DMSO (2.50 ppm), the residual solvent resonances (77.0 ppm for CHCl$_3$, and 40.0 ppm for DMSO) and BF$_3$•OEt$_2$ (0 ppm), respectively. Chemical shifts are reported in $\delta$ ppm. High-resolution mass spectra were recorded on a Thermo Fisher Scientific Exactive, JEOL JMS-T100LP mass spectrometer or JEOL JMS-T100GCv mass spectrometer at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. IR spectra were measured with a Perkin-Elmer Spectrum One. Melting points were determined on a micro melting point apparatus (Yanaco: MP-500D) using micro cover glass. GLC analyses were conducted on a Shimadzu GC-14B equipped with a flame ionization detector. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F$_{254}$. All reactions were carried out under a nitrogen atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. [Ir(OMe)(cod)]$_2$, Ph-SMAP$^{18}$ and PS-TPP$^{19}$ were prepared according to the literatures. Silica-SMAP,$^{20}$ Silica-TRIP$^{21}$ and Silica-TPP$^{22}$ were prepared with CARiACT Q-10$^{\circ}$ according to the reported procedures. CARiACT Q-10 (Catalyst grade, 75–150 $\mu$m) was purchased from Fuji Silysia Chemical Ltd. and dehydrated by heating at 150 °C for 10 h and stored in a glove box before use. All solvents for catalytic reactions were degassed via three freeze–pump–thaw cycles before use. Bis(pinacolato)diboron (2) was purchased from AllyChem Co., Ltd., and purified as follows: The diboron 2 was dissolved into hexane at room temperature, and traces of insoluble solids were removed by filtration. The filtrate was concentrated under vacuum, and the residue was recrystallized from pentane before use.

**Experimental Procedures**

**Typical Procedure for the Borylation of 2-Ethylbenzo[d]thiazole (1a) with Immobilized Ligands (Table 1, Entry 1).** In a glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.0040 mmol, 2 mol%), bis(pinacolato)diboron (2) (50.8 mg, 0.20 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]$_2$ (1.3 mg, 0.0020 mmol, 1 mol%) in THF (0.7 mL) and 2-ethylbenzo[d]thiazole (1a) (97.9 mg, 0.60 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 60 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was
added to the residue. The yields of the products 3a and 4a were determined by $^1$H NMR spectroscopy (82% and 32% yields, respectively). The crude material was then purified by Kugelrohr distillation (1 mmHg, 145 °C), to give the corresponding product 3a (43.1 mg, 75% yield) contaminated with the diborylation product 4a (<1%) and traces of impurities, as estimated by $^1$H NMR spectroscopy.

**Procedure for the Borylation of 1a on a Gram Scale (Table 1, Entry 2).** In a glove box, Silica-SMAP (0.07 mmol/g, 357 mg, 0.0250 mmol, 0.5 mol%), bis(pinacolato)diboron (2) (1.27 g, 5.0 mmol), and anhydrous, degassed THF (1 mL) were placed in a 50 mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]$_2$ (8.3 mg, 0.0125 mmol, 0.25 mol%) in THF (5 mL) and 2-ethylbenzo[d]thiazole (1a) (2.45 g, 15 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 90 °C for 24 h, and filtered through a glass pipette equipped with a cotton filter. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3a was determined by $^1$H NMR spectroscopy (71% yield). The crude material was then purified by Kugelrohr distillation (1 mmHg, 150 °C), to give the corresponding product 3a (780.8 mg, 2.7 mmol, 54% yield).

**Procedure for the Geminal Borylation of 2-Ethylbenzo[d]thiazole (1a) (Table 1, Entry 3).** In a glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.0040 mmol, 2 mol%), bis(pinacolato)diboron (2) (101.6 mg, 0.40 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]$_2$ (1.3 mg, 0.0020 mmol, 1 mol%) in THF (0.7 mL) and 2-ethylbenzo[d]thiazole (1a) (32.6 mg, 0.20 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 60 °C for 24 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yields of the products 3a and 4a were determined by $^1$H NMR spectroscopy (2% and 97% yields, respectively). The crude material was then purified by Kugelrohr distillation (1 mmHg, 180 °C), to give the corresponding product 4a [75.5 mg, 89% yield, contaminated with 3a (1.2 mg, 2% yield), as estimated by $^1$H NMR spectroscopy.]

**Typical Procedure for the Borylation of 2-Ethylbenzo[d]thiazole (1a) with Soluble**
Ligands (Table 1, Entry 7). In a glove box, bis(pinacolato)diboron (2) (50.8 mg, 0.20 mmol) was placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of Ph-SMAP (0.9 mg, 0.0040 mmol, 2 mol%) in anhydrous, degassed THF (0.3 mL), a solution of [Ir(OMe)(cod)]₂ (1.3 mg, 0.0020 mmol, 1 mol%) in THF (0.7 mL) and 2-ethylbenzo[d]thiazole (1a) (97.9 mg, 0.60 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 60 °C for 15 h. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3a was determined by ¹H NMR spectroscopy (0% yield).

Typical Procedure for the Borylation of 2-Alkyl-1,3-azole Derivatives (Table 2, Entry 1). In a glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.0040 mmol, 2 mol%), bis(pinacolato)diboron (2) (50.8 mg, 0.20 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]₂ (1.3 mg, 0.0020 mmol, 1 mol%) in THF (0.7 mL) and 2-ethylbenzo[d]oxazole (1b) (88.3 mg, 0.60 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 60 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3b was determined by ¹H NMR spectroscopy (78% yield). The crude material was then purified by Kugelrohr distillation (1 mmHg, 130 °C), to give the corresponding product 3b (26.8 mg, 49% yield) contaminated with C(sp²)–H borylation products (5.5 mg, 10% yield), as estimated by ¹H NMR spectroscopy.

Typical Procedure for the Borylation of 2-Alkyl-1,3-azole Derivatives Followed by Oxidation (Table 2, Entry 4 and Table 3, Entry 1). In a glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.0040 mmol, 2 mol%), bis(pinacolato)diboron (2) (50.8 mg, 0.20 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]₂ (1.3 mg, 0.0020 mmol, 1 mol%) in THF (0.7 mL) and 2-isopropyl-1-methyl-1H-benzo[d]imidazole (1d) (88.3 mg, 0.60 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 80 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. Solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yield of the product 3d
was determined by \(^1\)H NMR (83% yield). The resulting product was used to the next reaction without further purification. The crude boronate, THF (1.0 mL), water (1.0 mL) and NaBO\(_3\)•4H\(_2\)O (154 mg, 1.0 mmol) were placed in a round bottom flask containing a magnetic stirring bar, and the reaction mixture was stirred vigorously at room temperature for 5 h under air. The volatiles were evaporated under reduced pressure. The residue was suspended in CH\(_2\)Cl\(_2\), filtered through a pipette equipped with a cotton plug. The filtrate was concentrated under reduced pressure, and the crude mixture was then purified by silica gel chromatography (CHCl\(_3\)/MeOH/Et\(_3\)N 97:2:1) to give the alcohol 5d (22.2 mg, 0.117 mmol, 59% yield in two steps).

**Procedure for the Cu-Catalyzed Amination of 3a (Scheme 2).** In a glove box, 3a (43.4 mg, 0.15 mmol), Cu(OAc)\(_2\) (2.7 mg, 0.015 mmol, 10 mol%) and Ag\(_2\)CO\(_3\) (82.7 mg, 0.3 mmol, 2 equiv) were placed in a 10 mL glass tube containing a magnetic stirring bar. N-Methylaniline (24.1 mg, 0.225 mmol, 1.5 equiv) and toluene (300 µL) were then added, and the tube was sealed with a screw cap and removed from the glove box. The reaction mixture was heated at 100 °C for 12 h. After cooling to room temperature, the solvents were removed under reduced pressure, and the resulting mixture was purified by silica gel chromatography (hexane/EtOAc 70:30) to give the desired product 5 as pale yellow oil (32.2 mg, 0.120 mmol, 80% yield).

**Procedure for the Pd-Catalyzed Suzuki–Miyaura Coupling of 3a (Scheme 2).** In a glove box, 3a (47.7 mg, 0.165 mmol, 1.1 equiv), 4-chloroanisole (21.4 mg, 0.15 mmol), a RuPhos-ligated palladacycle precatalyst (RuPhos-Pd-G3, 6.3 mg, 0.0075 mmol, 5 mol%) and K\(_2\)CO\(_3\) (62.3 mg, 0.45 mmol, 3 equiv) were placed in a 10 mL glass tube containing a magnetic stirring bar. toluene (150 µL) and H\(_2\)O (150 µL) were added, and the tube was sealed with a screw cap and removed from the glove box. The reaction mixture was heated at 90 °C for 24 h. After cooling to room temperature, water was added to the tube, and the mixture was extracted with Et\(_2\)O. The organic layer was washed with water, dried over MgSO\(_4\), filtrate, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc 80:20) to give the desired product 6 (25.4 mg, 63% yield) contaminated with 4,4'-dimethoxy-1,1'-biphenyl (<2%), as estimated by \(^1\)H NMR spectroscopy.

**Procedure for the One-Carbon Homologation Followed by Oxidation of 3a (Scheme 2).** Under Ar atmosphere, the boronate 3a (43.4 mg, 0.15 mmol), bromochloromethane (38.8 mg,
0.30 mmol, 2 equiv), and anhydrous THF (2 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. The tube was sealed with a screw cap with a Teflon-coated silicon rubber septum. After the mixture was cooled to –78 °C, n-BuLi in hexane (1.6 M, 170 µL, 0.27 mmol, 1.8 equiv) was added. The mixture was stirred at –78 °C for 30 min, and stirred at room temperature for 3 h. The volatiles were evaporated under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue, and the yield of 1-methyl-2-(2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclopropyl)-1H-benzo[d]imidazole was determined by 1H NMR (81% yield) in the crude mixture. The resulting product was used to the next reaction without further purification. The crude boronate, THF (0.5 mL), water (0.5 mL) and NaBO₃•4H₂O (55.8 mg, 0.36 mmol, 3 equiv) were placed in a round bottom flask containing a magnetic stirring bar, and the reaction mixture was stirred vigorously at room temperature for 3 h under air. The volatiles were evaporated under reduced pressure. The residue was suspended in CHCl₃, filtered through a pipette equipped with a cotton plug. The filtrate was concentrated under reduced pressure, and the crude mixture was then purified by silica gel chromatography (hexane/EtOAc 70:30) to give the alcohol 7 (19.1 mg, 0.099 mmol, 66% yield in two steps).

**Preparation of Substrates**

The starting material 1g is commercially available. The starting materials 1a, 1b, 1c, 1d, 1e, 1f, 1h, 1i, 1j, 1k and 1l are reported in the literatures.

**2-Cycloheptyl-1-methyl-1H-benzo[d]imidazole (1m)**

The title compound (1m) was synthesized via the reaction of cycloheptylcarboxylic acid and o-phenylenediamine, followed by the methylation with MeI and NaH (92% yield).

![Structure](attachment:image.png)

Isolated by silica gel chromatography (CHCl₃/MeOH 98:2). White solids. **M.p.** 79.6–80.0 °C. 

**¹H NMR** (CDCl₃) δ 1.54–1.73 (m, 6H), 1.87–2.09 (m, 6H), 3.04 (sep, J = 4.0 Hz, 1H), 3.72 (s, 3H), 7.20–7.30 (m, 3H), 7.72–7.75 (m, 1H). 

**¹³C NMR** (CDCl₃) δ 26.81 (2C), 27.96 (2C), 29.59, 33.20 (2C), 38.03, 108.77, 119.20, 121.58, 121.80, 135.60, 142.44, 160.12.

**IR (ATR):**
Characterization of Products

2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzo[d]thiazole (3a)

Isolated by Kugelrohr distillation [1 mmHg, 145 °C, 43.1 mg, 75% yield, contaminated with the diborylation product (<1%) and trace of impurities]. Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.24 (s, 12H), 1.38 (t, $J = 7.6$ Hz, 2H), 3.24 (t, $J = 7.6$ Hz, 2H), 7.32 (td, $J = 8.4$, 1.2 Hz, 1H), 7.42 (td, $J = 7.6$, 0.8 Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 8.4$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 11.10 (br), 24.75 (4C), 28.85, 83.36 (2C), 121.42, 122.41, 124.42, 125.67, 135.19, 153.19, 173.81. $^{11}$B NMR (CDCl$_3$) δ 32.6. IR (ATR): 2976, 2930, 1519, 1436, 1370, 1313, 1142, 967, 845, 758 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{15}$H$_{21}$N$_2$, 229.16993; found, 229.16997.

2-(2,2-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzo[d]thiazole (4a)

Isolated by Kugelrohr distillation [1 mmHg, 180 °C, 75.5 mg, 89% yield, contaminated with 3a (1.2 mg, 2% yield)]. Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.21 (s, 12H), 1.24 (s, 12H), 1.44 (t, $J = 8.0$ Hz, 1H), 3.37 (d, $J = 8.0$ Hz, 2H), 7.30 (td, $J = 7.6$, 1.2 Hz, 1H), 7.40 (td, $J = 7.6$, 1.2 Hz, 1H), 7.80 (d, $J = 8.8$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 10.48 (br), 24.48 (4C), 24.75 (4C), 30.36, 83.33 (4C), 121.33, 122.36, 124.22, 125.46, 135.36, 153.11, 173.89. $^{11}$B NMR (CDCl$_3$) δ 32.5. IR (ATR): 2977, 2930, 1519, 1436, 1368, 1311, 1137, 968, 848, 758, 729 cm$^{-1}$. HRMS–EI (m/z): [M]$^+$ Calcd for C$_{21}$H$_{31}$O$_4$N$_{10}$B$_2$S, 415.21599; found, 415.21564.

2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzo[d]oxazole (3b)

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Isolated by Kugelrohr distillation [1 mmHg, 130 °C, 26.7 mg, 49% yield, contaminated with C(sp^{3})–H borylation products (4.6 mg, 9% yield) and diborylation product (0.83 mg, 1% yield)]. Colorless oil. ¹H NMR (CDCl₃) δ 1.24 (s, 12H), 1.36 (t, J = 7.2 Hz, 2H), 3.05 (t, J = 7.2 Hz, 2H), 7.26–7.28 (m, 2H), 7.44–7.47 (m, 1H), 7.64–7.66 (m, 1H). ¹³C NMR (CDCl₃) δ 23.24, 24.72 (4C), 83.40 (2C), 110.16, 119.46, 123.87, 124.20, 141.44, 150.86, 168.43. A signal for the carbon directly attached to the boron atom was not observed. ¹¹B NMR (CDCl₃) δ 32.6. IR (ATR): 2977, 2932, 1615, 1571, 1456, 1358, 1316, 1241, 1141, 968, 849, 744 cm⁻¹. HRMS–EI (m/z): [M]+ Calcd for C₁₅H₂₀O₃N₁₀B, 272.15725; found, 272.15662.

1-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-1H-benzo[d]imidazole (3c)

Isolated by Kugelrohr distillation [1 mmHg, 160 °C, 30.8 mg, 54% yield, contaminated with the diborylation product (<1% yield)]. White solids. M.p. 111.3–112.2 °C. ¹H NMR (CDCl₃) δ 1.23 (s, 12H), 1.38 (t, J = 8.0 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H), 3.72 (s, 3H), 7.19–7.24 (m, 2H), 7.25–7.29 (m, 1H), 7.67–7.71 (m, 1H). ¹³C NMR (CDCl₃) δ 8.97 (br), 21.87, 24.75 (4C), 29.59, 83.21 (2C), 108.68, 119.08, 121.45, 121.68, 135.93, 142.47, 156.62. ¹¹B NMR (CDCl₃) δ 32.5. IR (ATR): 2976, 2902, 1615, 1512, 1406, 1379, 1319, 1246, 1142, 969, 749 cm⁻¹. HRMS–EI (m/z): [M]+ Calcd for C₁₆H₂₄O₂N₂B, 286.19747; found, 286.19747.

2-(1-Methyl-1H-benzo[d]imidazol-2-yl)propan-1-ol (5d)

Isolated by silica gel chromatography (CHCl₃/MeOH/Et₃N 97:2:1) (22.2 mg, 0.117 mmol, 59% yield in two steps). Pale pink solids. M.p. 127.4–128.9 °C. ¹H NMR (CDCl₃) δ 1.39 (d, J = 7.2 Hz, 3H), 3.22–3.30 (m, 1H), 3.77 (s, 3H), 4.00–4.08 (m, 2H), 7.23–7.28 (m, 2H), 7.29–7.33 (m, 1H), 7.68–7.72 (m, 1H). ¹³C NMR (CDCl₃) δ 16.13, 29.68, 33.73, 65.56,

2-Methyl-2-(1-methyl-1H-benzo[d]imidazol-2-yl)propan-1-ol (5e)

Isolated by silica gel chromatography (CHCl₃/MeOH/Et₃N 97:2:1) (27.6 mg, 0.135 mmol, 68% yield in two steps). White solids. **M.p.** 106.8–109.5 °C. **¹H NMR** (CDCl₃) δ 1.47 (s, 6H), 3.85 (s, 2H), 3.90 (s, 3H), 5.18 (br, 1H), 7.24–7.33 (m, 3H), 7.67–7.69 (m, 1H). **¹³C NMR** (CDCl₃) δ 23.06 (2C), 31.75, 38.59, 72.61, 108.87, 119.19, 122.16, 122.46, 136.25, 141.02, 159.44. **IR** (ATR): 3142, 2921, 2823, 1724, 1612, 1452, 1325, 1289, 1070, 803, 744, 729 cm⁻¹. **HRMS–ESI** (m/z): [M+H]⁺ Calcd for C₁₂H₁₇ON₂, 205.13354; found, 205.13358

Benzo[4,5]imidazo[1,2-a]quinolin-6-ylmethanol (5f)

Isolated by silica gel chromatography (CHCl₃/MeOH/Et₃N 97:2:1) (35.0 mg, 0.141 mmol, 71% yield in two steps). White solids. **M.p.** 206.7–207.3 °C. **¹H NMR** (DMSO-d₆) δ 4.97 (d, J = 4.8 Hz, 2H), 5.61 (dd, J = 6.0 Hz, 1H), 7.51–7.59 (m, 3H), 7.81 (t, J = 7.6 Hz, 1H), 7.94–7.96 (m, 2H), 8.09 (d, J = 6.8 Hz, 1H), 8.72 (d, J = 7.6 Hz, 1H), 8.80 (d, J = 8.8 Hz, 1H). **¹³C NMR** (DMSO-d₆) δ 59.23, 115.11, 115.84, 120.36, 123.17, 123.45, 124.78, 124.96, 126.24, 129.40, 129.99, 131.00, 131.13, 134.37, 144.57, 146.71. **IR** (ATR): 3235, 2863, 1633, 1536, 1457, 1406, 1209, 1105, 1055, 759, 745 cm⁻¹. **HRMS–ESI** (m/z): [M+H]⁺ Calcd for C₁₆H₁₂ON₂Na, 271.08418; found, 271.08402.

4,5-Dimethyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)thiazole (3g)
Isolated by silica gel chromatography (hexane/EtOAc 80:20) (33.6 mg, 63% yield). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.21–1.26 (m, 14H), 2.26 (s, 3H), 2.29 (s, 3H), 3.00 (t, $J = 8.0$ Hz, 2H). $^{13}$C NMR (CDCl$_3$) δ 11.21, 11.75 (br), 14.55, 24.75 (4C), 27.80, 83.22 (2C), 124.59, 147.01, 168.42. $^{11}$B NMR (CDCl$_3$) δ 32.7. IR (ATR): 2977, 2923, 1559, 1407, 1370, 1313, 1247, 1143, 967, 947, 672 cm$^{-1}$. HRMS–EI (m/z): [M]$^+$ Calcd for C$_{13}$H$_{22}$O$_2$N$_{10}$BS, 266.15006; found, 266.14926.

2-(1-Methyl-1H-benzo[d]imidazol-2-yl)-1-phenylethan-1-ol (5h)$^{[32]}$

Isolated by silica gel chromatography (CHCl$_3$/MeOH/Et$_3$N 97:2:1) (34.8 mg, 0.138 mmol, 69% yield in two steps). White solids. $^1$H NMR (CDCl$_3$) δ 3.12–3.21 (m, 2H), 3.59 (s, 3H), 5.38 (dd, $J = 8.0$, 4.4 Hz, 1H), 5.46 (br, 1H), 7.24–7.32 (m, 4H), 7.37 (t, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 6.8$ Hz, 2H), 7.70–7.73 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ 29.53, 36.62, 71.46, 109.10, 119.09, 122.14, 122.38, 125.71 (2C), 127.66, 128.50 (2C), 135.20, 141.95, 143.24, 152.96. IR (ATR): 3575, 3140, 2988, 2901, 1614, 1475, 1447, 1395, 1243, 1078, 1049, 885, 699 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{17}$H$_{19}$ON$_2$, 267.14919; found, 267.14898.

1-(1-Methyl-1H-benzo[d]imidazol-2-yl)-3-phenylpropan-2-ol (5i)

Isolated by silica gel chromatography (CHCl$_3$/MeOH/Et$_3$N 97:2:1) (37.3 mg, 0.140 mmol, 70% yield in two steps). White solids. M.p. 128.3–131.9 °C. $^1$H NMR (CDCl$_3$) δ 2.87 (dd, $J = 19.6$, 13.6, 7.2 Hz, 2H), 2.97 (dd, $J = 16.0$, 2.8 Hz, 1H), 3.11 (dd, $J = 14.0$, 6.8 Hz, 1H), 3.63 (s, 3H), 4.50–4.57 (m, 1H), 4.98 (br, 1H), 7.22–7.34 (m, 8H), 7.66–7.70 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ 29.63, 32.84, 43.12, 70.34, 109.02, 119.04, 122.04, 122.26, 126.48, 128.52 (2C), 129.37 (2C), 135.20, 138.17, 141.98, 153.30. IR (ATR): 3575, 3140, 2988, 2901, 1614, 1475, 1395, 1243, 1078, 1049, 885, 699 cm$^{-1}$. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{17}$H$_{19}$ON$_2$, 267.14919; found, 267.14898.
1-(1-Methyl-1H-benzo[d]imidazol-2-yl)pentan-2-ol (5j)

Isolated by silica gel chromatography (CHCl₃/MeOH/Et₃N 97:2:1) (32.3 mg, 0.148 mmol, 74% yield in two steps). White solids. **M.p.** 125.1–126.8 °C. **¹H NMR** (CDCl₃) δ 0.98 (t, *J* = 6.8 Hz, 3H), 1.43–1.62 (m, 3H), 1.63–1.76 (m, 1H), 2.83 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.96 (dd, *J* = 16.0, 2.8 Hz, 1H), 3.70 (s, 3H), 4.26–4.32 (m, 1H), 4.88 (br, 1H), 7.22–7.31 (m, 3H), 7.67–7.70 (m, 1H). **¹³C NMR** (CDCl₃) δ 14.05, 18.92, 29.61, 34.06, 38.97, 68.72, 108.98, 119.00, 121.98, 122.20, 135.22, 141.99, 153.62. **IR** (ATR): 3675, 3084, 2958, 2901, 1475, 1448, 1394, 1242, 1056, 741 cm⁻¹. **HRMS−ESI (m/z):** [M+H]+ Calcd for C₁₃H₁₉ON₂, 219.14919; found, 219.14918. In the NOESY NMR analysis, a strong correlation peak between the proton at the position α to the alcohol group (4.65 ppm) and the proton at the position α to the azole group (3.10 ppm) is assignable to *cis* configuration for 5k.

cis-2-(1-Methyl-1H-benzo[d]imidazol-2-yl)cyclopentan-1-ol (5k)

Isolated by silica gel chromatography (CHCl₃/MeOH/Et₃N 97:2:1) (29.2 mg, 0.135 mmol, 67% yield in two steps). White solids. **M.p.** 114.0–116.9 °C. **¹H NMR** (CDCl₃) δ 1.79–1.91 (m, 2H), 1.98–2.08 (m, 2H), 2.10–2.21 (m, 2H), 3.10 (ddd, *J* = 11.2, 7.6, 3.6 Hz, 1H), 3.76 (s, 3H), 4.65 (t, *J* = 4.0 Hz, 1H), 6.21 (br, 1H), 7.24–7.30 (m, 2H), 7.31–7.34 (m, 1H), 7.68–7.71 (m, 1H). **¹³C NMR** (CDCl₃) δ 22.62, 28.92, 29.70, 33.89, 41.98, 74.69, 108.97, 119.15, 122.18, 122.36, 134.97, 141.58, 156.35. **IR** (ATR): 3277, 2919, 2870, 1727, 1615, 1501, 1471, 1443, 1399, 1322, 1236, 1088, 1005, 734 cm⁻¹. **HRMS−ESI (m/z):** [M+H]+ Calcd for C₁₃H₁₇ON₂, 217.13354; found, 217.13354. In the NOESY NMR analysis, a strong correlation peak between the proton at the position α to the alcohol group (4.65 ppm) and the proton at the position α to the azole group (3.10 ppm) is assignable to *cis* configuration for 5k.

trans-2-(1-Methyl-1H-benzo[d]imidazol-2-yl)cyclopentan-1-ol (5k’)

90
Isolated by silica gel chromatography (CHCl₃/MeOH/Et₃N 97:2:1) [6.9 mg, 0.032 mmol, 16% yield in two steps, contaminated with a phenol derivative derived from the corresponding arylboronate (0.53 mg, 1% yield)]. White solids. M.p. 166.2–168.9 °C. ¹H NMR (CDCl₃) δ 1.69–1.97 (m, 4H), 2.17–2.29 (m, 2H), 3.19 (q, J = 8.4 Hz, 1H), 3.33 (br, 1H), 3.68 (s, 3H), 4.81 (q, J = 7.2 Hz, 1H), 7.19–7.23 (m, 3H), 7.67–7.72 (m, 1H). ¹³C NMR (CDCl₃) δ 21.71, 29.53, 29.73, 33.61, 45.73, 77.20, 108.92, 118.96, 121.80, 122.04, 135.80, 142.13, 156.79. IR (ATR): 3201, 2963, 1613, 1504, 1476, 1444, 1413, 1320, 1283, 1100, 768 cm⁻¹. HRMS–ESI (m/z) [M+H]+ Calcd for C₁₃H₁₇N₂, 217.13354; found, 217.13359. In the NOESY NMR analysis, no correlation peak between the proton at the position α to the alcohol group (4.81 ppm) and the proton at the position α to the azole group (3.19 ppm) is assignable to trans configuration for 5k’.

trans-2-(1-Methyl-1H-benzo[d]imidazol-2-yl)cyclohexan-1-ol (5l)

Isolated by silica gel chromatography (CHCl₃/MeOH/Et₃N 98:1:1) [25.5 mg, 0.111 mmol, 55% yield in two steps, contaminated with a phenol derivative derived from the corresponding arylboronate (2.1 mg, 5% yield)]. White solids. M.p. 211.6–212.8 °C. ¹H NMR (CDCl₃) δ 1.34–1.52 (m, 3H), 1.61 (qd, J = 12.8, 3.6 Hz 1H), 1.81–1.91 (m, 2H), 1.98–2.03 (m, 1H), 2.16–2.21 (m, 1H), 2.83 (ddd, J = 12.0, 9.2, 4.0 Hz, 1H), 3.15 (br, 1H), 3.76 (s, 3H), 4.28 (td, J = 10.0, 4.0 Hz, 1H), 7.22–7.33 (m, 3H), 7.69–7.73 (m, 1H). ¹³C NMR (CDCl₃) δ 24.70, 25.60, 29.78, 30.73, 33.74, 44.96, 72.08, 109.07, 119.13, 121.99, 122.19, 135.69, 142.24, 156.65. IR (ATR): 3197, 2924, 2852, 1598, 1471, 1447, 1275, 1071, 978, 785, 758, 736 cm⁻¹. HRMS–ESI (m/z) [M+H]+ Calcd for C₁₄H₁₀ON₂, 231.14919; found, 231.14912. The ¹H NMR resonance for the proton at the position α to the alcohol group (4.28 ppm) is a triplet of doublets (J = 10.0, 4.0 Hz), The coupling constant is assignable to trans configuration for 5l. In the NOESY NMR analysis, no correlation peak
between the proton at the position $\alpha$ to the alcohol group (4.28 ppm) and the proton at the position $\alpha$ to theazole group (2.83 ppm) is also indicative of \textit{trans} configuration for 5l.

\textit{trans-2-(1-Methyl-1H-benzo[d]imidazol-2-yl)cycloheptan-1-ol (5m)}

![5m](image)

Isolated by silica gel chromatography (CHCl$_3$/MeOH/Et$_3$N 98:1:1) [21.1 mg, 0.086 mmol, 43% yield in two steps, contaminated with Ar–OH product (0.98 mg, 2% yield)]. Pale pink solids. M.p. 164.8–165.2 °C. $^1$H NMR (CDCl$_3$) $\delta$ 1.62–1.90 (m, 9H), 2.15 (ddd, $J = 12.8, 7.2, 4.0$ Hz, 1H), 3.03 (td, $J = 9.2, 2.8$ Hz, 1H), 3.41 (br, 1H), 3.73 (s, 3H), 4.44 (td, $J = 8.8, 3.6$ Hz, 1H), 7.21–7.32 (m, 3H), 7.68–7.74 (m, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 22.28, 26.41, 27.13, 29.69, 29.87, 35.88, 46.07, 74.39, 109.06, 119.08, 121.91, 122.13, 135.50, 142.15, 158.33. IR (ATR): 3300, 2922, 2856, 1612, 1496, 1467, 1436, 1317, 1052, 937, 769, 754 cm$^{-1}$. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{15}$H$_{21}$ON$_2$, 245.16484; found, 245.16474. The $^1$H NMR resonance for the proton at the position $\alpha$ to the alcohol group (4.44 ppm) is a triplet of doublets ($J = 8.8, 3.6$ Hz). The coupling constant is assignable to \textit{trans} configuration for 5m. In the NOESY NMR analysis, no correlation peak between the proton at the position $\alpha$ to the alcohol group (4.44 ppm) and the proton at the position $\alpha$ to theazole group (3.03 ppm) is also indicative of \textit{trans} configuration for 5m.

\textit{N-(2-(Benzo[d]thiazol-2-yl)ethyl)-N-methylaniline (5)}

![5](image)

Isolated by silica gel chromatography (EtOAc/hexane 70:30) (32.2 mg, 0.120 mmol, 80% yield). Pale yellow oil. $^1$H NMR (CDCl$_3$) $\delta$ 2.97 (s, 3H), 3.36 (t, $J = 8.0$ Hz, 2H), 3.88 (t, $J = 8.0$ Hz, 2H), 6.75 (t, $J = 7.2$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 2H), 7.24–7.28 (m, 2H), 7.36 (td, $J = 8.4, 1.2$ Hz, 1H), 7.47 (td, $J = 8.4, 0.8$ Hz, 1H), 7.84 (d, $J = 7.6$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 31.34, 38.55, 52.44, 112.61 (2C), 115.92, 121.52, 122.60, 124.82, 126.01, 129.34 (2C), 135.27, 148.54, 153.32, 168.93. IR (ATR): 3059, 2902, 1912, 1597,
1503, 1434, 1353, 1193, 990, 745, 728 cm$^{-1}$. **HRMS–ESI (m/z):** [M+H]$^+$. Calcd for C$_{16}$H$_{17}$N$_2$S, 269.11070; found, 269.11052.

**2-(4-Methoxyphenethyl)benzo[d]thiazole (6)**

Isolated by silica gel chromatography (EtOAc/hexane 70:30) [25.4 mg, 0.094 mmol, 63% yield, contaminated with 4,4’-dimethoxy-1,1’-biphenyl (<2%)]. White solids. **M.p.** 88.8–89.7 °C. ¹H NMR (CDCl$_3$) δ 3.15 (t, $J$ = 8.4 Hz, 2H), 3.40 (t, $J$ = 8.0 Hz, 2H), 3.79 (s, 3H), 6.84 (d, $J$ = 6.4 Hz, 2H), 7.17 (d, $J$ = 6.4 Hz, 2H), 7.35 (td, $J$ = 8.4, 0.8 Hz, 1H), 7.46 (td, $J$ = 8.4, 1.6 Hz, 1H), 7.83 (d, $J$ = 8.4 Hz, 1H), 7.98 (d, $J$ = 7.6 Hz, 1H). ¹³C NMR (CDCl$_3$) δ 34.70, 36.28, 55.23, 113.95 (2C), 121.50, 122.55, 124.71, 125.90, 129.37 (2C), 132.22, 135.12, 153.18, 158.16, 171.04. IR (ATR): 3053, 2997, 2835, 1608, 1582, 1508, 1432, 1243, 1180, 1034, 822, 756 cm$^{-1}$. **HRMS–ESI (m/z):** [M+H]$^+$ Calcd for C$_{16}$H$_{16}$ONS 270.09471; found, 270.09458.

**3-(benzo[d]thiazol-2-yl)propan-1-ol (7)**

Isolated by silica gel chromatography (EtOAc/hexane 70:30) (19.1 mg, 0.099 mmol, 66% yield in two steps). Pale yellow oil. ¹H NMR (CDCl$_3$) δ 2.15 (quin, $J$ = 6.8 Hz, 2H), 2.76 (br, 1H), 3.27 (t, $J$ = 7.6 Hz, 2H), 3.80 (t, $J$ = 6.0 Hz, 2H), 7.36 (td, $J$ = 6.8, 1.2 Hz, 1H), 7.46 (td, $J$ = 8.4, 1.2 Hz, 1H), 7.84 (d, $J$ = 7.6 Hz, 1H), 7.96 (d, $J$ = 8.0 Hz, 1H). ¹³C NMR (CDCl$_3$) δ 31.08, 31.61, 61.79, 121.50, 122.46, 124.84, 126.01, 135.06, 153.00, 171.66. IR (ATR): 3324, 2926, 1515, 1436, 1244, 1052, 756, 728 cm$^{-1}$. **HRMS–ESI (m/z):** [M+H]$^+$ Calcd for C$_{10}$H$_{12}$ONS, 194.06341; found, 194.06369.

References


Chapter 3

Pd-catalyzed Side Chain C(α) Allylation of 2-Alkylazaarenes without Using External Bases

Palladium-catalyzed side chain C(α) allylation of 2-alkylazaarenes with allylic carbonates proceeded in the absence of external bases. This reaction occurred with exceptional linear selectivity under relatively mild conditions. Acid- or base-sensitive functional groups were compatible in this allylation reaction.
**Introduction**

Alkyl-substituted azaarenes are ubiquitous structural motifs in biologically active compounds, agrochemicals and natural products.\(^1\) Thus, functionalization of the alkyl side chain of azaarenes is important for organic synthesis.\(^2\) Although transition-metal catalyzed direct functionalization reactions of side chain C(\(\alpha\))–H bond with 2-alkylazaarenes have emerged as a valuable method in modern organic synthesis,\(^3\) the introduction of allyl groups through the Pd-catalyzed Tsuji–Trost allylic alkylation reaction, which could afford a powerful strategy for C(sp\(^3\))–C(sp\(^3\)) bond formation, is still limited in scope. Indeed, the use of a stoichiometric amount of strong base and/or Lewis acid were required to activate the 2-alkylazaarene pronucleophiles as reported by Trost’s\(^3\) and Walsh’s\(^4\) groups, resulting in the restricted functional-group compatibility (Schemes 1a,b). Tunge and co-workers disclosed decarboxylative coupling of 2-alkylazaarenes bearing allylic esters under neutral conditions,\(^5\) but this protocol required the heating condition (~80 °C) and gave unusual branched allylation products (Scheme 1c).

**Scheme 1.** Transition-metal catalyzed side chain C(\(\alpha\)) alkylation of 2-alkylazaarenes

(a) Asymmetric Allylic alkylation of alkylazaarenes: Trost’s work

(b) Allylic alkylation of diarylmethane: Walsh’s work

(c) Decarboxylative alkylation of 2-alkylazaarenes: Tunge’s work

(d) Allylic alkylation of 2-alkylazaarenes without external bases: This chapter

This chapter describes the Pd-catalyzed side chain C(\(\alpha\)) alkylation of 2-alkylazaarenes
with allyl carbonates without using external bases (Scheme 1d). This reaction occurred with exceptional regioselectivity to give the linear allylation products with a tertiary carbon at the C(α) position of 2-alkylazaarenes. Owing to the neutral and mild conditions, base-sensitive functional groups were tolerable. The present Pd catalysis releasing only carbon dioxide and alcohol as byproducts would be attractive for pursuing environmentally benign organic synthesis.6

Results and Discussion

Ligand screening with palladium-catalyzed allylation with 2-alkylazaarenes. Initially, the reaction between 1a and allylic carbonate (2a) in the presence of Pd(OAc)₂ (5 mol%) and ligand (5-10 mol%) in CH₃CN at 25 ºC for 6 h were subjected to standard reaction conditions for Pd-catalyzed allylation reaction of 2-alkylazaarenes and various ligands were examined in the reaction between 1a and 2a (figure 1). The screening of monophosphine ligands revealed that P(2-furyl)₃ and P(OPh)₃ were effective to give the allylation product 3a in moderate linear selectivities. On the other hand, phosphite ligands have bulky 2,4-di-tert-butylphenyl substituents on the phosphorus atoms caused no reaction. Other phosphite and phosphoramidite type ligands did not produce the allylation product at all. The immobilized catalysts prepared from Silica-SMAP⁷, Silica-TRIP⁸ and PS-TPP⁹ with Pd(OAc)₂ did not show any activity. A Pd complex coordinated with N-heterocyclic carbene (IMes) was also useless. Theses result suggested that electron-deficient monophosphine ligands are suitable for this catalytic system and that the reaction was highly sensitive to steric demands of the ligand.

The results with various bidentate ligands are summarized in Figure 2. A large bite-angle bisphosphine Xantphos was effective for this transformation, giving 3a with the high linear selectivity in a moderate yield (57%). However, the Xantphos derivatives tBu-Xantphos and DTBM-Xantphos, which have aromatic substituents with increased steric demands on the phosphorus atoms, caused no reaction. During further bisphosphine screening, it was revealed that Ph-TRAP¹⁰, featuring an extraordinary large bite angle, was the most effective, causing smooth reaction. As a result, 3a was obtained in a high yield with exclusive linear selectivity (94%, 3aa/4aa >99:1). Nitrogen-based ligands such as 1,0-phenanthroline and TMEDA were not effective.
Figure 1. Screening of monodentate ligands. Reaction conditions:

\[
egin{align*}
\text{Pd(OAc)}_2 & (5 \text{ mol\%}, \text{ ligand} (P : 10 \text{ mol\%}), 1a (0.2 \text{ mmol}), 2a (0.3 \text{ mmol}), \text{CH}_3\text{CN} (1 \text{ mL}), 25 ^\circ\text{C}, 6 \text{ h}. \\
\text{Product yields and constitutional isomer ratio were determined by } & ^1\text{H NMR.}
\end{align*}
\]
Optimization of palladium-catalyzed allylation with 2-alkylazaarenes.

Ph-TRAP ligand (5 mol% M. Pd/ligand 1:1), various conditions and parameters in the reaction of 1a as a representative 2-alkylazaarene substrate were investigated (Table 1). The reaction between 1a and allylic carbonate (2a) in the presence of Pd(OAc)$_2$ (5 mol%) and Ph-TRAP (5 mol%) in MeCN were subjected to standard reaction conditions for Pd-catalyzed allylation reaction of 2-alkylazaarenes (table 1, entry 1).

Various metal precursors were also examined in MeCN solvent (entry 2-4). When the bivalent palladium precursor such as Pd(dba)$_2$ was employed instead of Pd(OAc)$_2$, the product was given in high yield with high regioselectivity (entry 2). The catalysts prepared from PdCl$_2$(CH$_3$CN)$_2$ and [PdCl(allyl)]$_2$ could be applied in allylic alkylation reaction (entry 3-4). Other transition metal precursors such as Ni(cod)$_2$, [RuCl$_2$(p-cymene)]$_2$, [RhCl(cod)]$_2$, [IrCl(cod)]$_2$ induced no reaction, indicating that the necessary of Pd catalyst in this transformation (entry 5-8).
The leaving group of allylic electrophile were investigated (with Ph-TRAP/Pd(OAc)$_2$ system, entry 9-13). When cinnamyl methyl carbonate was used instead of cinnamyl tert-butyl carbonate, the product was obtained in high yield and high linear selectivity (entry 9). Other leaving groups such as carbamate, chloride, phosphate, acetate, did not give the desired product in this allylation reaction. (entry 10-13). Theses results suggested that palladium alkoxide species acted as a base and abstracted proton from the 2-ethylpyridine pronucleophile and then, the allylation reaction proceeded without the use of external bases$^{11}$.

Pd-TRAP catalytic system was examined for catalytic activity in various solvent including aprotic solvents such as DMF, CH$_2$Cl$_2$, THF and toluene (entries 14-17). The allylation reaction proceeded in polar solvent such as CH$_3$CN and DMF and allylation product was moderate yield (entry 1 and 14). The allylation reaction proceeded in CH$_2$Cl$_2$ solvent resuting in allylation product was moderate yield and linear selectivity of allylation product was slightly decreased. (entry 15). Toluene and THF solvent were not effective in this reaction (entry 16-17). These results suggest that polar solvent was important in this catalytic reaction.

**Table 1.** Optimization of allylic alkylation between 1a and 2a under various conditions$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>LG</th>
<th>Solvent</th>
<th>NMR Yield of 3aa (%)$^b$</th>
<th>3aa/4aa$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>94 (91)$^d$</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>93</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$(CH$_3$CN)$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>78</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>[PdCl(allyl)]$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>90</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>Ni(cod)$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>[RuCl$_2$(p-cymene)]$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>[RhCl(cod)]$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>[IrCl(cod)]$_2$</td>
<td>OCO$_2^t$Bu</td>
<td>CH$_3$CN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>OCO$_2$Me</td>
<td>CH$_3$CN</td>
<td>95</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>OC(O)NMe$_2$</td>
<td>CH$_3$CN</td>
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</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$</td>
<td>OAc</td>
<td>CH$_3$CN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$</td>
<td>Cl</td>
<td>CH$_3$CN</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
13 Pd(OAc)$_2$ OP(O)(OEt)$_2$ CH$_3$CN 0
14 Pd(OAc)$_2$ OCO$_2$Bu DMF 76 >99:1
15 Pd(OAc)$_2$ OCO$_2$tBu CH$_2$Cl$_2$ 69 98:2
16 Pd(OAc)$_2$ OCO$_2$tBu THF 0
17 Pd(OAc)$_2$ OCO$_2$tBu Toluene 0

$^a$ Reaction conditions: Metal (5 mol%), Ph-TRAP (5 mol%), 1a (0.2 mmol), allylic alcohol derivative 2 (0.3 mmol), solvent (1 mL), 25 ºC, 6 h. $^b$ Determined by $^1$H NMR. $^c$ Constitutional isomer ratio determined by $^1$H-NMR analysis of crude reaction. $^d$ The yield of isolated product was shown in parentheses.

**Scope of 2-alkylpyridines.** Various 2-alkylpyridines with different substituents at the side chain C($\alpha$) position and E-allylic carbonate (2a) underwent the allylation of 1 with the Pd(OAc)$_2$/Ph-TRAP catalyst system under mild conditions (Table 1). The reactions proceeded with excellent linear selectivities (l/b >99:1) and high yield (83-97%). Specifically, pyridine substrates (1b and 1c) reacted in high product yields and linear selectivities. 2-alkylpyridines substituted terminal alkene and internal alkyne could be applied and allylation product was given in high yield and high linear selectivity (entry 3 and 4). Pyridines with a fused cyclohexane and cyclopentane ring were suitable substrates (entry 5 and 6). The chloro, silyl ether and acetal moiety in 2-alkylazaarene substrates were tolerated (entry 7-9). An acidic NH group of the secondary amide moiety in 2-alkylpyridine substrate did not hampered the allylation (entry 10). Notably, ketone or ester groups, which had α-carbonyl C–H bonds more acidic than that of azabenzylic positions, were compatible in the allylation, and only side chain C($\alpha$) allylation products were obtained in high yields (entry 11-12).

**Table 2.** Pd catalyzed allylation of various 2-alkylpyridines with 2a$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-alkylpyridines</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
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<td><img src="3ab.png" alt="3ab" /></td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td><img src="1c.png" alt="1c" /></td>
<td><img src="3ac.png" alt="3ac" /></td>
<td>91</td>
</tr>
</tbody>
</table>

103
<table>
<thead>
<tr>
<th></th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="1d.png" alt="Image" /></td>
<td><img src="3da.png" alt="Image" /></td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td><img src="1e.png" alt="Image" /></td>
<td><img src="3ea.png" alt="Image" /></td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td><img src="1f.png" alt="Image" /></td>
<td><img src="3fa.png" alt="Image" /></td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td><img src="1g.png" alt="Image" /></td>
<td><img src="3ga.png" alt="Image" /></td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td><img src="1h.png" alt="Image" /></td>
<td><img src="3ha.png" alt="Image" /></td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td><img src="1j.png" alt="Image" /></td>
<td><img src="3ja.png" alt="Image" /></td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td><img src="1k.png" alt="Image" /></td>
<td><img src="3ka.png" alt="Image" /></td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td><img src="1l.png" alt="Image" /></td>
<td><img src="3la.png" alt="Image" /></td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td><img src="1m.png" alt="Image" /></td>
<td><img src="3ma.png" alt="Image" /></td>
<td>90</td>
</tr>
</tbody>
</table>
**Reaction conditions:** Pd(OAc)$_2$ (5 mol%), Ph-TRAP (5 mol%), 1 (0.2 mmol), cinnamyl tert-butyl carbonate 2a (0.3 mmol), CH$_3$CN (1 mL), 25 ºC, 6 h. $^b$ Constitutional isomer ratios (l/b = >99:1, E/Z = >99:1) Determined by $^1$H-NMR analysis of crude reaction. Yield of isolated yield.

**Scope of 2-alkylaazaarenes.** In addition to pyridine, benzimidazole and isoquinoline were suitable for the side chain C($\alpha$) allylation of azaarenes. Specifically, The reaction of benzimidazole bearing phenethyl group (6a) occurred with a high yield and high linear selectivity. The allylation of Papaverine$^{12}$ as opium alkaloid antispasmodic drug proceeded at high selectivity. This result showed that the Pd-TRAP catalytic system could be applied to late-stage allylation of bioactivemolecules containing N-heteroarenes.

**Scheme 2.** Pd-calalyzed allylation of various 2-alkylaazaarenes with 2a

**Scope of allylic carbonates.** The reaction of cinnamyl carbonate derivatives with electronically and positionally diverse substituents including $p$-OMe, $m$-Br, $p$-CF$_3$, $p$-CO$_2$Me, 2-naphtyl, $o$-Me groups were compatible with the reaction conditions to afford the corresponding products in high yields (entry 1-6). The electron-donating group (OMe) on the meta-position of aromatic ring 2b reacted with 1a albeit with decreased linear selectivity.
Allylic carbonates having heteroarenes such as furan and thiazole were suitable substrates (entry 7-8). Simple allylic carbonate reacted to afford the corresponding allylation product with high yield (entry 9). The allylic carbonate substrates having acyclic and cyclic alkyl substituted group were suitable in this allylation reaction (entry 10-11). Allylic carbonates having functional groups such as cyano and phthalimide moieties at the terminal of aliphatic chain were compatible with the allylation reaction (entry 12-13).

**Table 3.** Pd catalyzed allylation reaction of various allylic carbonates with $1a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-alkylpyridines</th>
<th>Product</th>
<th>Yield (%)</th>
<th>l/b $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{OCO}_2\text{Bu}$</td>
<td>$\text{OCO}_2\text{Bu}$</td>
<td>95</td>
<td>15:1</td>
</tr>
<tr>
<td>2</td>
<td>$\text{Br}$</td>
<td>$\text{OCO}_2\text{Me}$</td>
<td>80</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>$\text{OCO}_2\text{Bu}$</td>
<td>$\text{OCO}_2\text{Bu}$</td>
<td>95</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>$\text{OCO}_2\text{Me}$</td>
<td>$\text{OCO}_2\text{Me}$</td>
<td>87</td>
<td>99:1</td>
</tr>
<tr>
<td>5</td>
<td>$\text{OCO}_2\text{Bu}$</td>
<td>$\text{OCO}_2\text{Bu}$</td>
<td>95</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>$\text{Me}$</td>
<td>$\text{OCO}_2\text{Bu}$</td>
<td>92</td>
<td>99:1</td>
</tr>
</tbody>
</table>
Reaction conditions: Pd(OAc)$_2$ (5 mol%), Ph-TRAP (5 mol%), 1 (0.2 mmol), cinnamyl tert-butyl carbonate 2a (0.3 mmol), CH$_3$CN (1 mL), 25 °C, 6 h. $^b$ Yield of isolated yield. $^c$ Constitutional isomer ratio: Determined by $^1$H-NMR analysis of crude reaction. $^d$ The reaction were carried out at 40 °C.

**Effect of alkene geometries of allylic carbonates.** Both cis and trans allylic carbonates participated in this allylation reactions, to provide product 3 with the same level of
yield and regioselectivity. The formation of the Z alkene was not observed. In addition, the reaction of secondary allylic carbonate (Z)-2p afforded 3ap with exceptional linear selectivity (>99:1) in high yield. These results indicated that this allylation reaction involve formation of π-allyl palladium species through oxidative addition of allylic carbonate to Pd(0) center. Isomerization of the Pd(II)-allyl complex would be faster than the C–C bond formation reaction, which occurred on the less hindered site of the allyl moiety.

**Figure 2.** Effect of alkene geometries of allylic carbonates.

![Figure 2](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(E or Z)-(2p)</th>
<th>Product Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>l/b&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>93</td>
<td>93:7</td>
</tr>
<tr>
<td>2</td>
<td>Z</td>
<td>91</td>
<td>96:4</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of isolated yield. <sup>b</sup> Constitutional isomer ratio: Determined by <sup>1</sup>H-NMR analysis of crude reaction.

**Conclusion**

The author have developed a palladium-catalyzed linear selective allylation reaction of 2-alkylaazaarenes with substituted primary allylic carbonates without the use of external bases to form the tertiary center at side chain C(α)–H bond with 2-alkylaazaarenes. The use of the large bite angle bisphosphine TRAP ligand was effective for high reaction efficacy and regioselectivity. Owing to the neutral and mild conditions, various functional groups were tolerable. For further detailed reaction mechanism is discussed with the chapter 4.

**Experimental Section**

**Instrumentation and Chemicals**

<sup>1</sup>H (400 MHz) and <sup>13</sup>C (100 MHz) NMR spectra were recorded on a JEOL JNM-ECX spectrometer. Chemical shift values for <sup>1</sup>H, <sup>13</sup>C and <sup>11</sup>B NMR spectra are referenced to Me₄Si (0 ppm) and the residual solvent resonances (77.0 ppm for CHCl₃), respectively. Chemical shifts are reported in δ ppm. High-resolution mass spectra were recorded on a Thermo Fisher Scientific Exactive, JEOL JMS-T100LP mass spectrometer or JEOL JMS-T100GCv mass
spectrometer at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. IR spectra were measured with a Perkin-Elmer Spectrum One. Melting points were determined on a micro melting point apparatus (Yanaco: MP-500D) using micro cover glass. GLC analyses were conducted on a Shimadzu GC-14B equipped with a flame ionization detector. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F254.

All reactions were carried out under a nitrogen atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. Pd(OAc)$_2$ from Aldrich Chemical Co. All solvents for catalytic reactions were degassed via three freeze–pump–thaw cycles before use.

**Experimental Procedures**

**Procedure for Allylic alkylation of 2-ethylpyridine (1a) with cinnamyl tert-butyl carbonate (2a) (Table 1, Entry 6).** In a glove box, (8.6 mg, 0.01 mmol), Pd(OAc)$_2$ (2.4 mg, 0.01 mmol), and anhydrous, degassed MeCN (1.0 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. 2-Ethylpyridine (1a; 21.4 mg, 0.2 mmol) and E-cinnamyl tert-butyl carbonate (2a; 70.3 mg, 0.3 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 25 ºC for 6 h, and the mixture was filtered through a short plug of silica-gel, which was then washed with ethyl acetate (5 mL). The residue was subjected to flash chromatography on silica-gel (hexane/EtOAc) to give (E)-3a (40.6 mg, 0.182 mmol) in 91 % yield.

**Preparation of Substrates**

The starting materials 1a, 1b, 1c, 1f, 1g and 6b is commercially available. The starting materials 1d,$^{13}$ 1e,$^{14}$ 1h,$^{15}$ 1j,$^{16}$ 1k,$^{17}$ 1l,$^{18}$ 1m,$^{19}$ 1n,$^{20}$ 6a,$^{21}$ 2a,$^{22}$ 2b,$^{22}$ 2d,$^{22}$ 2e,$^{23}$ 2f,$^{24}$ 2g,$^{25}$ 2h,$^{22}$ 2i,$^{26}$ 2j,$^{26}$ 2l,$^{22}$ 2p,$^{27}$ and 2p',$^{28}$ are reported in the literatures. Allylic carbonates 2c, 2k, 2m and 2n were prepared through Boc protection form corresponding allylic alcohol.

**(E)-3-(3-bromophenyl)allyl methyl carbonate (2c)**

The title compound (2c) was synthesized via the methyl carbonate protection of allylic alcohol with chloro methyl formate and pyridine (87% yield).
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 3.81 (s, 3H), 4.79 (dd, $J = 6.0$, 1.2 Hz, 1H), 6.29 (dt, $J = 16.0$, 6.4 Hz, 1H), 6.61 (d, $J = 16.0$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.54 (t, $J = 2.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 54.92, 67.94, 122.77, 124.05, 125.29, 129.51, 130.11, 131.01, 132.95, 138.14, 155.57.

**(E)-tert-butyl (5-phenylpent-2-en-1-yl) carbonate (2k)**

The title compound (2k) was synthesized via the Boc protection of allylic alcohol with Boc$_2$O and DMAP (92% yield).

![2k](image)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.49 (s, 9H), 2.38 (q, $J = 8.4$ Hz, 2H), 2.70 (t, $J = 7.2$ Hz, 2H), 4.50 (dd, $J = 6.4$, 0.8 Hz, 1H), 5.59–5.66 (m, 1H), 5.84 (dt, $J = 13.2$, 6.4 Hz, 1H). 7.16–7.22 (m, 3H), 7.26–7.30 (m, 2H). $^{13}$C NMR (CDCl$_3$) $\delta$ 27.76 (3C), 34.03, 35.23, 67.53, 82.01, 124.16, 125.89, 128.33 (2C), 128.37 (2C), 135.82, 141.52, 153.34.

**(E)-tert-butyl (4-cyanohept-2-en-1-yl) carbonate (2m)**

The title compound (2m) was synthesized via the Boc protection of allylic alcohol with Boc$_2$O and DMAP (85% yield).

![2m](image)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.49 (s, 9H), 1.52–1.61 (m, 2H), 1.62–1.71 (m, 2H), 2.11 (q, $J = 7.6$ Hz, 2H), 2.35 (t, $J = 7.2$ Hz, 2H), 4.50 (dd, $J = 6.4$, 0.8 Hz, 1H), 5.58–5.65 (m, 1H), 5.72–5.80 (m, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 16.98, 24.68, 27.72 (3C), 31.23, 67.32, 82.05, 119.55, 124.64, 135.18, 153.28.

**(E)-tert-butyl (7-(1,3-dioxoisooindolin-2-yl)hept-2-en-1-yl) carbonate (2n)**

The title compound (2n) was synthesized via the Boc protection of allylic alcohol with Boc$_2$O and DMAP (87% yield).

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Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.40–1.50 (m, 2H), 1.48 (s, 9H), 1.69 (quint, \(J = 7.2\) Hz, 2H), 2.11 (q, \(J = 7.2\) Hz, 2H), 3.69 (t, \(J = 7.2\) Hz, 2H), 4.48 (d, \(J = 6.4\) Hz, 2H), 5.55–5.62 (m, 1H), 5.73–5.80 (m, 1H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 25.98, 27.73 (3C), 28.05, 31.71, 37.72, 67.52, 81.94, 123.16 (2C), 124.06, 130.03, 132.07, 133.86 (2C), 153.31, 168.41 (2C).

Characterization of Products

\((E)-2-(5\text{-phenylpent-4-en-2-yl})\text{pyridine (3aa)}\)

Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.34 (t, \(J = 6.8\) Hz, 3H), 2.46–2.65 (m, 1H), 2.65–2.72 (m, 1H), 3.05 (sext, \(J = 6.8\) Hz, 1H), 6.13 (dt, \(J = 14.8, 6.8\) Hz, 1H), 6.37 (d, \(J = 15.6\) Hz, 1H), 7.08–7.12 (m, 1H), 7.14–7.19 (m, 2H), 7.22–7.37 (m, 4H), 7.59 (td, \(J = 7.6, 2.0\) Hz, 1H), 8.57 (dd, \(J = 2.8, 0.8\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 20.15, 40.42, 42.09, 121.93, 121.62, 125.95 (2C), 126.86, 128.20 (2C), 128.76, 129.82, 131.38, 136.29, 149.21, 165.59. HRMS–ESI (m/z): [M+H]\(^+\) Calcd for C\(_{16}\)H\(_{18}\)N, 224.14338; found, 224.14346.

\((E)-2-(1\text{-phenyloct-1-en-4-yl})\text{pyridine (3ba)}\)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.83 (t, \(J = 7.2\) Hz, 3H), 1.04–1.15 (m, 1H), 1.16–1.35 (m, 3H), 1.70–1.79 (m, 2H), 2.52–2.68 (m, 2H), 2.83–2.91 (m, 1H), 6.08 (dt, \(J = 15.6, 7.6\) Hz, 1H), 6.32 (d, \(J = 16.0\) Hz, 1H), 7.08–7.12 (m, 2H), 7.17 (sext, \(J = 4.4\) Hz, 1H), 7.25–7.26 (m, 4H), 7.58 (t, \(J = 8.0, 2.0\) Hz, 1H), 8.58 (dd, \(J = 5.6, 2.4\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 14.02, 12.75, 29.73, 34.65, 39.21,
48.11, 121.14, 122.80, 125.93 (2C), 126.80, 128.37 (2C), 128.90, 131.14, 136.01, 137.71, 149.38, 164.57. **HRMS–EI (m/z):** [M] Calcd for C_{19}H_{23}O_{2}N, 265.18305; found, 265.18219.

**(E)-2-(1,6-diphenylhex-5-en-3-yl)pyridine (3ca)**

Isolated by silica gel chromatography (hexane/EtOAc 9:5). Colorless oil. **\(^1\)H NMR** (CDCl\(_3\)) \(\delta\) 2.02–2.21 (m, 2H), 2.48 (t, \(J = 8.4\) Hz, 2H), 2.54–2.64 (m, 1H), 2.63–2.71 (m, 1H), 2.89–2.96 (m, 1H), 6.06 (dt, \(J = 11.8, 7.6\) Hz, 1H), 6.30 (d, \(J = 15.6\) Hz, 1H), 7.09–7.16 (m, 6H), 7.22–7.26 (m, 6H), 7.58 (td, \(J = 7.2, 1.6\) Hz, 1H), 8.61 (d, \(J = 4.8\) Hz, 1H). **\(^{13}\)C NMR** (CDCl\(_3\)) \(\delta\) 33.66, 36.39, 39.24, 47.48, 121.31, 123.06, 125.66, 125.92 (2C), 126.84, 128.23 (2C), 128.34 (3C), 128.47 (2C), 131.34, 136.09, 137.57, 142.22, 149.51, 163.94. **HRMS–ESI (m/z):** [M] Calcd for C_{23}H_{22}N, 313.18305; found, 313.18240.

**(E)-2-(1-phenylocta-1,7-dien-4-yl)pyridine (3da)**

Isolated by silica gel chromatography (hexane/EtOAc 9:5). Colorless oil. **\(^1\)H NMR** (CDCl\(_3\)) \(\delta\) 1.78–1.94 (m, 4H), 2.51–2.59 (m, 1H), 2.62–2.69 (m, 1H), 2.88–2.95 (m, 1H), 4.91–4.98 (m, 2H), 5.72–5.82 (m, 1H), 6.03–6.11 (m, 1H), 6.32, (d, \(J = 16.0\) Hz, 1H), 7.09–7.12 (m, 2H), 7.17 (sext, \(J = 4.4\) Hz, 1H), 7.24–7.25 (m, 4H), 7.57 (td, \(J = 6.4, 5.2\) Hz, 1H), 8.59 (d, \(J = 4.8\) Hz, 1H). **\(^{13}\)C NMR** (CDCl\(_3\)) \(\delta\) 31.60, 33.92, 39.17, 47.38, 114.60, 121.31, 123.06, 125.66, 125.92 (2C), 126.84, 128.23 (2C), 128.34 (3C), 128.47 (2C), 131.34, 136.09, 137.57, 142.22, 149.51, 163.94. **HRMS–ESI (m/z):** [M+H]^+ Calcd for C_{19}H_{22}N, 264.17468; found, 264.17467.

**(E)-2-(1-phenylocta-1,7-dien-4-yl)pyridine (3ea)**

Isolated by silica gel chromatography (hexane/EtOAc 9:5). Colorless oil. **\(^1\)H NMR** (CDCl\(_3\)) \(\delta\) 1.74 (t, \(J = 2.4\) Hz, 3H), 2.56–2.60 (m, 2H), 2.65–2.77 (m, 2H), 3.07 (quint, \(J = 6.8\) Hz, 1H),
6.08 (dt, $J = 15.6, 7.2$ Hz, 1H), 6.36 (d, $J = 15.4$ Hz, 1H), 7.10–7.14 (m, 1H), 7.16–7.18 (m, 2H), 7.23–7.27 (m, 4H), 7.59 (td, $J = 7.6, 2.0$ Hz, 1H), 8.59 (dt, $J = 2.8, 0.8$ Hz, 1H). \textbf{\textsuperscript{13}C NMR} (CDCl$_3$) $\delta$ 3.51, 24.28, 37.60, 47.21, 121.53, 122.90, 125.96 (2C), 126.90, 128.12, 128.37 (2C), 131.69, 136.01, 137.55, 149.34, 162.85. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{19}$H$_{20}$N, 262.15903; found, 262.15907.

\textbf{7-cinnamyl-6,7-dihydro-5H-cyclopenta}[b]pyridine (3fa)

![Chemical structure of 3fa]

Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. \textbf{\textsuperscript{1}H NMR} (CDCl$_3$) $\delta$ 1.82–1.91 (m, 1H), 2.28–2.36 (m, 1H), 2.38–2.46 (m, 1H), 2.80–2.99 (m, 3H), 3.28–3.35 (m, 1H), 6.26 (dt, $J = 14.4, 7.2$ Hz, 1H), 6.47 (d, $J = 16.0$ Hz, 1H), 7.04 (dd, $J = 8.0, 5.2$ Hz, 1H), 7.17–7.21 (m, 1H), 7.30 (t, $J = 7.6$ Hz, 1H), 7.37–7.35 (m, 2H), 7.49 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.40 (d, $J = 5.2$ Hz, 1H). \textbf{\textsuperscript{13}C NMR} (CDCl$_3$) $\delta$ 28.97, 29.14, 37.20, 45.34, 121.36, 125.97 (2C), 126.89, 128.42 (2C), 128.60, 131.39, 132.18, 136.92, 137.63, 147.61, 166.80. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{17}$H$_{18}$N, 236.14338; found, 236.14336.

\textbf{8-cinnamyl-5,6,7,8-tetrahydroquinoline (3ga)}

![Chemical structure of 3ga]

Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. \textbf{\textsuperscript{1}H NMR} (CDCl$_3$) $\delta$ 1.69–2.00 (m, 4H), 2.48 (dt, $J = 10.8, 8.0$ Hz, 1H), 2.70–2.82 (m, 2H), 2.96–3.08 (m, 2H), 6.25–6.31 (m, 1H), 6.45 (d, $J = 15.6$ Hz, 1H), 7.03–7.05 (m, 1H), 7.17–7.23 (m, 1H), 7.29 (t, $J = 7.6$ Hz, 2H), 7.34–7.37 (m, 3H), 8.43 (dd, $J = 5.6, 2.0$ Hz, 1H). \textbf{\textsuperscript{13}C NMR} (CDCl$_3$) $\delta$ 19.76, 27.17, 29.20, 38.72, 40.75, 120.94, 125.97, 126.84, 128.44, 129.47, 131.47, 132.44, 136.74, 137.75, 146.94, 159.61. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{18}$H$_{20}$N, 250.15903; found, 250.15913.

\textbf{(E)-2-(7-chloro-1-phenylept-1-en-4-yl)pyridine (3ha)}
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.19–1.43 (m, 2H), 1.67–1.85 (m, 4H), 2.52–2.68 (m, 2H), 2.88 (dquint, $J = 6.8$, 0.8 Hz, 1H), 3.41–3.49 (m, 2H), 6.07 (dt, $J = 14.4$, 7.6 Hz, 1H), 6.32 (d, $J = 15.6$ Hz, 1H), 7.11 (td, $J = 6.0$, 0.8 Hz, 2H), 7.17 (sext, $J = 4.0$ Hz, 1H), 7.25–7.26 (m, 4H), 7.58 (td, $J = 7.6$, 2.0 Hz, 1H), 8.58 (dd, $J = 2.0$, 1.6 Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 24.80, 32.59, 33.98, 39.19, 44.91, 47.92, 121.32, 122.89, 125.93 (2C), 126.88, 128.38 (2C), 128.51, 131.37, 136.12, 137.57, 149.46, 163.97. HRMS–EI ($m/z$): [M] Calcd for C$_{19}$H$_{22}$NCl, 299.14408; found, 299.14333.

$^{(E)}$-2-$(1-((tert-butyldimethylsilyl)oxy)-5-phenylpent-4-en-2-yl)pyridine (3ja)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ -0.10 (s, 3H), -0.07 (s, 3H), 0.82 (s, 9H), 2.63-2.75 (m, 2H), 3.09 (quint, $J = 6.4$ Hz, 1H), 3.85–3.92 (m, 2H), 6.12 (dt, $J = 15.6$, 7.6 Hz, 1H), 6.36 (d, $J = 16.0$ Hz, 1H), 7.09–7.12 (m, 1H), 7.15–7.19 (m, 2H), 7.24–7.26 (m, 4H), 7.57 (td, $J = 7.6$, 2.0 Hz, 1H), 8.57 (dd, $J = 4.8$, 0.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ -5.57 (2C), 18.19, 25.81 (3C), 34.49, 50.46, 66.26, 121.44, 123.96, 125.93 (2C), 126.84, 128.37 (2C), 128.53, 131.32, 135.78, 137.66, 149.23, 162.26. HRMS–EI ($m/z$): [M] Calcd for C$_{22}$H$_{31}$NOSi, 353.21749; found, 353.21669.

$^{(E)}$-2-$(1-(1,3-dioxolan-2-yl)-5-phenylpent-4-en-2-yl)pyridine (3ka)

Isolated by silica gel chromatography (hexane/EtOAc 70:30). White solid. $^1$H NMR (CDCl$_3$) $\delta$ 2.02 (ddd, $J = 13.8$, 6.6, 4.8 Hz, 1H), 2.27–2.34 (m, 1H), 2.56–2.71 (m, 2H), 3.12–3.20 (m, 1H), 3.71–3.81 (m, 2H), 3.89–3.94 (m, 2H), 4.67 (ddd, $J = 7.2$, 4.0 Hz, 1H), 6.06 (dt, $J = 15.6$, 8.0 Hz, 1H), 6.32 (d, $J = 16.0$ Hz, 1H), 7.09–7.19 (m, 3H), 7.23–7.26 (m, 4H), 7.57 (td, $J =
7.6, 1.6 Hz, 1H), 8.59 (ddd, J = 6.0, 1.8, 0.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 38.60, 39.47, 43.62, 64.71, 64.75, 103.10, 121.36, 123.16, 125.98, 126.89, 128.16, 128.36, 131.69, 136.11, 137.58, 149.46, 163.43. HRMS–EI (m/z): [M] Calcd for C$_{19}$H$_{21}$NO$_2$, 295.15723; found, 295.15648.

$(E)$-N-(5-phenyl-2-(pyridin-2-yl)pent-4-en-1-yl)pivalamide (3la)

Isolated by silica gel chromatography (hexane/EtOAc 70:30). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.13 (s, 9H), 2.55–2.70 (m, 2H), 3.15–3.22 (m, 1H), 3.58–3.71 (m, 2H), 6.07–6.14 (m, 1H), 6.34 (d, J = 16.0 Hz, 1H). 6.65 (br, 1H), 7.13–7.19 (m, 3H), 7.23–7.26 (m, 4H), 7.61 (td, J = 7.6, 2.0 Hz, 1H), 8.58 (d, J = 4.4 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 27.48, 36.50, 38.62, 42.90, 46.27, 121.80, 123.58, 126.01, 127.02, 127.52, 128.39, 131.91, 136.55, 137.34, 149.24, 162.54, 178.42. HRMS–EI (m/z): [M] Calcd for C$_{21}$H$_{26}$N$_2$O, 322.20451; found, 322.20361.

ethyl $(E)$-7-phenyl-4-(pyridin-2-yl)hept-6-enoate (3ma)

Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.21 (t, J = 7.6 Hz, 3H), 2.06–2.20 (m, 4H), 2.54–2.61 (m, 1H), 2.63–2.71 (m, 1H), 2.92 (quint, J = 8.0 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 6.07 (dt, J = 14.4, 7.6 Hz, 1H), 6.33 (d, J = 16.0 Hz, 1H), 7.10–7.20 (m, 3H), 7.23–7.26 (m, 4H), 7.59 (td, J = 7.6, 2.0 Hz, 1H), 8.58 (dd, J = 3.6, 2.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 14.18, 29.72, 32.25, 39.11, 47.27, 60.24, 121.50, 123.08, 125.96 (2C), 126.90, 128.17, 128.37 (2C), 131.56, 136.24, 137.52, 149.55, 163.15, 173.43. HRMS–EI (m/z): [M] Calcd for C$_{20}$H$_{23}$NO$_2$, 309.17288; found, 309.17183.

$(E)$-8-phenyl-5-(pyridin-2-yl)oct-7-en-2-one (3na)
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.98–2.13 (m, 2H), 2.05 (s, 3H), 2.23–2.37 (m, 2H), 2.56 (quint, \(J = 6.8\) Hz, 1H), 2.66 (quint, \(J = 6.8\) Hz, 1H), 2.86–2.93 (m, 1H), 6.07 (dt, \(J = 14.4, 7.6\) Hz, 1H), 6.33 (d, \(J = 15.2\) Hz, 1H), 7.09–7.19 (m, 3H), 7.24–7.26 (m, 4H), 7.60 (quint, \(J = 6.8\) Hz, 1H), 8.58 (d, \(J = 4.4\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 28.59, 29.89, 39.23, 41.49, 47.21, 121.51, 122.91, 125.96 (2C), 126.92, 128.18, 128.38 (2C), 131.57, 136.29, 137.51, 149.50, 163.42, 208.71. HRMS–ESI \((m/z)\): [M+H]\(^+\) Calcd for C\(_{19}\)H\(_{22}\)NO, 280.16959; found, 280.16981.

\((E)-2-(5-(4-methoxyphenyl)pent-4-en-2-yl)pyridine (3ab)\)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.34 (d, \(J = 6.8\) Hz, 3H), 2.47 (quint d, \(J = 8.0, 1.6\) Hz, 1H), 2.66 (quint d, \(J = 8.4, 1.6\) Hz, 1H), 3.03 (sext, \(J = 7.2\) Hz, 1H), 3.78 (s, 3H), 6.00 (td, \(J = 8.0, 1.2\) Hz, 1H), 6.31 (d, \(J = 15.6\) Hz, 1H), 6.81 (td, \(J = 6.0, 3.2\) Hz, 2H), 7.08–7.12 (m, 1H), 7.13–7.15 (m, 1H), 7.22 (d, \(J = 8.8\) Hz, 2H), 7.59 (td, \(J = 7.6, 2.0\) Hz, 1H), 8.56 (dt, \(J = 8.0, 0.8\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 20.12, 40.44, 42.23, 55.24, 113.81, 121.15, 121.62, 126.59 127.04, 130.52, 130.71, 136.26, 149.22, 158.65, 165.73. HRMS–ESI \((m/z)\): [M] Calcd for C\(_{15}\)H\(_{17}\)NO, 253.14666; found, 253.14608.

\((E)-2-(5-(3-bromophenyl)pent-4-en-2-yl)pyridine (3ac)\)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.34 (d, \(J = 6.8\) Hz, 3H), 2.46–2.53 (m, 1H), 2.65–2.74 (m, 1H), 3.05 (sext, \(J = 7.2\) Hz, 1H), 6.14 (dt, \(J = 15.6, 7.6\) Hz, 1H), 6.28 (d, \(J = 16.0\) Hz, 1H), 7.10–7.19 (m, 4H), 7.28–7.30 (m, 1H), 7.40–7.43 (m, 1H), 7.61 (td, \(J = 8.0, 2.0\) Hz, 1H), 8.57 (dd, \(J = 4.8, 0.8\) Hz, 1H). \(^13\)C
NMR (CDCl$_3$) $\delta$ 20.22, 40.33, 41.97, 121.28, 121.63, 122.61, 124.64, 128.79, 129.71, 129.90, 130.02, 130.49, 136.35, 139.81, 149.26, 165.35. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{16}$H$_{17}$NBr, 302.05389; found, 302.05405.

(E)-2-(5-(4-(trifluoromethyl)phenyl)pent-4-en-2-yl)pyridine (3ad)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.35 (d, $J = 7.2$ Hz, 3H), 2.49–2.56 (m, 1H), 2.66–2.75 (m, 1H), 3.08 (sext, $J = 6.8$ Hz, 1H), 6.20–6.28 (m, 1H), 6.38 (d, $J = 16.0$ Hz, 1H), 7.11–7.17 (m, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 7.61 (td, $J = 8.0$, 2.0 Hz, 1H), 8.57 (dd, $J = 4.4$, 0.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 20.24, 40.47, 41.94, 52.00, 121.30, 121.63, 125.80 (2C), 128.31, 129.80 (2C), 130.62, 131.81, 136.37, 142.14, 149.26, 165.30, 166.94. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{18}$H$_{20}$NO$_2$, 282.14886; found, 282.14877.

methyl (E)-4-(4-(pyridin-2-yl)pent-1-en-1-yl)benzoate (3ae)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.35 (d, $J = 6.8$ Hz, 3H), 2.49–2.56 (m, 1H), 2.69–2.75 (m, 1H), 3.07 (sext, $J = 7.2$ Hz, 1H), 3.89 (s, 3H), 6.27 (dt, $J = 14.4$, 6.8 Hz, 1H), 6.40 (d, $J = 16.0$ Hz, 1H), 7.10–7.16 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.61 (td, $J = 7.6$, 1.6 Hz, 1H), 7.93 (d, $J = 8.4$ Hz, 2H), 8.58 (d, $J = 3.6$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 20.24, 40.47, 41.94, 52.00, 121.30, 121.63, 125.80 (2C), 128.31, 129.80 (2C), 130.62, 131.81, 136.37, 142.14, 149.26, 165.30, 166.94. HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{18}$H$_{20}$NO$_2$, 282.14886; found, 282.14877.

(E)-2-(5-(naphthalen-2-yl)pent-4-en-2-yl)pyridine (3af)
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.37 (d, $J = 7.2$ Hz, 3H), 2.51–2.58 (m, 1H), 2.71–2.77 (m, 1H), 3.09 (sext, $J = 7.2$ Hz, 1H), 6.23–6.31 (m, 6H), 6.52 (d, $J = 15.6$ Hz, 1H), 7.11 (dd, $J = 6.8$, 5.2 Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.37–7.46 (m, 2H), 7.52 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.57–7.62 (m, 2H), 7.71–7.77 (m, 3H), 8.58 (d, $J = 4.8$ Hz, 1H).

$^{13}$C NMR (CDCl$_3$) δ 20.19, 40.57, 42.10, 121.23, 121.66, 123.50, 125.44, 126.08, 127.55, 127.77, 127.95, 129.22, 131.50, 132.62, 133.58, 135.08, 136.34, 149.21, 165.55. HRMS–EI (m/z): [M] Calcd for C$_{20}$H$_{19}$N, 273.15175; found, 273.15156.

(E)-2-(5-(o-tolyl)pent-4-en-2-yl)pyridine (3ag)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.35 (d, $J = 6.8$ Hz, 3H), 2.23 (s, 3H), 2.52 (quint d, $J = 7.2$, 1.6 Hz, 1H), 2.71 (quint d, $J = 6.8$, 1.2 Hz, 1H), 3.06 (sext, $J = 6.8$ Hz, 1H), 5.99 (dt, $J = 14.4$, 7.2 Hz, 1H), 6.52 (d, $J = 15.6$ Hz, 1H), 7.08–7.35 (m, 7H), 7.59 (td, $J = 8.4$, 1.6 Hz, 1H), 8.57 (dd, $J = 5.2$, 1.2 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 19.74, 20.20, 40.71, 42.14, 121.17, 121.75, 125.51, 125.91, 126.83, 129.45, 130.03, 130.10, 134.94, 136.26, 136.92, 149.23, 165.61. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{17}$H$_{20}$N, 238.15903; found, 238.15906.

(E)-2-(5-(furan-2-yl)pent-4-en-2-yl)pyridine (3ah)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.33 (d, $J = 7.2$ Hz, 3H), 2.42–2.49 (m, 1H), 2.64–2.71 (m, 1H), 3.03 (sext, $J = 6.8$ Hz, 1H), 6.04–6.12 (m, 1H), 6.19 (d, $J = 15.6$ Hz, 1H), 6.32 (dd, $J = 3.2$, 2.0 Hz, 1H), 7.09–7.13 (m, 1H), 7.15 (d, $J = 7.6$ Hz, 1H), 7.26–7.28 (m, 1H), 7.60 (td, $J = 7.6$, 1.6 Hz, 1H), 8.57 (dd, $J = 2.0$, 0.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 20.16, 40.23, 42.00, 106.24, 111.05, 120.00, 121.22, 121.66, 127.75, 136.32, 141.25, 149.25, 153.06, 165.52. HRMS–ESI (m/z): [M] Calcd for C$_{14}$H$_{15}$NO, 213.11536; found, 213.11576.
(E)-2-(5-(thiophen-3-yl)pent-4-en-2-yl)pyridine (3ai)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.33 (d, \(J = 6.8\) Hz, 3H), 2.41–2.49 (m, 1H), 2.62–2.69 (m, 1H), 3.03 (sext, \(J = 6.4\) Hz, 1H), 5.99 (dt, \(J = 14.8, 6.8\) Hz, 1H), 6.38 (d, \(J = 15.6\) Hz, 1H), 7.01 (d, \(J = 2.8\) Hz, 1H), 7.09–7.15 (m, 3H), 7.21 (dd, \(J = 5.2, 3.2\) Hz, 1H), 7.59 (td, \(J = 8.0, 2.0\) Hz, 1H), 8.56 (d, \(J = 4.4\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 20.14, 40.30, 42.06, 120.59, 121.16, 121.58, 124.92, 125.61, 125.66, 128.68, 136.27, 140.22, 149.20, 165.58. HRMS–ESI (m/z): [M+H]\(^+\) Calcd for C\(_{15}\)H\(_{21}\)N\(_2\), 229.16993; found, 229.16997.

2-(pent-4-en-2-yl)pyridine (3aj)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.30 (d, \(J = 6.8\) Hz, 3H), 2.30–2.38 (m, 1H), 2.50–2.57 (m, 1H), 2.94 (sext, \(J = 6.8\) Hz, 1H), 4.94–5.02 (m, 2H), 5.68–5.78 (m, 1H), 7.0–7.14 (m, 2H), 7.60 (td, \(J = 8.0, 2.0\) Hz, 1H), 8.55 (d, \(J = 4.0\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 20.09, 41.26, 41.71, 116.07, 121.12, 121.58, 124.92, 125.61, 125.66, 128.68, 136.27, 140.22, 149.20, 165.71.

(E)-2-(7-phenylhept-4-en-2-yl)pyridine (3ak)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.25 (d, \(J = 6.8\) Hz, 3H), 2.22–2.28 (m, 3H), 2.40–2.47 (m, 1H), 2.60 (t, \(J = 8.4\) Hz, 2H), 2.89 (sext, \(J = 6.8\) Hz, 1H), 5.29–5.46 (m, 2H), 7.06–7.18 (m, 5H), 7.22–7.27 (m, 2H), 7.58 (td, \(J = 7.6, 1.6\) Hz, 1H), 8.54 (dd, \(J = 4.4, 0.8\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 19.96, 34.36, 35.99, 40.06, 42.09, 121.02, 121.60, 125.65, 128.18 (2C), 128.42 (2C), 128.78, 131.25, 136.14, 142.03, 149.10, 165.94.

(E)-2-(5-cyclohexylpent-4-en-2-yl)pyridine (3al)

119
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \( ^1H \text{NMR} \) (CDCl\(_3\)) \( \delta \) 0.91-1.02 (m, 2H), 1.05-1.23 (m, 3H), 1.28 (d, \( J = 7.2 \) Hz, 3H), 1.56-1.70 (m, 5H), 1.79-1.87 (m, 1H), 2.21-2.28 (m, 1H), 2.38-2.44 (m, 1H), 2.91 (sext, \( J = 7.6 \) Hz, 1H), 5.23-5.34 (m, 2H), 7.07-7.11 (m, 2H), 7.58 (td, \( J = 8.0, 2.0 \) Hz, 1H), 8.54 (d, \( J = 4.8 \) Hz, 1H). \( ^{13}C \text{NMR} \) (CDCl\(_3\)) \( \delta \) 19.87, 26.00, 26.16, 33.07, 33.12, 40.22, 40.65, 42.25, 120.97, 121.65, 125.28, 136.08, 138.43, 149.07, 166.03. \( \text{HRMS–ESI (m/z)} \): [M+H]\(^+\) Calcd for C\(_{16}\)H\(_{24}\)N, 230.19033; found, 230.19061.

\( (E)-9-(\text{pyridin}-2-\text{yl})\text{dec}-6\)-enenitrile (3am) \( \)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \( ^1H \text{NMR} \) (CDCl\(_3\)) \( \delta \) 1.28 (d, \( J = 6.8 \) Hz, 3H), 1.38-1.46 (m, 2H), 1.47-1.56 (m, 2H), 2.27 (t, \( J = 6.8 \) Hz, 2H), 2.25-2.32 (m, 1H), 2.42-2.48 (m, 1H), 2.93 (sext, \( J = 6.8 \) Hz, 1H), 5.27-5.38 (m, 2H), 7.09-7.13 (m, 2H), 7.61 (td, \( J = 7.6, 1.6 \) Hz, 1H), 8.55 (d, \( J = 4.4 \) Hz, 1H). \( ^{13}C \text{NMR} \) (CDCl\(_3\)) \( \delta \) 16.91, 20.17, 24.47, 28.20, 31.46, 40.03, 42.07, 119.74, 121.12, 121.65, 129.31, 130.76, 136.29, 149.06, 165.76. \( \text{HRMS–ESI (m/z)} \): [M+H]\(^+\) Calcd for C\(_{15}\)H\(_{21}\)N\(_2\), 229.16993; found, 229.17006.

\( (E)-2-(8-(\text{pyridin}-2-\text{yl})\text{non}-5\)-en-1-yl)\text{isoindoline}-1,3-dione (3an) \( \)

Isolated by silica gel chromatography (hexane/EtOAc 80:20). Colorless oil. Colorless oil. \( ^1H \text{NMR} \) (CDCl\(_3\)) \( \delta \) 1.27 (d, \( J = 7.2 \) Hz, 3H), 1.30-1.36 (m, 2H), 1.58 (quint, \( J = 7.6 \) Hz, 2H), 1.95-1.99 (m, 2H), 2.24-2.29 (m, 1H), 2.40-2.45 (m, 1H), 2.92 (sext, \( J = 6.8 \) Hz, 1H), 3.64 (t, \( J = 7.2 \) Hz, 2H), 5.27-5.37 (m, 2H), 7.06-7.12 (m, 2H), 7.58 (td, \( J = 7.6, 1.6 \) Hz, 1H), 7.70 (dd, \( J = 5.6, 2.4 \) Hz, 1H), 7.84 (dd, \( J = 5.2, 2.4 \) Hz, 1H), 8.53 (d, \( J = 4.4 \) Hz, 1H). \( ^{13}C \text{NMR} \) (CDCl\(_3\)) \( \delta \) 20.03, 26.62, 27.93, 31.99, 37.84, 40.03, 42.00, 121.07, 121.69, 123.12 (2C), 120.
128.63, 131.52, 132.11, 133.84 (2C), 136.32, 148.89, 165.81, 168.40. **HRMS–ESI** (m/z): [M+H]^+ Calcd for C_{22}H_{25}N_{2}O_{2}, 349.19105; found, 349.19107.

*(E)-2-(1,5-diphenylpent-4-en-2-yl)-1-methyl-1H-benzo[d]imidazole (6a)*

![Diagram of 6a](https://via.placeholder.com/150)

Isolated by silica gel chromatography (hexane/EtOAc 70:30). White solid. **^1H NMR** (CDCl$_3$) \(\delta\) 2.77-2.84 (m, 1H), 2.95-3.04 (m, 1H), 3.18-3.21 (m, 2H), 3.24-3.31 (m, 1H), 6.11 (dt, \(J = 14.4, 6.4\) Hz, 1H), 6.98 (dd, \(J = 7.2, 2.4\) Hz, 2H), 7.14-7.19 (m, 5H), 7.21-7.29 (m, 6H), 7.82 (dd, \(J = 6.8, 1.2\) Hz, 1H). **^13C NMR** (CDCl$_3$) \(\delta\) 29.06, 38.21, 40.81, 41.75, 109.13, 119.23, 121.78, 121.85, 126.05 (2C), 126.37, 127.14, 127.50, 128.37 (2C), 128.43 (2C), 128.94 (2C), 132.30, 135.14, 137.23, 139.65, 142.69, 157.01. **HRMS–ESI** (m/z): [M+H]^+ Calcd for C$_{22}$H$_{25}$N$_2$O$_2$, 353.20123; found, 353.20133.

*(E)-3-(1-(3,4-dimethoxyphenyl)-4-phenylbut-3-en-1-yl)-6,7-dimethoxyisoquinoline (6b)*

![Diagram of 6b](https://via.placeholder.com/150)

Isolated by silica gel chromatography (hexane/EtOAc 70:30). Colorless oil. **^1H NMR** (CDCl$_3$) \(\delta\) 3.09 (quint, \(J = 6.8\) Hz, 1H), 3.40 (quint, \(J = 6.0\) Hz, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 4.74 (t, \(J = 7.6\) Hz, 1H), 6.26 (dt, \(J = 14.2, 6.8\) Hz, 1H), 6.44 (d, \(J = 16.0\) Hz, 1H), 6.76 (d, \(J = 8.4\) Hz, 1H), 6.89–6.93 (m, 2H), 7.01 (s, 1H), 7.12-7.16 (m, 1H), 7.20-7.27 (m, 4H), 7.40-7.42 (m, 2H), 8.47 (d, \(J = 5.6\) Hz, 1H). **^13C NMR** (CDCl$_3$) \(\delta\) 39.31, 49.47, 55.68 (2C), 55.86, 103.53, 105.26, 110.87 (2C), 118.41, 120.05, 122.75, 125.87 (2C), 126.75, 128.30 (2C), 129.47, 131.11, 133.19, 136.36, 137.66, 140.58, 147.44, 148.91, 149.55, 152.07, 159.05. **HRMS–ESI** (m/z): [M+H]^+ Calcd for C$_{29}$H$_{30}$N$_2$O$_4$, 456.21693; found, 456.21713.
References


Chapter 4

Pd-catalyzed Enantioselective Allylation of 2-Alkylpyridines

Palladium-catalyzed enantioselective allylation reaction of 2-alkylpyridines without the use of external bases has been developed. This reaction occurred with exceptional linear selectivity and enantioselectivity under mild conditions by using a newly developed chiral monophosphine ligand.
Introduction

2-Alkylpyridines having a stereogenetic center on the side chain C(α) position are widely found in biologically active compounds, agrochemicals and natural products\(^1\). Therefore, the development of asymmetric catalysts for enantioselective transformations of the alkyl side chain of pyridine substrates is important in organic synthesis. Recently, the use of 2-alkylazaarenes as pronucleophiles in asymmetric catalysis has received much attention because of atom- and step-economical approach. However, in many cases, using stoichiometric amounts of strong bases\(^2\) or introducing electron-withdrawing groups to azaarene substrates\(^3\) were required to generate nucleophilic enamide species via deprotonation of the side chain C(α) position, resulting in limited applicability.

In Chapter 3, the author disclosed that palladium-catalyzed side chain C(α) allylation of 2-alkylaazaarenes with allylic carbonates without the use of external bases. Owing to the neutral and mild conditions, this catalyst system exhibited broad functional group compatibility. This results encouraged the author to extend this protocol to the asymmetric version.

This chapter describes the enantioselective side chain C(α) allylation of 2-alkylpyridines with the Pd catalyst system using a newly synthesized chiral diamidophosphine ligand. This reaction occurred with exceptional regioselectivity to provide an allyl-substituted stereogenic tertiary carbon center at the side chain C(α) position of 2-alkylaazaarenes.

Results and Discussion

Ligand screening for Pd-catalyzed enantioselective allylation of 1a with 2a. Initially, various chiral phosphine ligands were examined in the reaction between 1a and 2a with 5 mol% of Pd(db)\(_2\) as a Pd source in MeCN at 25 °C for 12 h (Table 2). Although (S,S)-(R,R)-Ph-TRAP\(^4\) (L1), describing the usefulness in the non-asymmetric allylation reactions in Chapter 3, induced only low enantioselectivity (11% ee, entry 1), a more bulky 3,5-di-phenyl-subsitututed TRAP-type ligand L2\(^5\) improved the enantioselectivity to 56% ee. In contrast, biferrocene-based bis(oxazoline) ligand L3 produced no reaction (entry 3). The Trost ligands L3 and L4\(^2b\), which was employed in the side chain C(α)-allylation in combination with a stoichiometric amount of BF\(_3\)-OEt\(_2\) and LHMD, induced no activity. (entry 4 and 5). Although binol- and spinol-based monodentate phosphoramidite ligands (L6\(^6\) and L7) induced no reaction, a biphenol-based phosphoramidite ligand (L8) promoted the allylation with inefficient enantioselectivity (−42% ee, entry 8). D-Mannitol-based ligand
(L9)\(^7\) gave a high yield and moderate enantioselectivity (53\% ee, entry 9).

After further screening of chiral ligands, diamidophosphate-type ligands were good candidates for the present asymmetric side chain C(\(\alpha\)) allylation. The diamidophosphate ligand can be synthesized for versatile structural modification (Scheme 1). 1,3-propanediol-based bis(diamidophosphate) ligand was effective to give 3a in high yield and 60\% ee (entry 9). 1,4-butanediol and 1,5-pentanediol-based ligands also gave a high yield and moderate enantioselectivity (entry 10 and 11). Further enantioselectivity was improved by using chiral diol-based bis(diamidophosphate) ligand (entry 13-16). Accordingly, (2S,5S)-2,5-hexanediol-based bis(diamidophosphate) ligand L14 increased enantioselectivity to 62\% (entry 14), albeit the Ph-DPEN-based bis(diamidophosphate) ligand L13\(^8\) did not form an active catalyst (entry 13). The use of taddol-derived bis phosphorodiamidite ligand L15 gave better product yield, but induced slightly lower enantioselectivity (entry 15). Specifically, Isomannide-based bis(diamidophosphate) ligand\(^9\) L16 featuring a large bite angle and a rigid structure similar to TRAP-type ligands, was effective for increasing both enantioselectivity and catalytic activity (entry 16).

**Table 1.** Screening of chiral ligand for the enantioselective reaction between 1a and 2a\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)[b]</th>
<th>Ee, % [c]</th>
<th>3a/4a[^d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>97</td>
<td>11</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>94</td>
<td>56</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
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<td></td>
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<tr>
<td>7</td>
<td>L7</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>L8</td>
<td>99</td>
<td>-42</td>
<td>97:3</td>
</tr>
<tr>
<td>9</td>
<td>L9</td>
<td>94</td>
<td>53</td>
<td>99:1</td>
</tr>
<tr>
<td>10</td>
<td>L10</td>
<td>87</td>
<td>60</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>11</td>
<td>L11</td>
<td>91</td>
<td>61</td>
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</tr>
<tr>
<td>12</td>
<td>L12</td>
<td>96</td>
<td>64</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

---

[^a]: Yields and enantiomeric excesses were determined by 
NMR spectroscopy. 
[^b]: Yield is based on consumption of 1a. 
[^c]: Ee measured by HPLC analysis. 
[^d]: Isolation yield of product 3a.
Reaction conditions: Pd(OAc)$_2$ (5 mol%), ligand (P: 10 mol%), 1a (0.2 mmol), 2a (0.3 mmol), CH$_3$CN (1 mL), 25 ºC, 12 h. $^b$Yield of isolated yield. $^c$Determined by HPLC analysis. $^d$Constitutional isomer ratio: Determined by $^1$H-NMR analysis of crude reaction.
Scheme 1. Synthesis of chiral diamidophosphate ligands.

Modification of Ligand. The change of the N-phenyl group of L16 to various functional group was summarized in Table 2 (entry 1-6). The use of L17 and L18 which aryl moiety was introduced by the substituent into ortho-position induced no reaction (entry 1 and 2). When ligand L19 and L20 having methyl group and fluoro group at the meta position into N-aryl group was used for enantioselective allylation, the low enantioselectivity and reactivity was observed (entry 3-5). 4-fluorophenyl group (L21) slightly improved the enantioslectivity (entry 6). 4-trifluoromethyl group (L22) gave product in high yield, but induced lower enantioselectivity.

During this study, it revealed that an isomannide-based monodentate diamidophosphate ligand showed high performance (entry 7-12). L24, introducing a benzoyl protected alcohol group, was effective for enantioselective allylation (entry 7). From this result, it found that the second phosphorus atom was not required necessarily for expression of enantioselectivity. L24, having a benzyl-protected alcohol moiety, showed higher ligand performance than bis(diamidophosphate) analogues L21 (entry 8). The enantioselectivity was not changed by using the L25, having silyl-protected alcohol moiety (entry 9 and 10). Finally, trityl-protected monophosphine L26 was determined to be most effective to give the linear allylation product in 84% ee at 25 °C (entry 11). The enantioselectivity was improved to 93%ee by lowering the reaction temperature to –20 °C (for 36 h) without significant loss of the conversion (91% yield) (entry 12).

Table 2. Modification of ligand for the enantioselective reaction between 1a and 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%) b</th>
<th>Ee (%) c</th>
<th>3a/4a d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L17</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>L18</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>L19</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>L20</td>
<td>98</td>
<td>38</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

a. Reaction conditions: 1a (0.5 mmol), 2a (1.0 mmol), Ph3PO (0.1 mmol), L (0.01 mmol), DMAP (0.01 mmol), allylbromide (0.04 mmol), THF, room temperature.
Determination of Absolute Configuration. The title compound 3a was subjected to ozonolysis and reduction. Ir-catalyzed decarbonylation of aldehyde compound 9 was carried out to afford the compound 10\textsuperscript{11}. Next, Ir-Silica-SMAP-catalyzed C(sp\textsuperscript{3})–H borylation of compound 11\textsuperscript{12} was carried out to give the corresponding borylation product 12, and then desired alcohol product 13\textsuperscript{13} was given by oxidation of alkylboronate 12. Absolute
Stereochemistry was assigned by optical rotation determination.

**Scope of 2-alkylpyridines.** With the Pd(dba)$_2$/L catalyst system, the scope of 2-alkylazaarenes was investigated (in CH$_3$CN at $-20$ to $-10$ °C). The results are summarized in Table 3. N-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine underwent selective allylation at C(sp$^3$)–H bond located β to the pyridine N atom 3b. 2,3-Cyclopentenopyridine was converted to C($\alpha$)-allylation product 3c. Non-fused 2-alkylpyridines were suitable substrates (–10 °C, 36 h), but their enantioselectivities were slightly decreased than those of fused ones (entry 3-9). The silyl ether, methoxymethyl and acetal moiety in 2-alkylpyridine substrates were tolerated to give the corresponding allylation product in moderate enantioselectivity (entry 4-6). An acidic NH group of the secondary amide moiety in 2-alkylpyridine substrate 1h did not hampered the allylation and desired product 3h was obtained in 78% ee (entry 7). Notably, ketone or ester groups, which had $\alpha$-carbonyl C–H bonds more acidic than that of azabenzylc positions, were compatible in the allylation, and only side chain C($\alpha$) allylation products were obtained in high yields and high enantioselectivities (entry 8 and 9).

**Table 3.** Scope of enantioselective allylation reaction with 2-Alkylpyridines$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Alkylpyridine 1</th>
<th>Product 3</th>
<th>Yield (%)$^b$</th>
<th>Ee (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-N-Ph</td>
<td>3b</td>
<td>95</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1) O$_3$/MeOH/CH$_2$Cl$_2$ at -78 °C for 10 min; 2) Me$_2$S (5 equiv) in MeOH/CH$_2$Cl$_2$ at -78 °C to rt, 5 h; 3) [IrCl(cod)]$_2$ (Ir: 5 mol%), PPh$_3$ (5 mol%) in dioxane at 110 °C for 12 h. $^b$NMR yield. $^c$Optical rotation.
Scope of allylic carbonates. Enantioenriched tertiary tertiary carbon at the C(α) position of 1,2,3,4-tetrahydroquinoline (1a) were obtained through the Pd-catalyzed allylation with various cinnamyl carbonates (Table 4). The electron-donating group (OMe) on the para-position of aromatic ring 2b reacted with high product yield, linear selectivity and
enantioselectivity (entry 1). The cinnamyl carbonates disubstituted functional group on aromatic ring such as 3,5-diOMe and benodioxole reacted at –20 °C to afford the corresponding allylation product in good yield with high enantioselectivity (entry 2 and 3). On the other hand, the substitution of the aromatic ring with electro-withdrawing Br group result in the slightly decrease in the enantioselectivity (entry 4). The 1-naphthyl allylic carbonate 2g reacted with high yield and enantioselectivity (entry 5). Allylic carbonates having heteroarenes such as furan, thiazole and indole were suitable substrates (entry 6, 7 and 8).

**Table 4.** Scope of enantioselective allylation reaction with allylic carbonates

<table>
<thead>
<tr>
<th>entry</th>
<th>Allylic carbonate 2</th>
<th>Product 3</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
<tr>
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<td><img src="image" alt="2b" /></td>
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<td><img src="image" alt="2g" /></td>
<td><img src="image" alt="3o" /></td>
<td>91</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup>
Reaction conditions: Pd(dba)$_2$ (5 mol%), L26 (5 mol%), 1 (0.2 mmol), 2a (0.3 mmol), CH$_3$CN (1 mL), −20 °C, 36 h. Constitutional isomer ratios (l/b = >99:1, E/Z = >99:1) Determined by $^1$H-NMR analysis of crude reaction. Yield of isolated yield. Determined by HPLC analysis. The reaction was carried out at −20 °C for 48 h. The reaction was carried out at −10 °C for 36 h.

**Pd-catalyzed allylation with the secondary allylic carbonate.** When the reaction was conducted with secondary allylic carbonate 2a' instead of 2a, the same levels of yield, linear selectivity and enantioselectivity as the reaction of the primary allylic carbonate 2a was obtained. This result indicated that rapid σ-π-σ isomerization of the allyl-palladium species was involved in this catalytic process.$^{14}$

**Evaluation of Pd-ligand coordination.** The effect of L26/Pd molar ratios on the catalytic activity and enantioselectivity in the reaction between 1a and 2a was investigated. As show in Figure 1, no reaction occurred without L26 and with half equivalent of L26 against the Pd atom (L26/Pd 0 or 0.9). The molar ratio in 1.0 was most effective, to give the product in high
yield. Although the product yields were gradually decreased with increasing the loading of L26 in the range from 1.0 to 4.0, the enantioselectivity (91% ee) was unchanged. These results suggested that a Pd-phosphine 1:1 complex would be active in this transformation. The pyridine substrate could coordinate to such coordinatively unsaturated Pd species, and subsequently undergo the side chain α-deprotonation.

Figure 1. Effect of L26/Pd molar ratio toward the catalytic activity and enantioselectivity in the reaction between 1a (0.2 mmol) and 2a (0.3 mmol).

<table>
<thead>
<tr>
<th>Entry</th>
<th>L26/Pd ratio</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
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<td>4</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>93</td>
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<td>6</td>
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</tr>
<tr>
<td>10</td>
<td>4</td>
<td>43</td>
<td>91</td>
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</table>
Studies on kinetics of the Pd catalysis. To gain insight the reaction mechanism, the kinetic studies on the reaction between 1k and 2a with the [L26/Pd] system were carried out. The reactions were monitored by $^1$H NMR spectroscopy in CD$_3$CN. A plot of concentration of 3s versus time in the reactions of different initial concentrations of 1k ($[1k]_0$ 0.1, 0.15 and 0.2 M) showed that the initial rate was pseudo-first order in concentration of 2-alkylpyridine (Table 4, Figure 2). In contrast, the initial concentration of the allylic carbonate ($[2a]_0$ 0.1 M, 0.2 M and 0.3 M) was almost independent of the initial rate (Table 5 and Figure 3). Furthermore, a first order reaction dependency on concentration of the palladium catalyst was observed (0.005 M, 0.075 M, 0.01 M; Table 6 and Figure 4). These results suggested that both Pd complexes and 2-alkylpyridine substrates would participate in a turnover-limiting step of the catalytic cycle.

Table 4. Initial rates of varying initial concentrations of 1k

<table>
<thead>
<tr>
<th>Entry</th>
<th>$[1k]_0$ [M]</th>
<th>$d[3s]/dt$ [M/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.00813</td>
</tr>
<tr>
<td>2</td>
<td>0.15</td>
<td>0.00906</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.00114</td>
</tr>
</tbody>
</table>
Figure 2. (a) Initial rate kinetic experiments for 1k (b) Plot of (d[1k]/dt) versus 1k (M).
Table 5. Initial rates of varying concentrations of $2a$

<table>
<thead>
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<th>Entry</th>
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<th>$d[3s]/dt$ [M/min]</th>
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Figure 3. (a) Initial rate kinetic experiments for $1k$ (b) Plot of ln($d[3s]/dt$) versus ln $1k$ [M].

Table 6. Initial rates of varying concentrations of $Pd$

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Figure 4. (a) Initial rate kinetic experiments for Pd (b) Plot of In (d[3s]/dt) versus In Pd [M].

Kinetic isotope effect. To determine whether the side chain C(α)-deprotonation of 2-alkylpyridines is involved in the turnover-limiting step of the catalytic cycle, the kinetic isotope effect was investigated. A large kinetic isotope effect value ($k_H/k_D = 4.1$) measured in the reactions of 1k and 1k-d (Tables 7 and 8; Figure 5) revealed that the C(α)-deprotonation was involved in the turnover-limiting step.
Table 7. Initial rate of 1k

![Chemical structure of 1k and 2a](image)

<table>
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<th>Entry</th>
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<th>Rate [M/min]</th>
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Table 8. Initial rate of 1k-d

![Chemical structure of 1k-d and 2a](image)

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Figure 5. Kinetic isotope effects. Conditions: reaction between 1k or 1k-d (0.2 M) and 2a (0.3 M). Conditions: Pd(dbu)₂, 5.0 mM, L26, 5.0 mM, dibenzyl, 0.05 M, CH₃CN (1 mL); 25 °C.
**Proposed catalytic reaction pathways.** A proposed reaction pathway on the basis of the mechanistic studies is shown in Figure 6. This catalytic reaction starts from an oxidative addition of an allylic carbonate to the palladium(0)-phosphine complex A, forming (π-allyl)(alkoxide)palladium complex B along with elimination of CO₂. Coordination of 2-alkylpyridine to the palladium center followed by the side chain C(α)-deprotonation by the alkoxy ligand through a transition state A(TS) leads to a palladium-enamide complex C. The KIE experiment (Figure 5) supported that this C–H bond cleavage is the rate-determining step. A subsequent C–C bond formation step can be considered to have the following three pathways. The first is a nucleophilic attack pathway from the palladium-enamide species to the terminal carbon of the π-allyl moiety through a transition state B(TS). The second is a pericyclic concerted mechanism, similar to the homo-Cope rearrangement proposed by Stolts and Morken, through a transition state B(TS). The third is allyl-benzyl reductive elimination. Finally, reductive elimination gave the desired product and the catalytically active palladium(0)-phosphine complex A.
Figure 6. Proposed reaction pathways.

Conclusion

A palladium-catalyzed enantioselective allylation of 2-alkylazaarenes with allylic carbonates without the use of external bases have been developed. Newly developed chiral isomannide-based monodentate diamidophosphite L17 was effective for the enantioselective allylation. The comparative experiment of regioisomeric allylic carbonates showed that rapid $\sigma$-$\pi$-$\sigma$ isomerization of the allyl-palladium species was involved in this catalytic process. The kinetic experiments found that rate-determining step was C–H deprotonation. From these experiments, reaction pathway is suggested that Pd alkoxide enable the side chain
C(α)-deprotonation leading to palladium-enamide complex for C–C bond formation.

Experimental Section

Instrumentation and Chemicals

\(^1\)H (400 MHz) and \(^{13}\)C (100 MHz) NMR spectra were recorded on a JEOL JNM-ECX spectrometer. Chemical shift values for \(^1\)H, \(^{13}\)C and \(^{11}\)B NMR spectra are referenced to Me\(_4\)Si (0 ppm) and the residual solvent resonances (77.0 ppm for CHCl\(_3\)), respectively. Chemical shifts are reported in δ ppm. High-resolution mass spectra were recorded on a Thermo Fisher Scientific Exactive, JEOL JMS-T100LP mass spectrometer or JEOL JMS-T100GCv mass spectrometer at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. HPLC analyses were conducted on a HITACHI Chromaster with HITACHI 5430 diode array detector. Optical rotations were measured on a JASCO P-2200. IR spectra were measured with a Perkin-Elmer Spectrum One. Melting points were determined on a micro melting point apparatus (Yanaco: MP-500D) using micro cover glass. GLC analyses were conducted on a Shimadzu GC-14B equipped with a flame ionization detector. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F\(_{254}\).

All reactions were carried out under a nitrogen atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. Pd(dba)\(_2\), L\(_4\), L\(_5\), L\(_7\) from Aldrich Chemical Co. All solvents for catalytic reactions were degassed via three freeze–pump–thaw cycles before use. Chiral phosphine ligand L\(_6\)\(^6\), L\(_8\)\(^{17}\), L\(_9\)\(^{18}\), L\(_{10}\)\(^{19}\) and L\(_{13}\)\(^{8d}\) were found in the literature.

Experimental Procedures

Procedure for allylation of tetrahydroquinoline (1a) with cinnamyl methyl carbonate (2a) (Table 2, Entry 12). In grove box, L\(_{26}\) (8.2 mg, 0.01 mmol), Pd(dba)\(_2\) (5.6 mg, 0.01 mmol), and anhydrous, degassed MeCN (1.0 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. Tetrahydroquinoline (1a; 26.6 mg, 0.2 mmol) was added successively. The tube was sealed with a Teflon-coated silicon rubber septum and removed from the grove box. The reaction mixture was stirred at room temperature for 5 min, and E-cinnamyl methyl carbonate (2a; 50.7 mg, 0.3 mmol) was added at –20 °C. After 36 h of stirring at –20 °C, the reaction was quenched with water and through a short plug of silica-gel, which was then washed with ethyl acetate (5 mL), The residue was subjected to flash
chromatography on silica-gel (hexane/EtOAc) to give (E)-3a (46.4 mg, 0.186 mmol) in 93 % yield.

**Kinetic Experiment: Initial Rate Kinetic Analysis.** To an NMR sample tube were added a Pd(dba)$_2$ (2.6 mg, 0.005 mmol, 0.005 M), L$_2$ (4.1 mg, 0.005 mmol, 0.005 M), dibenzyl (9.1 mg, 0.05 mmol, 0.05M), 2-ethylpyridine 1k (21.7 mg, 0.2 mmol, 0.2 M) and CD$_3$CN (1 mL) in a glove box. The mixture was stirred at room temperature for 5 min. The tube was added allylic carbonate 2a (50.8 mg, 0.3 mmol, 0.3 M) and the tube was sealed with a rubber septum. The reaction mixture was analyzed by $^1$H-NMR spectroscopy to determine the yield of 3s based on the relative intergration value of the peaks at (6.20) and (2.91) ppm (for dibenzyl) at the specified time.

**Kinetic Experiment: Kinetic Isotope Effect.** To an NMR sample tube were added a Pd(dba)$_2$ (2.6 mg, 0.005 mmol, 0.005 M), L$_2$ (4.1 mg, 0.005 mmol, 0.005 M), dibenzyl (9.1 mg, 0.05 mmol, 0.05M), 2-ethylpyridine 1k (21.7 mg, 0.2 mmol, 0.2 M) and CD$_3$CN (1 mL) in a glove box. The mixture was stirred at room temperature for 5 min. The tube was added allylic carbonate 2a (50.8 mg, 0.3 mmol, 0.3 M) and the tube was sealed with a rubber septum. The reaction mixture was analyzed by $^1$H-NMR spectroscopy to determine the yield of 3s based on the relative intergration value of the peaks at (6.20) and (2.91) ppm (for dibenzyl) at the specified time. The reaction with deuterated 2-ethylpyridine (1k-d) was preformed independently under the identical reaction conditions.

**Preparation of Substrates**

The starting material 1a, 1c, 1d, 1l are commercially available. The starting materials 1b$^{20}$, 1g$^{21}$, 1h$^{22}$, 1j$^{23}$, 1k-d$^{24}$, 2a$^{25}$ 2b$^{25}$, 2c$^{26}$, 2d$^{27}$, 2e$^{25}$, 2f$^{25}$, 2h$^{28}$, 2i$^{29}$, 9a$^{30}$ and 9b$^{31}$ were reported in the literatures.

**benzyl 4-(pyridin-2-yl)butanoate (1i)**

The title compound (1i) was synthesized via the reaction of 2-bromopyridine and benzyl 4-bromobutanoate with Ni-dtbpy catalyst system (63%)$^{32}$.
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) δ 2.10 (quint, $J = 7.6$ Hz, 2H), 2.42 (t, $J = 8.0$ Hz, 2H), 2.83 (t, $J = 7.6$ Hz, 2H), 5.11 (s, 2H), 7.09–7.13 (m, 2H), 7.30–7.38 (m, 5H), 7.58 (td, $J = 8.0$, 2.0 Hz, 1H), 8.52 (d, $J = 5.2$ Hz, 1H).

$^{13}$C NMR (CDCl$_3$) δ 24.79, 33.60, 37.36, 66.12, 121.14, 122.84, 128.16 (2C), 128.51 (2C), 135.96, 136.31, 149.30, 161.02, 173.16.

HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{16}$H$_{18}$N, 256.13321; found, 256.13354.

**Ligand Synthesis**

![Ligand Synthesis diagram]

Compound 7. To solution of Pd(dba)$_2$ (402 mg, 0.7 mmol), rac-BINAP (436 mg, 0.7 mmol) and NaO’Bu (1.75 g, 18.2 mmol) in toluene (20 mL) was added (S,S)-1,2-diphenylenediamine 5 (1.49 g, 7.0 mmol) and Bromobenzene (2.52 g, 16.1 mmol). After being stirred at 110 °C for 12 h, the reaction mixture was filtered through a pad of celite, and the celite was washed with EtOAc. Solvent was concentrated. The crude product was purified by column chromatography (silica gel, 10 EtOAc/hexane) to yield the product 7a (86%) as a white solid.

**Ligand L10.** Distilled phosphorus trichloride (96 mg, 1.0 mmol) was added to dichloroethane (5 mL) under argon at 0 °C. Triethylamine (710 mg, 5.0 mmol) was added dropwise. 7a (356 mg, 1.0 mmol) was added at -20 °C. The reaction was warmed to room temperature over 30 min, then heated to 70 °C for 3 h. The solution was cooled to 0 °C and
added the 1,3-propanediol (38 mg, 0.5 mmol). The reaction was allowed to stir to room temperature over 30 min, then heat to 70 °C for 12 h. After cooling to room temperature, triethylamine HCl salt was filtered and the reaction mixture was concentrated. Separation using neutral alumina and 5% diethyl ether in hexane isolated the diamidophosphite as a white solid (198 mg, 46% yield). $^1$H NMR (CDCl$_3$) $\delta$ 1.49 (t, $J = 5.2$ Hz, 2H), 3.83 (br, 4H), 4.92 (d, $J = 4.8$ Hz, 2H), 5.11 (d, $J = 6.8$ Hz, 2H), 6.78 (m, 4H), 6.92–6.97 (m, 8H), 7.03–7.09 (m, 8H), 7.14–7.26 (m, 20H). $^{13}$C NMR (CDCl$_3$) $\delta$ 33.40, 61.54, 71.65, 71.73, 72.88, 7297, 116.73 (2C), 116.87 (2C), 120.23 (2C), 120.42 (2C), 120.53 (2C), 121.28 (2C), 127.38 (4C), 127.44 (4C), 127.53 (2C), 127.68 (2C), 128.51 (4C), 128.55 (4C), 128.82 (4C), 128.85 (4C), 139.52, 139.55, 139.82 (2C), 142.76, 142.87, 144.04, 144.26. $^{31}$P NMR (CDCl$_3$) $\delta$ 128.68. HRMS–ESI (m/z): [M+Na]$^+$ Calcd for C$_{55}$H$_{50}$O$_2$N$_4$NaP$_2$, 883.33012; found, 883.33285. $[\alpha]_{25}^D = -71.65$ (c 1.0 CHCl$_3$).

**Ligand L11.** White Solid. (46% yield). $^1$H NMR (CDCl$_3$) $\delta$ 1.26-1.46 (m, 4H), 3.72–3.78 (m, 4H), 4.91 (d, $J = 5.6$ Hz, 2H), 5.10 (d, $J = 7.6$ Hz, 2H), 6.75–6.81 (m, 4H), 6.91–6.97 (m, 8H), 7.02–7.14 (m, 12H), 7.20–7.23 (m, 16H). $^{13}$C NMR (CDCl$_3$) $\delta$ 27.63, 27.67, 64.60, 64.75, 71.67, 71.75, 72.80, 72.89, 116.77 (2C), 116.91 (2C), 120.23 (2C), 120.38 (2C), 120.49 (2C), 121.23 (2C), 127.39 (4C), 127.43 (4C), 127.54 (2C), 127.67 (2C), 128.47 (4C), 128.53 (4C), 128.79 (8C), 139.42, 139.45, 139.73 (2C), 142.77, 142.87, 144.08, 144.30. $^{31}$P NMR (CDCl$_3$) $\delta$ 127.47. HRMS–ESI (m/z): [M+Na]$^+$ Calcd for C$_{56}$H$_{52}$O$_2$N$_4$NaP$_2$, 897.34577; found, 897.34814. $[\alpha]_{25}^D = -124.84$ (c 1.00 CHCl$_3$).

**Ligand L12.** White Solid. (54% yield). $^1$H NMR (CDCl$_3$) $\delta$ 1.26-1.35 (m, 6H), 3.72–3.86 (m, 4H), 4.91 (dd, $J = 7.2$, 2.4 Hz, 2H), 5.17 (d, $J = 7.2$ Hz, 2H), 6.74–6.82 (m, 4H), 6.92–6.98 (m, 8H), 7.04–7.15 (m, 12H), 7.19–7.27 (m, 16H). $^{13}$C NMR (CDCl$_3$) $\delta$ 21.88, 22.64, 31.00, 31.03, 31.57, 65.03, 65.18, 71.72, 71.79, 72.83, 72.92, 116.76 (2C), 116.90 (2C), 120.21 (2C), 120.38 (2C), 120.49 (2C), 121.19, 121.21, 127.42 (8C), 127.54 (2C), 127.67 (2C), 128.47
(4C), 128.53 (4C), 128.79 (4C), 139.52, 139.55, 139.83 (2C), 142.83, 142.93, 144.13, 144.35. 

\[^{31}\text{P NMR (CDCl}_3\text{)}\] \(\delta\) 127.53. HRMS–ESI (m/z): [M+Na]^+ Calcd for C\(_{57}\)H\(_{54}\)N\(_4\)O\(_2\)NaP\(_2\), 911.36142; found, 911.36407. \([\alpha]_{25}^D = -70.54\) (c 1.1 CHCl\(_3\)).

Ligand L14. \(^1\text{H NMR (CDCl}_3\text{)}\) \(\delta\) 0.92 (br, 4H), 1.07 (d, \(J = 5.6\) Hz, 6H), 3.94 (br, 2H), 4.87 (d, \(J = 7.2\) Hz, 2H), 5.09 (d, \(J = 7.6\) Hz, 2H), 6.75–6.83 (m, 4H), 6.90–6.96 (m, 8H), 7.05–7.12 (m, 12H), 7.19–7.25 (m, 16H). \(^{13}\text{C NMR (CDCl}_3\text{)}\) \(\delta\) 22.40 (2C), 33.20 (2C), 71.43, 71.51, 71.78, 71.98, 116.13 (2C), 116.29 (2C), 119.70 (2C), 121.29 (2C), 121.38 (2C), 121.44 (2C), 127.45 (2C), 127.52 (4C), 127.59 (2C), 128.41 (4C), 128.48 (4C), 128.74 (4C), 139.31, 139.34, 140.24 (2C), 142.89, 143.00, 144.21, 144.43. 

\[^{31}\text{P NMR (CDCl}_3\text{)}\] \(\delta\) 128.33. HRMS–ESI (m/z): [M+Na]^+ Calcd for C\(_{58}\)H\(_{56}\)O\(_2\)N\(_4\)NaP\(_2\), 925.37707; found, 925.37787. 

\([\alpha]_{24}^D = -80.00\) (c 1.0 CHCl\(_3\)).

Ligand L15. White Solid. (38% yield). \(^1\text{H NMR (CDCl}_3\text{)}\) \(\delta\) 1.29 (s, 6H), 3.64 (m, 2H), 3.79-3.80 (m, 4H), 4.94 (dd, \(J = 7.6, 2.4\) Hz, 2H), 5.12 (d, \(J = 7.6\) Hz, 2H), 6.51 (d, \(J = 7.6\) Hz, 2H), 6.79 (dt, \(J = 14.8, 6.8\) Hz, 4H), 6.97-7.14 (m, 20 H), 7.22-7.24 (m, 10H), 7.38-7.46 (m, 2H), 7.87-7.90 (m, 2H). \(^{13}\text{C NMR (CDCl}_3\text{)}\) \(\delta\) 27.02, 65.38 (d, \(J = 14.3\) Hz), 71.63 (d, \(J = 7.6\) Hz), 72.94 (d, \(J = 14.3\) Hz), 77.61 (d, \(J = 3.8\) Hz), 109.62, 117.26 (d, \(J = 14.3\) Hz), 120.02, 120.56 (t, \(J = 3.9\) Hz), 121.44, 124.85, 127.48 (d, \(J = 6.7\) Hz, 2C), 127.64, 127.75, 128.31, 128.36, 128.49, 128.55, 128.73, 128.76, 128.93, 131.08, 137.50, 139.15, 139.37, 142.55, 142.65, 143.90, 144.11, 149.28, 163.84. 

\[^{31}\text{P NMR (CDCl}_3\text{)}\] \(\delta\) 129.00. HRMS–ESI (m/z): [M+Na]^+ Calcd for C\(_{58}\)H\(_{56}\)N\(_4\)O\(_2\)NaP\(_2\), 969.36690; found, 969.36856. 

\([\alpha]_{25}^D = -107.87\) (c 1.00 CHCl\(_3\)).
**Ligand L16.** White Solid. (54% yield). $^1$H NMR (CDCl$_3$) $\delta$ 3.56 (t, $J = 8.8$ Hz, 2H), 3.72 (t, $J = 6.8$ Hz, 2H), 3.86 (t, $J = 1.6$ Hz, 2H), 4.48 (br, 2H), 4.92 (dd, $J = 7.2$, 2.4, 2H), 5.19 (d, $J = 7.2$ Hz, 2H), 6.80–6.83 (m, 4H), 6.94–6.96 (m, 4H), 6.99–7.02 (m, 4H), 7.05–7.13 (m, 12H), 7.21–7.25 (m, 16H). $^{13}$C NMR (CDCl$_3$) $\delta$ 71.38, 71.46, 71.61, 71.65, 72.97, 73.05, 74.33, 80.88 (2C), 116.89 (2C), 117.04 (2C), 120.54 (2C), 120.85 (2C), 128.46 (4C), 128.53 (4C), 128.67 (4C), 128.86 (4C), 139.12, 139.16, 139.48 (2C), 142.26, 142.36, 143.81, 144.03. $^{31}$P NMR (CDCl$_3$) $\delta$ 126.64. HRMS–ESI (m/z): [M+Na]$^+$ Caled for C$_{58}$H$_{52}$N$_{4}$O$_{4}$NaP$_{2}$, 953.33560; found, 953.33838. $[^{[\alpha]}]_{24D}^D$ = –44.69 (c 1.1 CHCl$_3$).

**Ligand L21.** White solid (65% yield). $^1$H NMR (CDCl$_3$) $\delta$ 3.62 (t, $J = 8.4$ Hz, 2H), 3.75 (t, $J = 8.0$ Hz, 2H), 3.89 (d, $J = 4.4$ Hz, 2H), 4.48 (br, 2H), 4.87 (d, $J = 8.4$, 2H), 5.13 (d, $J = 8.4$ Hz, 2H), 6.77–6.83 (m, 8H), 6.86–6.89 (m, 4H), 6.96–6.99 (m, 4H), 7.08–7.09 (m, 4H), 7.20–7.23 (m, 16H). $^{13}$C NMR (CDCl$_3$) $\delta$ 71.53 (d, $J = 4.8$ Hz, 2C), 71.88 (d, $J = 7.6$ Hz, 2C), 73.55 (d, $J = 8.6$ Hz, 2C), 74.27 (d, $J = 12.4$ Hz, 2C), 80.96 (2C), 115.34 (d, $J = 5.8$ Hz, 2C), 115.55 (d, $J = 5.7$ Hz, 2C), 118.31 (d, $J = 7.6$ Hz, 2C), 118.45 (d, $J = 7.6$ Hz, 2C), 122.91 (d, $J = 7.6$ Hz, 2C), 127.52 (4C), 127.74 (4C), 127.82 (2C), 127.94 (2C), 128.52 (4C), 128.54 (4C), 138.69 (d, $J = 7.6$ Hz), 138.24 (d, $J = 2.8$ Hz, 2C), 138.85 (2C), 139.87 (d, $J = 21.9$ Hz), 157.53 (d, $J = 238.4$ Hz), 158.12 (d, $J = 240.3$ Hz). $^{19}$F NMR (CDCl$_3$) $\delta$ -121.00, -123.27. $^{31}$P NMR (CDCl$_3$) $\delta$ 127.21. HRMS–ESI (m/z): [M+Na]$^+$ Caled for C$_{58}$H$_{48}$N$_{4}$O$_{4}$F$_{4}$NaP$_{2}$, 1025.29791; found,1025.29858. $[^{[\alpha]}]_{24D}^D$ = –122.45 (c 1.0 CHCl$_3$).
The title compound (9c) was synthesized via the triphenylsilyl protection of isomannide with SiPh₃Cl and imidazole (56% yield). Colorless oil. ¹H NMR (CDCl₃) δ 2.86 (d, J = 8.8 Hz, 1H), 3.68–3.73 (m, 2H), 3.80 (dd, J = 8.8, 6.0 Hz, 1H), 3.99 (dd, J = 9.2, 6.0 Hz, 1H), 4.19–4.26 (m, 2H), 4.37 (t, J = 5.2 Hz, 1H), 4.40–4.45 (m, 1H), 7.37–7.47 (m, 9H), 7.65–7.68 (m, 6H). ¹³C NMR (CDCl₃) δ 72.25, 72.63, 74.18, 74.73, 76.69, 81.40, 81.54, 127.95 (6C), 130.27 (3C), 133.51 (3C), 135.37 (6C). [α]₂⁰° = +45.13 (c 2.4 CHCl₃).

(3R,3aR,6R,6aS)-6-((triphenylsilyl)oxy)hexahydrofuro[3,2-b]furan-3-ol (9c)

To solution of ZnCl₂ (1.36 g, 10 mmol) and 4 (1.46 g, 10 mmol) in CH₃CN (mL) was added trityl chloride (2.78 g, 10 mmol) under argon at 0 °C. The reaction was allowed to stir to room temperature over 2 h. Then, a solution of Et₃N in the CH₃CN (20 mL) was added during 12 h. After quenching with aqueous 5% citric acid buffer at pH = 5–6 (mL) and stirring for other 30 min, the orgaince solvent was evaporated under reduced pressure and resulting suspension extracted with dichloromethane. The solvent was concentrated. The
crude product was purified by column chromatography (silica gel, 30-50 EtOAc/hexane) to yield the product 9 (72%) as a white solid. $^1$H NMR (CDCl$_3$) $\delta$ 2.67 (d, $J = 7.2$ Hz, 1H), 3.00 (t, $J = 7.6$ Hz, 1H), 3.22 (t, $J = 8.8$ Hz, 1H), 3.67 (dd, $J = 8.8$, 5.6 Hz, 1H), 3.94–3.98 (m, 2H), 4.06–4.11 (m, 2H), 7.22–7.26 (m, 3H), 7.29–7.33 (m, 6H), 7.53–7.54 (m, 6H). $^{13}$C NMR (CDCl$_3$) $\delta$ 70.40, 72.46, 74.35, 75.13, 80.75, 81.18, 87.55, 127.25 (3C), 128.00 (6C), 128.56 (6C), 144.22 (3C). HRMS–ESI (m/z): [M+Na]$^+$ Calcd for C$_{25}$H$_{24}$O$_4$Na, 411.15668; found, 411.15677. $[\alpha]_{24}^D = +107.35$ (c 1.0 CHCl$_3$).

Ligand L23. white solid (54% yield). $^1$H NMR (CDCl$_3$) $\delta$ 3.67 (t, $J = 8.4$ Hz, 1H), 3.84 (t, $J = 6.8$ Hz, 1H), 3.92 (t, $J = 5.2$ Hz, 1H), 3.94–4.02 (m, 2H), 4.52–4.60 (m, 1H), 4.74 (t, $J = 4.8$ Hz, 1H), 4.89 (dd, $J = 8.4$, 4.4 Hz, 1H), 5.17 (d, $J = 8.0$ Hz, 1H), 5.27 (q, $J = 6.0$ Hz, 1H), 6.81 (td, $J = 8.4$, 3.6 Hz, 4H), 6.87–6.90 (m, 2H), 6.98–7.02 (m, 2H), 7.08–7.11 (m, 2H), 7.19–7.27 (m, 8H), 7.44 (t, $J = 7.2$ Hz, 2H), 7.57 (t, $J = 7.2$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (CDCl$_3$) $\delta$ 70.95, 71.25 (d, $J = 4.8$ Hz), 71.79 (d, $J = 7.6$ Hz), 73.59 (d, $J = 8.6$ Hz), 74.10 (d, $J = 13.3$ Hz), 74.52, 80.56, 81.28, 115.34 (d, $J = 5.7$ Hz, 2C), 115.56 (d, $J = 4.7$ Hz, 2C), 118.42 (d, $J = 7.6$ Hz), 118.55 (d, $J = 7.6$ Hz), 122.97 (d, $J = 7.6$ Hz, 2C), 127.60 (2C), 127.77 (2C), 127.84, 127.96, 128.40 (2C), 128.53 (2C), 128.54 (2C), 129.47, 129.76 (2C), 137.95 (d, $J = 2.8$ Hz), 138.04, 138.13 (d, $J = 3.8$ Hz), 138.77, 139.73, 139.95 (d, $J = 1.9$ Hz), 157.58 (d, $J = 238.4$ Hz), 158.16 (d, $J = 241.2$ Hz), 165.96. $^{19}$F NMR (CDCl$_3$) $\delta$ –120.91, –123.17. $^{31}$P NMR (CDCl$_3$) $\delta$ 126.78. HRMS–ESI (m/z): [M+Na]$^+$ Calcd for C$_{30}$H$_{33}$N$_2$O$_5$F$_2$NaP, 701.19874; found, 701.19958. $[\alpha]_{25}^D = –4.05$ (c 1.0 CHCl$_3$).
**Ligand L24.** white solid (75% yield). $^1$H NMR (CDCl$_3$) $\delta$ 3.59–3.64 (m, 2H), 3.73–3.84 (m, 2H), 4.43 (t, $J = 1.6$ Hz, 1H), 4.51–4.55 (m, 2H), 4.71–4.75 (m, 1H), 4.85–4.87 (m, 1H), 5.14–5.16 (m, 1H), 6.77–6.86 (m, 6H), 6.97 (m, 2H), 7.07–7.08 (m, 2H), 7.21–7.24 (m, 8H), 7.29–7.36 (m, 5H). $^{13}$C NMR (CDCl$_3$) $\delta$ 70.72, 71.12 (d, $J = 4.8$ Hz), 71.79 (d, $J = 7.6$ Hz), 72.48, 73.63 (d, $J = 7.6$ Hz), 74.57 (d, $J = 13.3$ Hz), 79.07, 80.04, 81.31, 115.30 (d, $J = 5.7$ Hz, 2C), 115.52 (d, $J = 5.7$ Hz, 2C), 118.33 (d, $J = 7.7$ Hz), 118.47 (d, $J = 7.6$ Hz), 123.01 (t, $J = 7.6$ Hz, 2C), 127.60 (2C), 127.77 (2C), 127.94 (2C), 128.45 (2C), 128.50 (2C), 137.67, 138.04, 138.18, 138.85, 139.87 (d, $J = 21.9$ Hz), 157.52 (d, $J = 238.3$ Hz), 158.14 (d, $J = 243.2$ Hz). $^{19}$F NMR (CDCl$_3$) $\delta$ –121.07, –123.33. $^{31}$P NMR (CDCl$_3$) $\delta$ 127.66. HRMS–ESI (m/z): [M+Na]$^+$ Calcd for C$_{50}$H$_{45}$N$_2$O$_4$F$_2$NaPSi, 855.25900; found, 855.25970. $[\alpha]_{D}^{25}$ = –27.38 (c 1.0 CHCl$_3$).

**Ligand L25.** white solid (59% yield). $^1$H NMR (CDCl$_3$) $\delta$ 3.64–3.66 (m, 2H), 3.76 (t, $J = 8.4$ Hz, 1H), 3.87–3.90 (m, 2H), 4.10 (t, $J = 4.4$ Hz, 1H), 4.33 (q, $J = 7.2$ Hz, 1H), 4.50 (br, 1H), 4.86 (d, $J = 7.6$ Hz, 1H), 5.14 (d, $J = 8.4$ Hz, 1H), 6.74–7.07 (m, 10H), 7.21 (m, 8H), 7.35–7.43 (m, 9H), 7.64–7.66 (m, 6H). $^{13}$C NMR (CDCl$_3$) $\delta$ 71.86 (t, $J = 6.7$ Hz, 2C), 72.19, 73.57 (d, $J = 8.9$ Hz), 74.13, 74.50 (d, $J = 11.4$ Hz), 80.91, 81.14, 115.29 (d, $J = 5.7$ Hz, 2C), 115.52 (d, $J = 6.6$ Hz, 2C), 118.33 (d, $J = 7.7$ Hz), 118.47 (d, $J = 7.6$ Hz), 122.84 (t, $J = 7.6$ Hz, 2C), 122.57 (2C), 127.73 (2C), 127.92 (6C), 128.50 (4C), 130.19 (3C), 151
133.74 (3C), 135.36 (6C), 138.83 (dd, $J = 10.5, 1.9$ Hz), 138.27 (d, $J = 2.8$ Hz), 138.88, 139.90 (d, $J = 23.8$, Hz), 157.08 (dd, $J = 100.0, 2.9$ Hz), 157.51 (d, $J = 184.0$ Hz). $^{19}$F NMR (CDCl$_3$) δ -121.07, -123.26. $^{31}$P NMR (CDCl$_3$) δ 126.94. HRMS–ESI ($m/z$): [M+Na]$^+$ Calcd for C$_{50}$H$_{43}$N$_2$O$_4$F$_2$NaPSi, 855.25900; found, 855.25970. $[\alpha]_{25}^{D} = -10.08$ (c 1.0 CHCl$_3$).

Ligand L26. white solid (62% yield). $^1$H NMR (CDCl$_3$) δ 2.86 (t, $J = 7.2$ Hz, 1H), 3.20 (t, $J = 8.8$ Hz, 1H), 3.80 (t, $J = 4.8$ Hz, 1H), 3.89–3.99 (m, 3H), 4.45 (m, 1H), 4.84 (dd, $J = 8.4$, 2.4 Hz, 1H), 5.09 (d, $J = 7.6$ Hz, 1H), 6.72–6.87 (m, 6H), 6.90–6.94 (m, 2H), 7.04–7.06 (m, 2H), 7.14–7.31 (m, 17H), 7.51–7.53 (m, 6H). $^{13}$C NMR (CDCl$_3$) δ 70.18 (d, $J = 7.6$ Hz), 70.58, 71.94 (d, $J = 4.8$ Hz), 73.57 (d, $J = 7.7$ Hz), 74.50 (d, $J = 11.4$ Hz), 74.81, 80.20, 80.87, 87.42, 115.28 (d, $J = 5.7$ Hz, 2C), 115.50 (d, $J = 5.7$ Hz, 2C), 118.28 (d, $J = 7.6$ Hz), 118.41 (d, $J = 7.6$ Hz), 122.85 (t, $J = 9.0$ Hz, 2C), 127.18 (3C), 127.56 (2C), 127.71 (2C), 127.87, 127.95 (6C), 128.47 (2C), 128.49 (2C), 128.57 (6C), 138.10 (dd, $J = 10.5, 1.9$ Hz), 138.17 (d, $J = 2.8$ Hz), 138.94, 139.90 (dd, $J = 23.9, 1.9$ Hz), 144.38 (3C), 157.48 (d, $J = 238.3$ Hz), 158.06 (d, $J = 246.4$ Hz). $^{19}$F NMR (CDCl$_3$) δ -121.07, -123.40. $^{31}$P NMR (CDCl$_3$) δ 126.78. HRMS–ESI ($m/z$): [M+Na]$^+$ Calcd for C$_{51}$H$_{43}$N$_2$O$_4$F$_2$NaP, 839.28207; found, 839.28284. $[\alpha]_{25}^{D} = -33.319$ (c 1.0 CHCl$_3$).

Characterization of Products

8-cinnamyl-5,6,7,8-tetrahydroquinoline (3a)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.69–2.00 (m, 4H), 2.48 (dt, $J = 10.8, 8.0$ Hz, 1H), 2.70–2.82 (m, 2H), 2.96–3.08 (m, 2H), 6.25–6.31 (m, 1H), 6.45 (d, $J = 15.6$ Hz, 1H), 7.03–7.05 (m, 1H), 7.17–7.23 (m, 1H), 7.29 (t, $J = 7.6$ Hz, 2H), 7.34–7.37 (m, 3H), 8.43 (dd, $J = 5.6, 2.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ
19.76, 27.17, 29.20, 38.72, 40.75, 120.94, 125.97, 126.84, 128.44, 129.47, 131.47, 132.44, 136.74, 137.75, 146.94, 159.61.

HRMS–ESI (m/z): [M+H]^+ Calcd for C_{15}H_{21}N_2, 229.16993; found, 229.16997. [α]_{24}D^P = +102.11 (91% ee, c 1.0, CHCl_3). The ee value (91% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 13.98 min and 17.23 min for isomer.]

7-cinnamyl-6,7-dihydro-5H-cyclopenta[b]pyridine (3c)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. 1H NMR (CDCl₃) δ 1.82–1.91 (m, 1H), 2.28–2.36 (m, 1H), 2.38–2.46 (m, 1H), 2.80–2.99 (m, 3H), 3.28–3.35 (m, 1H), 6.26 (dt, J = 14.4, 7.2 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 7.04 (dd, J = 8.0, 5.2 Hz, 1H), 7.17–7.21 (m, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.37–7.35 (m, 2H), 7.49 (dd, J = 7.6, 1.2 Hz, 1H), 8.40 (d, J = 5.2 Hz, 1H). 13C NMR (CDCl₃) δ 28.97, 29.14, 37.20, 45.34, 121.36, 125.97 (2C), 126.89, 128.42 (2C), 128.60, 131.39, 132.18, 136.92, 147.61, 166.80. HRMS–ESI (m/z): [M+H]^+ Calcd for C_{17}H_{18}N, 236.14338; found, 236.14336. [α]_{23}D^B = +137.71 (87% ee, c 1.0, CHCl_3). The ee value (87% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 20.55 min and 22.85 min for isomer.]

(E)-2-(1,6-diphenylhex-5-en-3-yl)pyridine (3d)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. 1H NMR (CDCl₃) δ 2.02–2.21 (m, 2H), 2.48 (t, J = 8.4 Hz, 2H), 2.54–2.64 (m, 1H), 2.63–2.71 (m, 1H), 2.89–2.96 (m, 1H), 6.06 (dt, J = 11.8, 7.6 Hz, 1H), 6.30 (d, J = 15.6 Hz, 1H), 7.09–7.16 (m, 6H), 7.22–7.26 (m, 6H), 7.58 (td, J = 7.2, 1.6 Hz, 1H), 8.61 (d, J = 4.8 Hz, 1H). 13C NMR (CDCl₃) δ 33.66, 36.39, 39.24, 47.48, 121.31, 123.06, 125.66, 125.92 (2C), 126.84, 128.23 (2C), 128.34 (3C), 128.47 (2C), 131.34, 136.09, 137.57, 142.22, 149.51, 163.94. HRMS–EI (m/z): [M] Calcd for C_{23}H_{23}N, 313.18305; found, 313.18240. [α]_{22}D = −46.2 (78% ee, c 1.0,
The ee value (78% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 43.67 min and 48.83 min for isomer.]

\((E)-2-(1-\text{(methyl}diphenylsilyl)\text{oxy})-5\text{-phenylpent-4-en-2-yl})\text{pyridine (3e)}\)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\text{H NMR}\) (CDCl₃) \(\delta\) 0.51 (s, 3H), 2.63–2.76 (m, 2H), 3.15 (quint, \(J = \text{6.4 Hz, 1H}\)), 3.96–4.04 (m, 2H), 6.07 (dt, \(J = \text{14.4, 6.8 Hz, 1H}\)), 6.32 (d, \(J = \text{15.6 Hz, 1H}\)), 7.10–7.13 (m, 1H), 7.15–7.18 (m, 2H), 7.21–7.26 (m, 4H), 7.29–7.40 (m, 4H), 7.45–7.50 (m, 4H), 7.56 (td, \(J = \text{8.0, 2.0 Hz, 1H}\)), 8.55 (dd, \(J = \text{4.8, 0.8 Hz, 1H}\)). \(^{13}\text{C NMR}\) (CDCl₃) \(\delta\) 34.56, 39.25, 44.52, 55.13, 65.66, 96.38, 121.38, 123.21, 125.95 (2C), 126.88, 128.37 (2C), 131.49, 136.12, 137.58, 149.52, 163.55. \([\alpha]_{25}^D = \text{–23.21 (76% ee, c 1.0, CHCl}_3\text{). The ee value (71% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 24.99 min and 29.30 min for isomer.]}\)

\((E)-2-(1-\text{(methoxymethoxy})-6\text{-phenylhex-5-en-3-yl})\text{pyridine (3f)}\)

Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. \(^1\text{H NMR}\) (CDCl₃) \(\delta\) 2.03–2.17 (m, 2H), 2.55–2.69 (m, 2H), 3.07–3.13 (m, 1H), 3.30 (S, 2H), 3.32–3.37 (m, 2H), 3.42–3.48 (m, 1H), 6.08 (dt, \(J = \text{14.4, 7.2 Hz, 1H}\)), 6.33 (d, \(J = \text{16.0 Hz, 1H}\)), 7.09–7.19 (m, 3H), 7.24–7.26 (m, 4H), 7.58 (td, \(J = \text{7.6, 2.0 Hz, 1H}\)), 8.58 (dd, \(J = \text{4.0, 3.2 Hz, 1H}\)). \(^{13}\text{C NMR}\) (CDCl₃) \(\delta\) 34.56, 39.25, 44.52, 55.13, 65.66, 96.38, 121.38, 123.21, 125.95 (2C), 126.88, 128.37 (2C), 131.49, 136.12, 137.58, 149.52, 163.55. \([\alpha]_{25}^D = \text{–43.49 (76% ee, c 1.2, CHCl}_3\text{). The ee value (76% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 98:2, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 16.59 min and 17.98 min for isomer.]}\)
(E)-2-(1-(1,3-dioxolan-2-yl)-5-phenylpent-4-en-2-yl)pyridine (3g)

Isolated by silica gel chromatography (hexane/EtOAc 70:30). White solid. $^1$H NMR (CDCl$_3$) δ 2.02 (ddd, $J = 13.8$, 6.6, 4.8 Hz, 1H), 2.27–2.34 (m, 1H), 2.56–2.71 (m, 2H), 3.12–3.20 (m, 1H), 3.71–3.81 (m, 2H), 3.89–3.94 (m, 2H), 4.67 (dd, $J = 7.2$, 4.0 Hz, 1H), 6.06 (dt, $J = 15.6$, 8.0 Hz, 1H), 6.32 (d, $J = 16.0$ Hz, 1H), 7.09–7.19 (m, 3H), 7.23–7.26 (m, 4H), 7.57 (td, $J = 7.6$, 1.6 Hz, 1H), 8.59 (ddd, $J = 6.0$, 1.8, 0.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 38.60, 39.47, 43.62, 64.71, 64.75, 103.10, 121.36, 123.16, 125.98, 126.89, 128.16, 128.36, 131.69, 136.11, 136.58, 149.46, 163.43. HRMS–EI (m/z): [M] Calcd for C$_{19}$H$_{21}$N$_2$O$_2$, 295.15723; found, 295.15648. $[\alpha]_{23}^D = -6.55$ (76% ee, c 0.60, CHCl$_3$). The ee value (69% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 98:2, 0.5 mL/min, 40 ºC, 220 nm UV detector, retention time = 29.90 min and 34.45 min for isomer.]

benzyl (E)-(5-phenyl-2-(pyridin-2-yl)pent-4-en-1-yl)carbamate (3h)

Isolated by silica gel chromatography (hexane/EtOAc 50:50). Colorless oil. $^1$H NMR (CDCl$_3$) δ 2.55–2.65 (m, 2H), 3.15 (quint, $J = 6.0$ Hz, 1H), 3.57–3.68 (m, 2H), 5.06 (s, 2H), 5.34 (br, 1H), 6.08 (dt, $J = 15.2$, 7.6 Hz, 1H), 6.33 (d, $J = 16.0$ Hz, 1H), 7.10–7.20 (m, 2H), 7.25–7.26 (m, 4H), 7.28–7.33 (m, 4H), 7.57 (td, $J = 7.2$, 1.6 Hz, 1H), 8.55 (d, $J = 4.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 36.55, 44.43, 47.10, 66.54, 121.77, 123.64, 126.00 (2C), 127.01, 127.39, 128.03, 128.07, 128.39 (2C), 128.45 (2C), 128.55, 131.92, 136.42, 136.58, 137.34, 149.43, 156.38, 161.93. HRMS–ESI (m/z): [M+H]$^+$ Calcd for C$_{24}$H$_{25}$N$_2$O$_2$, 373.19105; found, 373.19156. $[\alpha]_{23}^D = -9.34$ (76% ee, c 1.0, CHCl$_3$). The ee value (71% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 90:10, 0.5 mL/min, 40 ºC, 220 nm UV detector, retention time = 28.61 min and 32.47 min for isomer.]

(E)-2-(1-((methyldiphenylsilyl)oxy)-5-phenylpent-4-en-2-yl)pyridine (3i)

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Isolated by silica gel chromatography (hexane/EtOAc 70:30). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 2.10–2.18 (m, 2H), 2.22–2.25 (m, 2H), 2.52–2.59 (m, 1H), 2.62–2.70 (m, 1H), 2.91 (quint, $J = 8.0$ Hz, 1H), 5.06 (s, 2H), 6.05 (dt, $J = 14.8$, 7.2 Hz, 1H), 6.32 (d, $J = 16.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 7.08–7.11 (m, 1H), 7.14–7.19 (m, 1H), 7.22–7.25 (m, 4H), 7.29–7.36 (m, 4H), 7.55 (td, $J = 8.0$, 2.0 Hz, 1H), 8.56–8.58 (m, 1H).

$^{13}$C NMR (CDCl$_3$) $\delta$ 29.64, 32.15, 39.08, 47.14, 66.07, 121.48, 123.10, 125.94 (2C), 126.89, 128.11, 128.13, 128.16 (2C), 128.34 (2C), 128.47 (2C), 131.56, 135.91, 136.19, 137.47, 149.54, 163.01, 173.18.

HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{25}$H$_{30}$NO$_2$, 372.19581; found, 372.19647. $[\alpha]_{D}^{29} = -72.61$ (84% ee, c 1.5, CHCl$_3$). The ee value (84% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 28.97 min and 30.53 min for isomer.]

(E)-8-phenyl-5-(pyridin-2-yl)oct-7-en-2-one (3j)

Isolated by silica gel chromatography (hexane/EtOAc 80:20). Colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.98–2.13 (m, 2H), 2.05 (s, 3H), 2.23–2.37 (m, 2H), 2.56 (quint, $J = 6.8$ Hz, 1H), 2.66 (quint, $J = 6.8$ Hz, 1H), 2.86–2.93 (m, 1H), 6.07 (dt, $J = 14.4$, 7.6 Hz, 1H), 6.33 (d, $J = 15.2$ Hz, 1H), 7.09–7.19 (m, 3H), 7.24–7.26 (m, 4H), 7.60 (td, $J = 7.2$, 1.6 Hz, 1H), 8.58 (d, $J = 4.4$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 28.59, 29.89, 39.23, 41.49, 47.21, 121.51, 122.91, 125.96 (2C), 126.92, 128.18, 128.38 (2C), 131.57, 136.29, 137.51, 149.50, 163.42, 208.71.

HRMS–ESI ($m/z$): [M+H]$^+$ Calcd for C$_{19}$H$_{22}$NO, 280.16959; found, 280.16981. $[\alpha]_{D}^{23} = -27.97$ (81% ee, c 1.0, CHCl$_3$). The ee value (81% ee) was determined by chiral HPLC analysis. [CHIRALCEL® AD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 98:2, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 30.12 min and 33.39 min for isomer.]
**[(E)-8-(3-(4-methoxyphenyl)allyl)-5,6,7,8-tetrahydroquinoline (3k)](\text{image})**

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.69–1.99 (m, 4H), 2.41–2.49 (m, 1H), 2.70–2.82 (m, 2H), 2.93–3.05 (m, 2H), 3.80 (s, 3H), 6.12 (ddd, $J = 14.8, 6.4, 2.0$ Hz, 1H), 6.40 (d, $J = 16.0$ Hz, 1H), 6.82–6.86 (m, 2H), 7.03 (dd, $J = 7.6, 4.4$ Hz, 1H), 7.27–7.30 (m, 2H), 7.36 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.43 (dd, $J = 5.2, 1.2$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 19.73, 27.10, 29.22, 38.73, 40.84, 55.28, 113.85 (2C), 120.91, 127.05 (2C), 127.27, 130.62, 130.80, 132.43, 136.73, 146.94, 158.65, 159.73. HRMS–EI (m/z): [M] Calcd for C$_{19}$H$_{21}$N$_2$O, 279.16231; found, 279.16127. [$\alpha$]$_{D}^{24}$ = +117.36 (94% ee, c 1.0, CHCl$_3$). The ee value (94% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 13.76 min and 16.93 min for isomer.]

**[(E)-8-(3-(3,5-dimethoxyphenyl)allyl)-5,6,7,8-tetrahydroquinoline (3l)](\text{image})**

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. $^1$H NMR (CDCl$_3$) δ 1.70–2.00 (m, 4H), 2.47 (dt, $J = 11.0, 8.4$ Hz, 1H), 2.70–2.82 (m, 2H), 2.95–3.07 (m, 2H), 3.80 (s, 6H), 6.22–6.29 (m, 1H), 6.34 (t, $J = 2.4$ Hz, 1H), 6.39 (d, $J = 16.4$ Hz, 1H), 6.51 (d, $J = 2.0$ Hz, 2H), 7.04 (dd, $J = 8.0, 4.8$ Hz, 1H), 7.36 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.43 (dd, $J = 4.4, 1.2$ Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 19.79, 27.21, 29.20, 38.63, 40.71, 55.30 (2C), 99.11, 104.08 (2C), 120.96, 130.14, 131.41, 132.44, 136.75, 139.81, 146.95, 159.54. HRMS–EI (m/z): [M] Calcd for C$_{20}$H$_{23}$NO$_2$, 309.17288; found, 309.17256. [$\alpha$]$_{D}^{25}$ = +93.03 (93% ee, c 1.00, CHCl$_3$). The ee value (93% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, 157]
hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retention time = 19.86 min and 22.18 min for isomer.]

(E)-8-(3-(benzo[d][1,3]dioxol-5-yl)allyl)-5,6,7,8-tetrahydroquinoline (3m)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.68-1.99 (m, 4H), 2.45 (dt, \(J = 13.6, 9.2\) Hz, 1H), 2.69–2.81 (m, 2H), 2.92–3.05 (m, 2H), 5.93 (s, 2H), 6.10 (dt, \(J = 15.6, 4.4\) Hz, 1H), 6.36 (d, \(J = 16.0\) Hz, 1H), 6.72–6.78 (m, 2H), 6.90 (d, \(J = 1.6\) Hz, 1H), 7.03 (dd, \(J = 7.6, 4.8\) Hz, 1H), 7.35 (d, \(J = 6.8\) Hz, 1H), 8.42 (dd, \(J = 4.8, 2.0\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 19.74, 27.13, 29.18, 38.59, 40.77, 100.88, 105.40, 108.15, 120.29, 120.91, 127.68, 130.97, 132.28, 132.41, 136.72, 146.55, 146.90, 147.84, 159.59. HRMS–ESI (m/z): [M+H] \(^+\) Calcd for C\(_{19}\)H\(_{19}\)NO\(_2\), 293.1405; found, 293.14158. \([\alpha]_{21}^{D} = +111.74\) (92% ee, c 1.0, CHCl\(_3\)). The ee value (92% ee) was determined by chiral HPLC analysis. [CHIRALCEL\(^R\) OD-3 column, 4.6 mm \(\times\) 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retention time = 15.40 min and 19.52 min for isomer.]

(E)-8-(3-(3-bromophenyl)allyl)-5,6,7,8-tetrahydroquinoline (3n)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.68-2.01 (m, 4H), 2.49 (dt, \(J = 9.2, 8.0\) Hz, 1H), 2.70-2.82 (m, 2H), 2.96-3.06 (m, 2H), 6.24–6.31 (m, 1H), 6.38 (d, \(J = 16.0\) Hz, 1H), 7.04 (dd, \(J = 7.6, 5.2\) Hz, 1H), 7.14 (t, \(J = 8.0\) Hz, 1H), 7.24 (d, \(J = 7.6\) Hz, 1H), 7.31 (dd, \(J = 8.0, 1.6\) Hz, 1H), 7.36 (t, \(J = 8.0\) Hz, 1H), 7.48–7.49 (m, 1H), 8.43 (dd, \(J = 5.2, 1.2\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 19.81, 27.30, 29.16, 38.60, 40.64, 121.00, 122.64, 124.64, 128.79, 129.79, 129.93, 130.09, 131.19, 132.42, 136.77, 139.89, 146.92, 159.32. HRMS–ESI (m/z): [M+H]\(^+\) Calcd for C\(_{19}\)H\(_{19}\)NBr, 328.06954; found, 328.06989. \([\alpha]_{22}^{D} = +93.15\) (90% ee, c 1.0, CHCl\(_3\)). The ee value (90% ee) was determined by chiral HPLC analysis. [CHIRALCEL\(^R\) OD-3 column, 4.6 mm \(\times\) 250 mm, Daicel
Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retension time = 11.77 min and 14.66 min for isomer.]

\((E)-8-(3-(naphthalen-1-yl)allyl)-5,6,7,8-tetrahydroquinoline (3o)\)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.72–1.81 (m, 1H), 1.87–1.99 (m, 3H), 2.01–2.09 (m, 1H), 2.61–2.69 (m, 1H), 2.72–2.84 (m, 2H), 3.06–3.15 (m, 2H), 6.24–6.31 (m, 1H), 7.05 (dd, \(J = 7.6, 4.8\) Hz, 1H), 7.17 (d, \(J = 15.6,\) Hz, 1H), 7.37 (d, \(J = 7.6\) Hz, 1H), 7.42 (t, \(J = 8.0\) Hz, 1H), 7.46–7.50 (m, 2H), 7.55 (d, \(J = 7.2\) Hz, 1H), 7.74 (d, \(J = 8.4\) Hz, 1H), 7.83 (dd, \(J = 6.8, 2.8\) Hz, 1H), 8.09 (d, \(J = 7.2\) Hz, 1H), 8.46 (d, \(J = 3.2\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 19.94, 27.37, 29.25, 39.04, 40.79, 120.96, 123.59, 123.96, 125.60, 125.64, 125.77, 127.26, 128.40, 128.76, 131.06, 132.52, 132.70, 133.54, 136.64. HRMS – EI (m/z): [M] Calcd for C\(_{22}\)H\(_{21}\)N, 299.16740; found, 299.16700. \(\boldsymbol{[\alpha]}\)\(_{25}^D\) = +93.34 (88% ee, c 1.0, CHCl\(_3\)). The ee value (88% ee) was determined by chiral HPLC analysis. [CHIRALCEL\(^\circledR\) OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retension time = 20.01 min and 24.83 min for isomer.]

\((E)-8-(3-(5-methylfuran-2-yl)allyl)-5,6,7,8-tetrahydroquinoline (3p)\)

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.68–1.91 (m, 3H), 1.94–2.00 (m, 1H), 2.29 (s, 3H), 2.33–2.44 (m, 1H), 2.69–2.82 (m, 2H), 2.94–3.04 (m, 2H), 5.92–5.99 (m, 1H), 6.01 (d, \(J = 2.8\) Hz, 1H), 6.08–6.16 (m, 1H), 6.21 (d, \(J = 15.6\) Hz, 1H), 7.03 (dd, \(J = 7.2, 4.4\) Hz, 1H), 7.35 (dd, \(J = 8.0, 0.8\) Hz, 1H), 8.42 (dd, \(J = 4.4, 1.2\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 13.64, 19.70, 27.10, 29.18, 38.50, 40.76, 107.03, 107.23, 120.30, 120.90, 126.65, 132.40, 136.73, 146.87, 151.17, 151.59, 159.62. HRMS – EI (m/z): [M] Calcd for C\(_{17}\)H\(_{19}\)NO, 253.14666; found, 253.14658. \(\boldsymbol{[\alpha]}\)\(_{25}^P\) = +26.07 (87% ee, c 0.30, CHCl\(_3\)). The ee value (87% ee) was determined by chiral HPLC analysis.
[CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 17.71 min and 22.48 min for isomer.]

\((E)-8-(3\text{-}(\text{thiophen-3-yl})\text{allyl})-5,6,7,8\text{-tetrahydroquinoline (3q)}\)

\[
\text{Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil.} \quad \text{\textsuperscript{1}H NMR (CDCl}_3\text{) } \delta 1.69–2.00 (m, 4H), 2.43 (dt, J = 12.8, 8.4 Hz, 1H), 2.70–2.82 (m, 2H), 2.93–3.05 (m, 2H), 6.08–6.16 (m, 1H), 6.46 (d, J = 16.0 Hz, 1H), 7.02–7.06 (m, 2H), 7.19 (dd, J = 4.8, 1.2 Hz, 1H), 7.23–7.25 (m, 1H), 7.35 (d, J = 7.6 Hz, 1H), 8.42 (dd, J = 4.8, 1.6 Hz, 1H).
\]

\text{\textsuperscript{13}C NMR (CDCl}_3\text{) } \delta 19.73, 27.13, 29.19, 38.62, 40.71, 120.53, 120.94, 124.99, 125.72, 125.75, 129.42, 132.43, 136.74, 140.36, 146.93, 159.60.

\text{HRMS – ESI (m/z): } [M] \text{ Calcd for } C_{16}H_{17}NS, 255.10817; \text{ found, 255.10762. } [\alpha]_{20}^D = +191.94 \text{ (91% ee, c 1.0, CHCl}_3\text{). The ee value (91% ee) was determined by chiral HPLC analysis.} \quad \text{[CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 16.49 min and 22.24 min for isomer.}]

\((E)-8-(3\text{-}(1\text{-}tosyl\text{-}1H\text{-}indol-3-yl)\text{allyl})-5,6,7,8\text{-tetrahydroquinoline (3r)}\)

\[
\text{Isolated by silica gel chromatography (hexane/EtOAc 80:20). Colorless oil.} \quad \text{\textsuperscript{1}H NMR (CDCl}_3\text{) } \delta 1.72-2.05 (m, 4H), 2.33 (s, 3H), 2.50-2.60 (m, 1H), 2.71-2.83 (m, 2H), 6.29-6.36 (m, 1H), 2.50 (d, J = 16.0 Hz, 1H), 7.05 (dd, J = 7.6, 5.2 Hz, 1H), 7.207-7.26 (m, 3H), 7.31 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.52 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 3.6 Hz, 1H).
\]

\text{\textsuperscript{13}C NMR (CDCl}_3\text{) } \delta 19.81, 21.55, 27.30, 29.19, 39.21, 40.79, 113.67, 120.36, 120.92, 121.00, 121.79, 122.80, 123.32, 124.73, 126.80, 129.28, 129.84, 131.17, 132.45, 135.12, 135.42, 136.79, 144.87, 146.94, 159.46. \text{HRMS – ESI (m/z): } [M+H]^+ \text{ Calcd for } C_{27}H_{27}N_2O_2S,
$[\alpha]_{25}^D = +17.76$ (93% ee, c 0.50, CHCl$_3$). The ee value (93% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:2, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 37.48 min and 40.23 min for isomer.]

References


Publication List

1. Publications related to this thesis

1) Stereoselective C–H Borylations of Cyclopropanes and Cyclobutanes with Silica-Supported Monophosphane-Ir Catalysts.

2) Site-selective and Stereoselective C(sp3)–H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Ir Catalyst.

2. Other publications (not related to this thesis)


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