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

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Contents

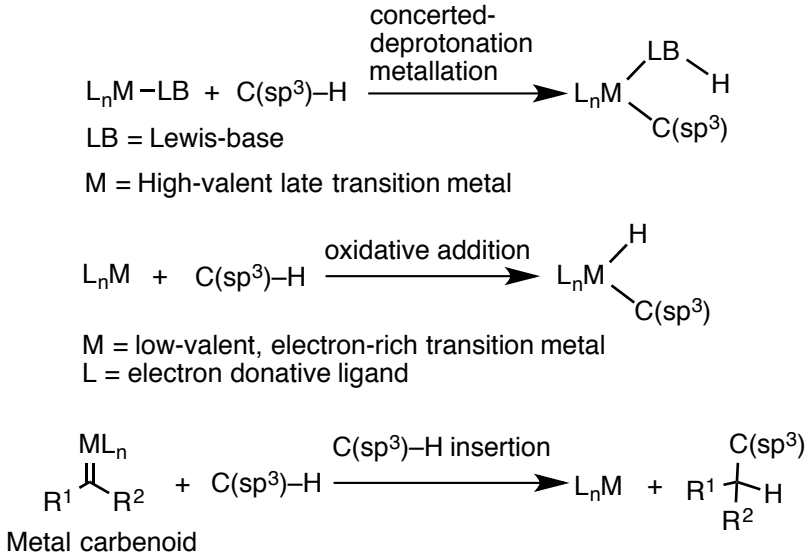
General Introduction

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 π-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]

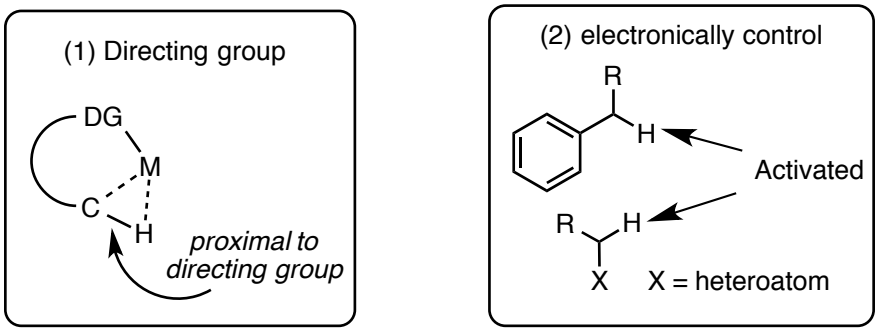
1.1. Types of C(sp^3)–H Activation. The main types of C(sp^3)–H activation with transition metal catalysts can be categorized as follows: 1) concerted metalation-deprotonation (CMD) of C(sp^3)–H bonds; 2) oxidative addition of C(sp^3)–H bonds; and 3) metal-carbene insertion into C(sp^3)–H bonds. These 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[4]. 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[5]. 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.

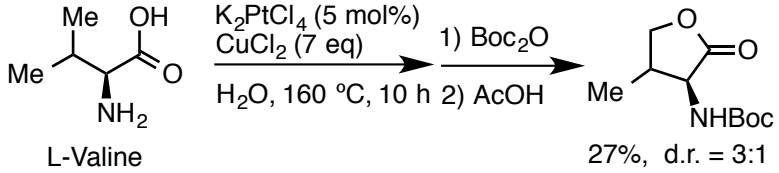
Scheme 2. Strategies for Controlling Site-selectivity



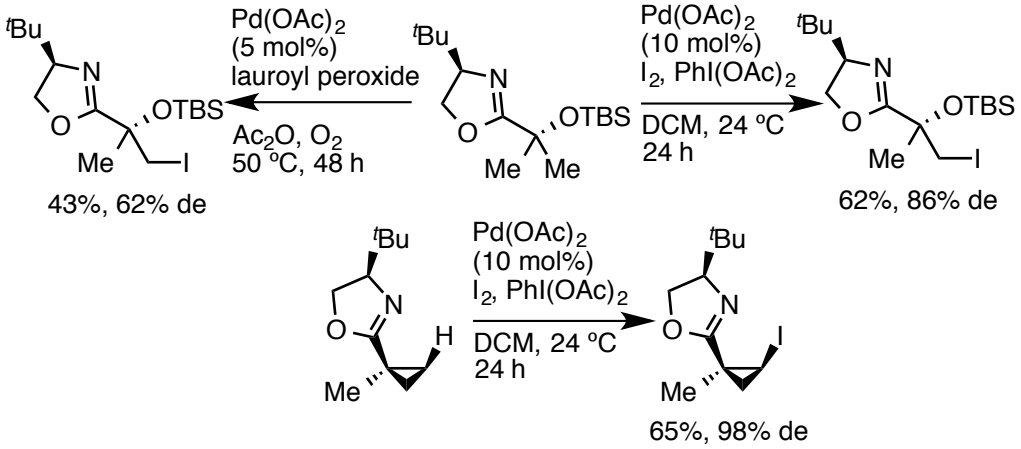
1.3. Site-selective and Stereoselective C(sp^3)–H Functionalization

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.

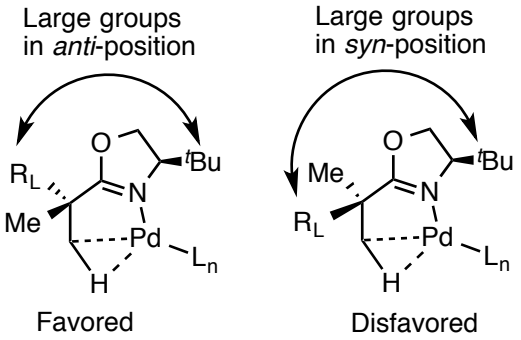
Scheme 3. Chiral Substrate-controlled Diastereoselective Reaction: The First Report



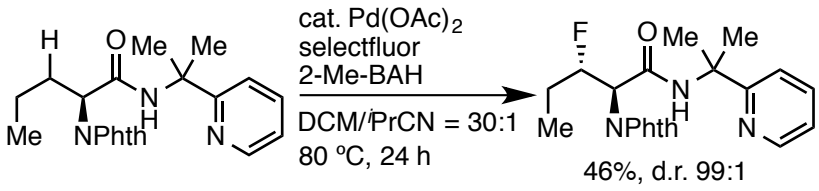
Scheme 4. Auxiliaries-controlled Diastereoselective C(sp^3)–H Functionalization



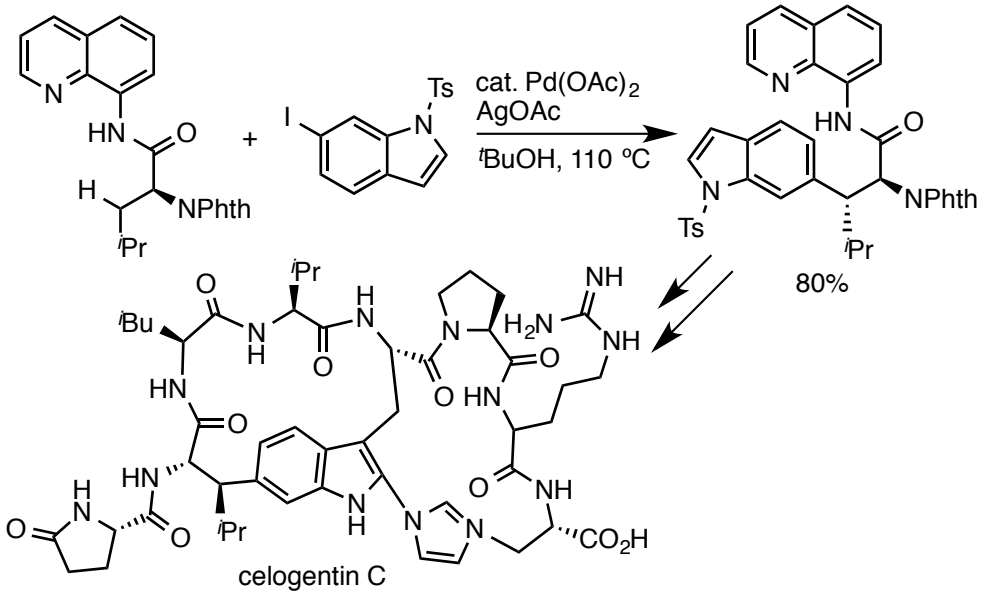
Scheme 5. Asymmetric Induction Model: Yu's work



Scheme 6. Stereoselective C(sp^3)–H Fluorination

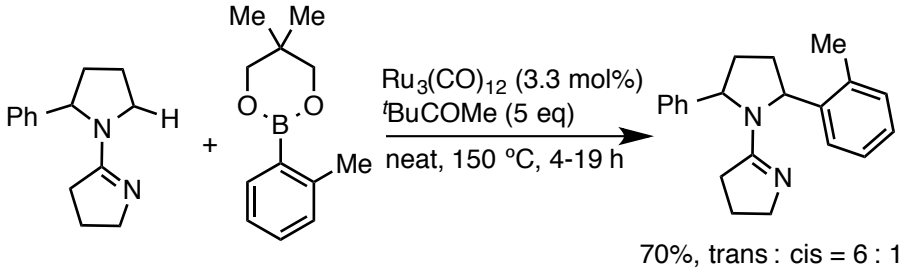


Scheme 7. Synthesis of Natural Product Based on C(sp^3)–H Functionalization Strategy

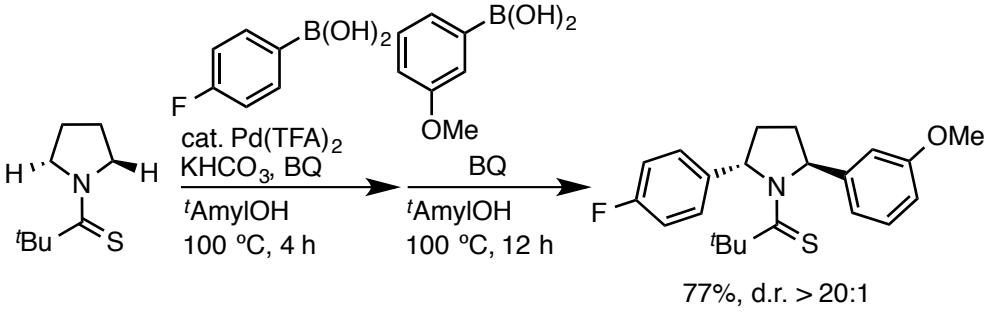


1.3.2. Stereoselective C(sp^3)–H functionalization. Stereoselective C(sp^3)–H functionalization controlled by chiral directing groups has been a mainstay of organic chemistry. The transition metal-catalyzed stereoselective C(sp^3)–H functionalization of achiral substrates offers an alternative strategy 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].

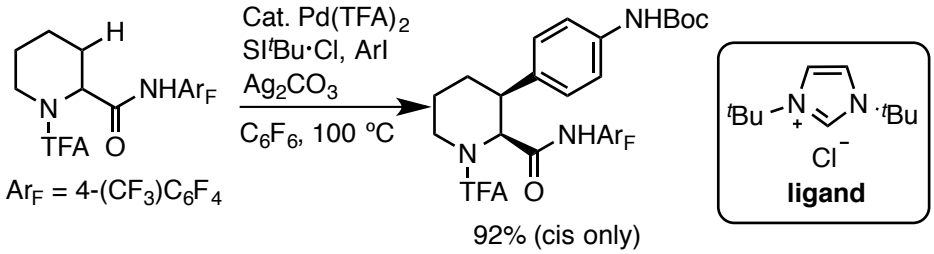
Scheme 8. Stereoselective C(sp^3)–H Arylation: First Report



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

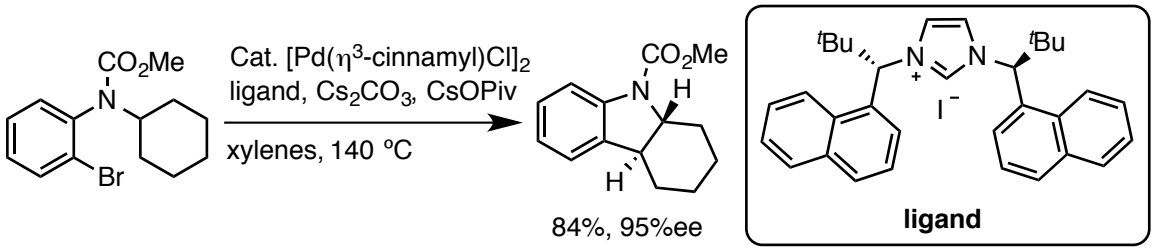


Scheme 10. Ligand-enabled Stereoselective C(sp^3)–H Arylation: Yu group

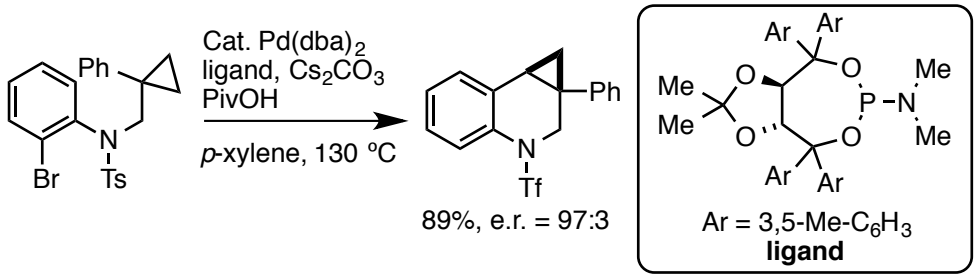


1.3.3. Enantioselective C(sp^3)–H functionalization. The enantioselective functionalization of prochiral C(sp^3)–H bonds could be a useful and direct method for the synthesis of chiral compounds[16]. Recently, many groups have achieved enantioselective C(sp^3)–H functionalization reactions. Kundig's 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

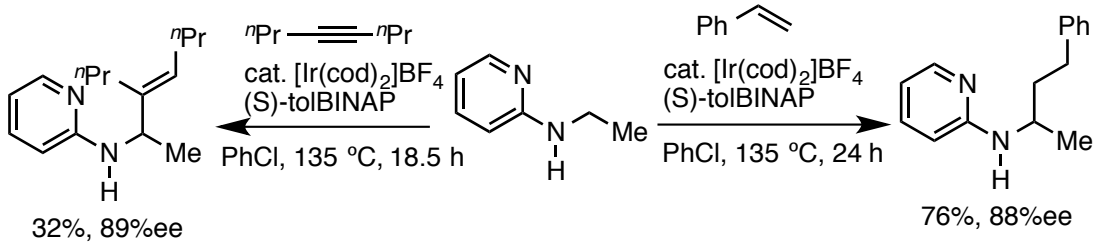


Scheme 12. Enantioselective Intramolecular C(sp^3)–H Functionalization: Cramer group

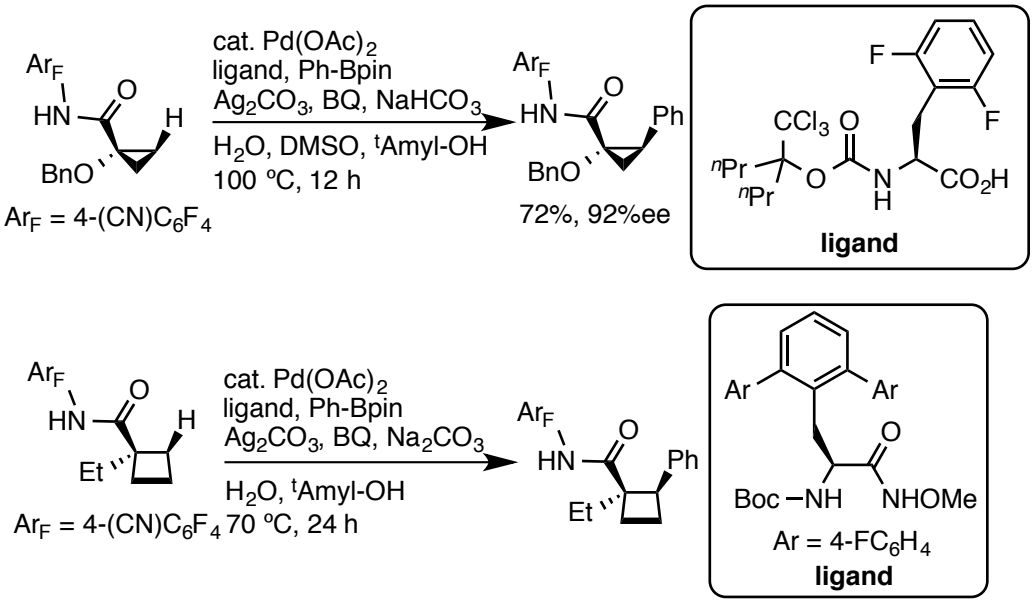


Enantioselective intermolecular C(sp^3)–H functionalization reactions are more challenging and still rare[19]. Shibata and co-workers reported enantioselective nitrogen-adjacent C(sp^3)–H alkylation and alkenylation of 2-(alkylamino)pyridines with a cationic chiral bisphosphine-Ir complex (Scheme 13)[20]. Yu and co-worker described the enantioselective C–H functionalization of small-ring carbocycles such as cyclopropanes[21] and cyclobutanes[22] 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 phospholic acid. This catalytic reaction revealed that the chiral anionic ligand was effective for the Pd-catalyzed enantioselective C(sp^3)–H functionalization (Scheme 15)[23]. Additionally, the Yu group reported enantioselective unactivated C(sp^3)–H arylation with palladium catalysts prepared from chiral acetyl-protected aminoethyl quinoline (APAQ) ligands (Scheme 16)[24]. These reports have broken the barrier to transition metal-catalyzed enantioselective unactivated C(sp^3)–H functionalizations.

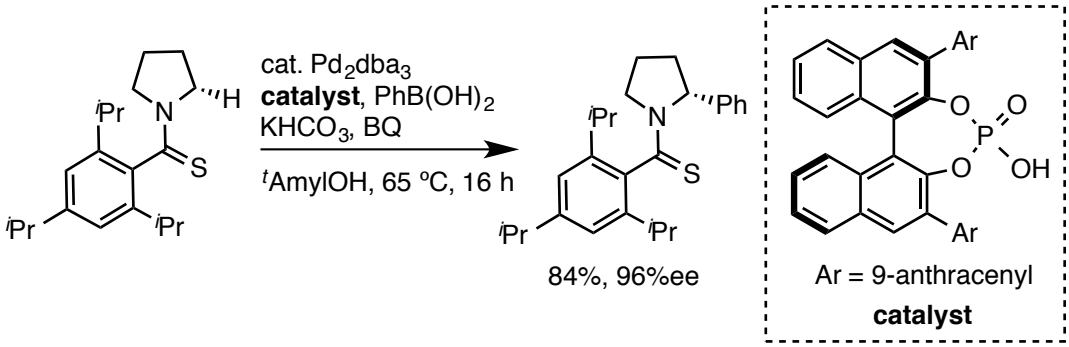
Scheme 13. Chiral Ir-catalyzed Enantioselective N-adjacent C(sp^3)–H Functionalization



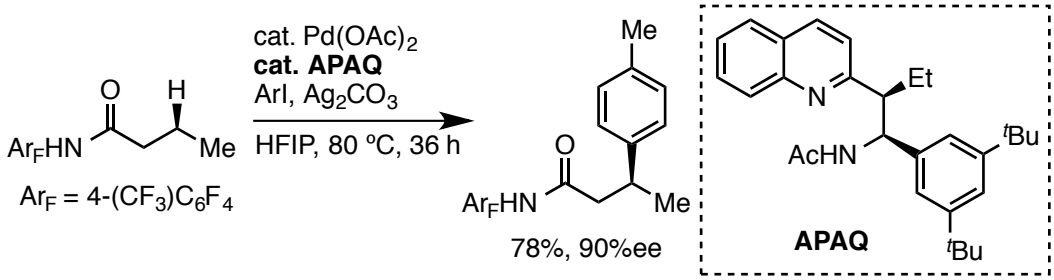
Scheme 14. Pd-catalyzed Enantioselective C(sp^3)–H Functionalization of Small-ring Carbocycles



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



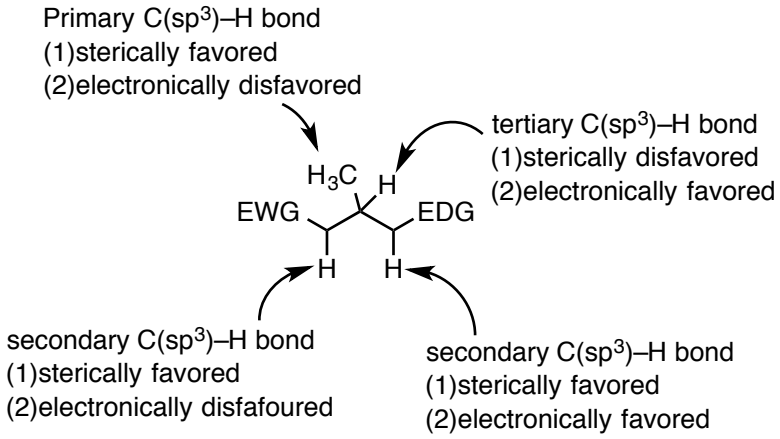
Scheme 16. Pd-catalyzed Enantioselective Unactivated C(sp^3)–H Arylation



1.4. Enantioselective Functionalization of Internal C(sp^3)–H Bonds through Metal Carbenoid Insertion

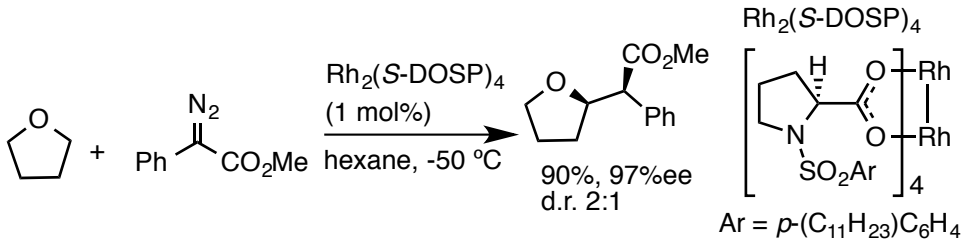
The carbene C–H insertion is a powerful method for functionalization of unactivated C–H bonds. The metal carbenoid species are generally prepared from diazo compounds. The carbene-induced C(sp^3)–H insertion can lead to high levels of site- and stereoselectivity. The rhodium-catalyzed C(sp^3)–H insertion reaction was found to be particularly effective. The regioselectivity of this C(sp^3)–H insertion chemistry is summarized in Scheme 17[25]. The C(sp^3)–H carbenoid reactions proceed with electronically activated C(sp^3)–H bonds for stabilization of the polarization, and thus the C(sp^3)–H insertion occurs with a partial positive charge build-up at the carbon atom.

Scheme 17. Carbenoid Reactivity

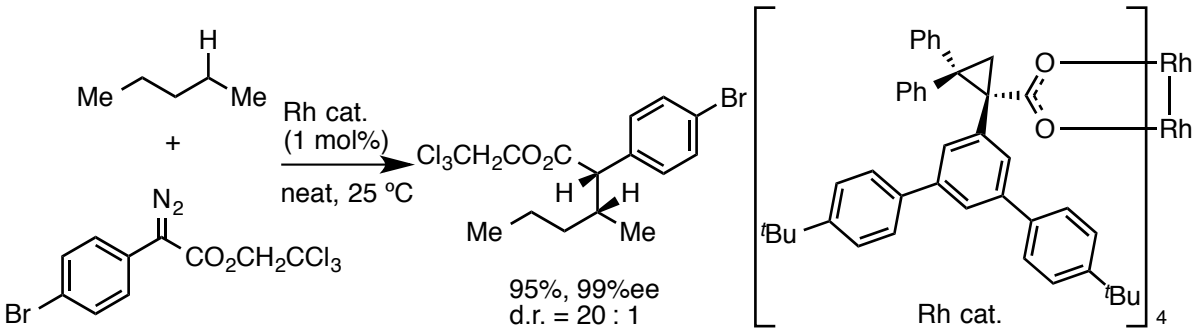


Davies and co-worker reported that rhodium carbenoids derived from methyl diazoacetates enabled the effective catalytic asymmetric internal C(sp^3)–H functionalization (Scheme 18)[26]. This reaction occurred with high regio- and enantioselectivity. Recently, the same group reported that site-selective and stereoselective functionalization of unactivated internal C(sp^3)–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(sp^3)–H Bonds



Scheme 19. Rhodium-catalyzed Enantioselective Unactivated C(sp^3)–H Insertion Reaction

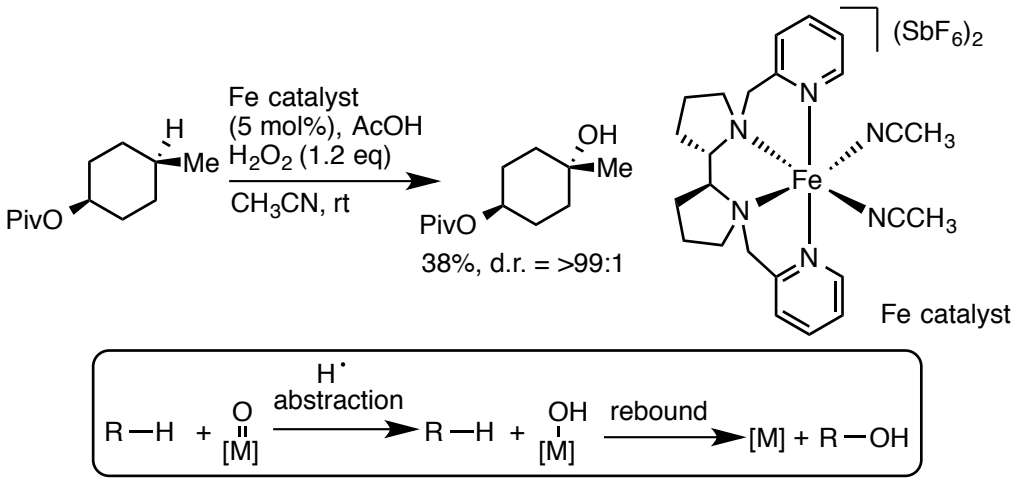


1.5. Site-selective C(sp^3)–H Functionalization with Metal-oxo Insertion

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(sp^3)–H functionalizations through generation of alkyl radical species have been well-studied for synthetic purposes[28]. Recently, White and co-workers reported the iron-catalyzed stereoselective oxidation of unactivated C(sp^3)–H bonds (Scheme 20)[29]. 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



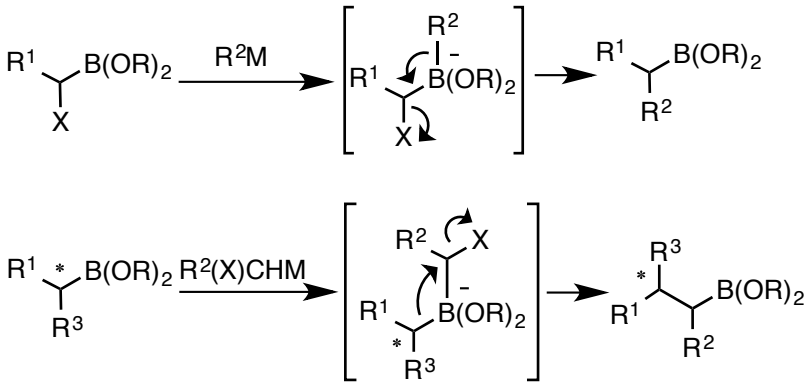
2. Transition Metal-catalyzed Site- and Stereoselective C(sp^3)–H Borylation

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.

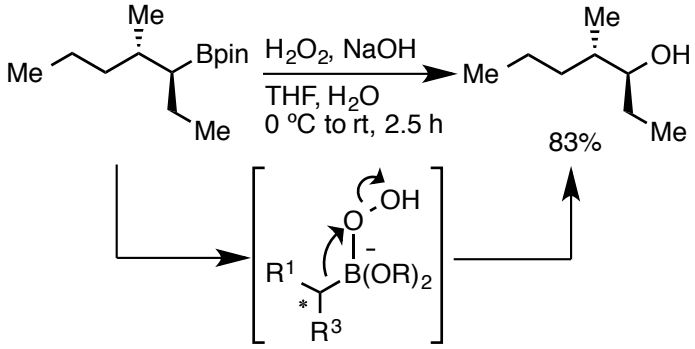
2.1.1. 1,2-Rearrangement[30]. In 1963, Matteson reported that 1,2-rearrangement of an organic group on a boron atom to the α-carbon occurred with organometallic reagents such as organolithium. Furthermore, the addition of α-alkyl carbanions to alkylboronates leads to one-carbon homologation of alkylboronates 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



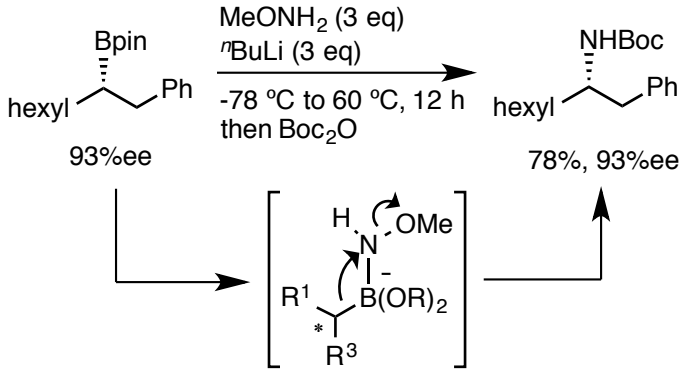
2.1.2. Oxidation. Alkylboronates can be converted into alcohol products by treatment with alkaline hydrogen peroxide (Scheme 22)[31]. The oxidation of α–chiral alkylboronates proceeds with retention of the configuration to afford the chiral alcohol products. The oxidation reaction proceeds with a boron 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)[32]. This amination occurred with retention of configuration, affording the chiral amine products.

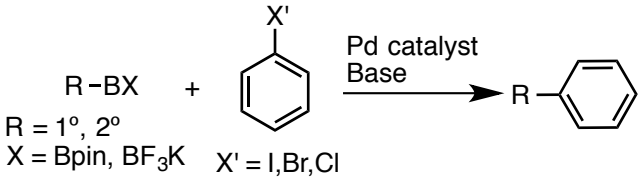
Scheme 23. Amination of Alkylboronates



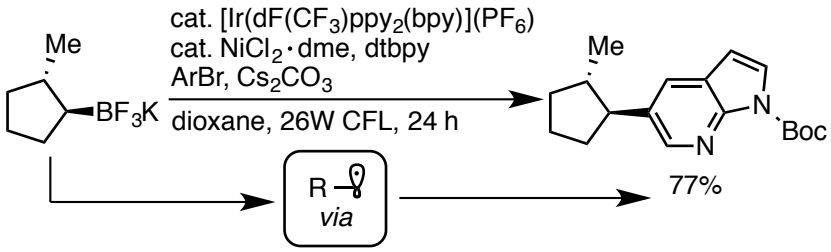
2.1.4. Transition metal-catalyzed cross-coupling with alkylboronates. In 1979, Suzuki and Miyaura reported the Pd-catalyzed cross-coupling reaction between aryl halides and alkenyl boranes[33]. This finding led to a breakthrough in organic synthesis. However, alkylboronates have been known to be unwilling 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[34]. To date, many groups have reported efficient Pd-catalyzed cross-coupling reactions between alkylboronates and aryl halides (Scheme 24)[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)[36].

Scheme 24. Suzuki-Miyaura Cross-coupling with Alkylboronates

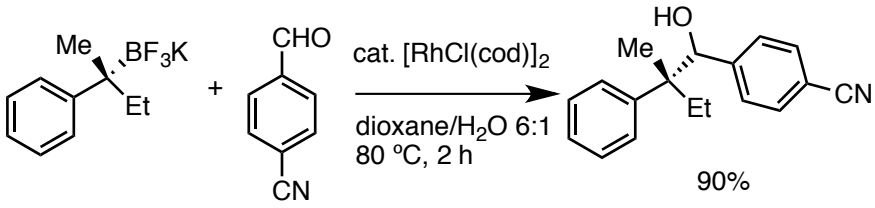


Scheme 25. Dual Catalyst: Photoredox / Cross-coupling



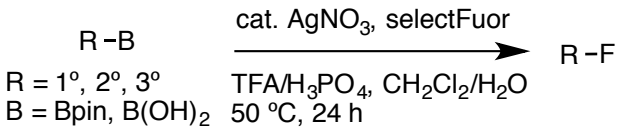
2.1.5. Rh-catalyzed 1,2-addition of alkylboronates to aldehydes. The rhodium-catalyzed 1,2-addition of boronic acid to aldehydes was achieved by Miyaura and co-workers[37]. However, the use of sp^3-carbon boron derivatives has been limited. Recently, Aggarwal and co-worker reported Rh-catalyzed stereoretention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

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



2.1.6. Ag-catalyzed fluorination of alkylboronates. In 2014, Li and co-workers achieved $AgNO_3$-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.

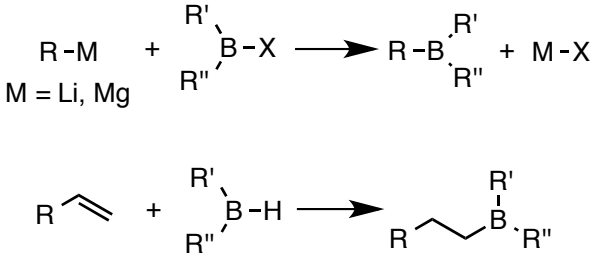
Scheme 27. Ag-catalyzed Fluorination of Alkylboronates: Li Group



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.

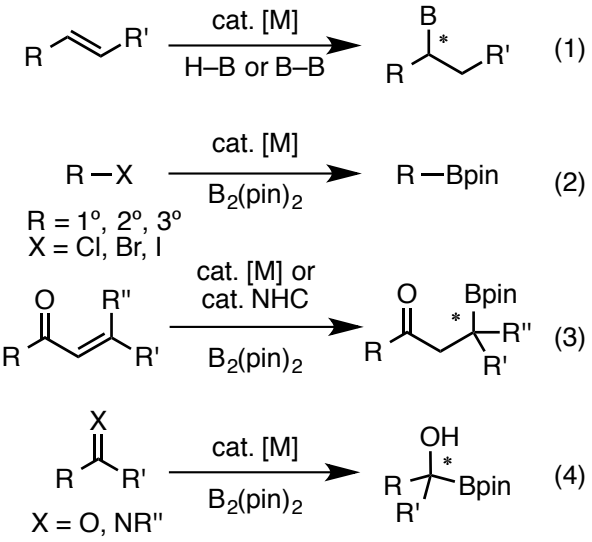
Scheme 28. Classical Reaction



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 reported[41]. 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 conditions[42]. 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 catalysts[43] or organocatalysts[44] has been developed. The asymmetric

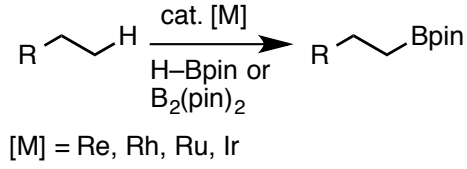
catalysis gives the corresponding chiral alkylboronates. 4) Cu-catalyzed 1,2-addition of diboron to carbonyl compounds was reported[45]. Recently, the Cu-catalyzed enantioselective addition reaction to give chiral α-alkoxy alkylboronates was achieved[46].

Scheme 29. Synthesis of Alkylboronates: Transition Metal Catalysts



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 achived by Hartwig and co-workers in 1999[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[48]. The regioselectivity of these catalytic reactions is controlled by the steric properties of the substrate.

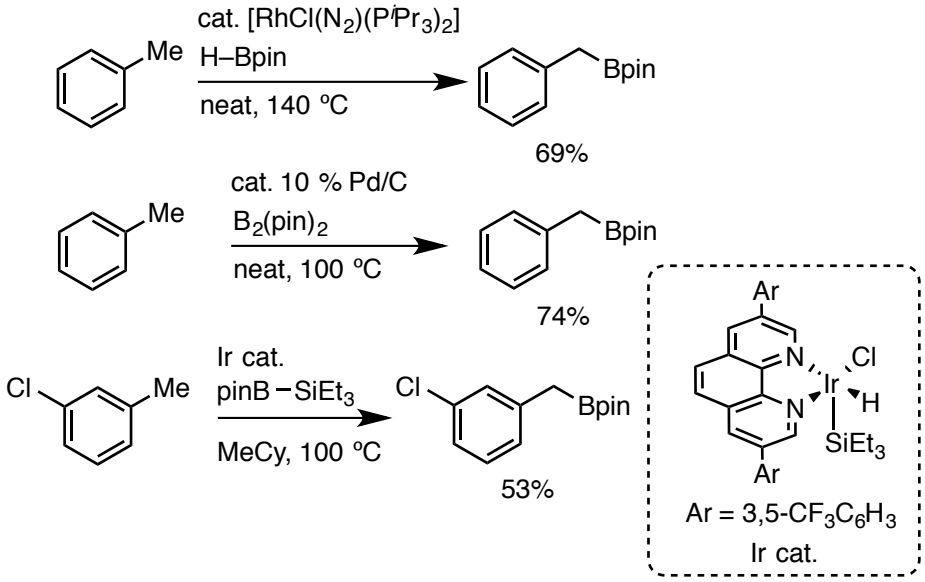
Scheme 30. Selective Borylation of Primary C(sp^3)–H Bonds



Marder and co-workers reported Rh-catalyzed benzylic C–H borylation[49]. However, this reaction competed with arene C–H borylation to give undesired products. Ishiyama, Miyaura

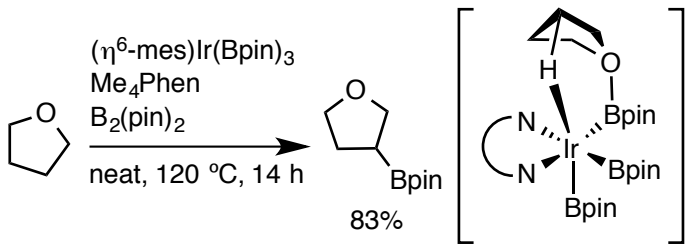
and co-workers described that a heterogeneous palladium-carbon catalyst was effective for benzylic C–H borylation of toluene[50]. The Hartwig group also developed Ir-catalyzed site-selective benzylic C–H borylation using $Et_3SiBpin$ as a boron source[51].

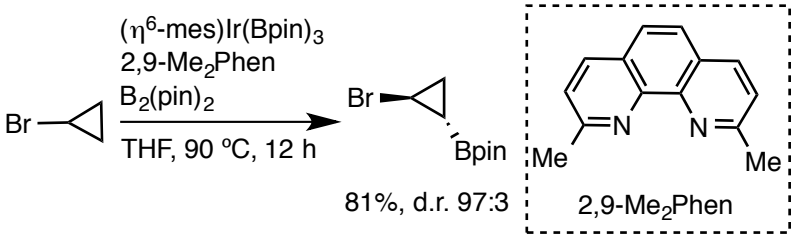
Scheme 31. Benzylic C(sp^3)–H Borylation



Recently, Hartwig and co-worker reported that an Ir–phenanthroline catalytic system enabled secondary C(sp^3)–H borylation within heterocyclic compounds such as cyclic ethers[52]. The origin of selective β–C(sp^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[53]. This stereoselectivity is due to avoidance of the substituent on the cyclopropane ring.

Scheme 32. Secondary C(sp^3)–H Borylation

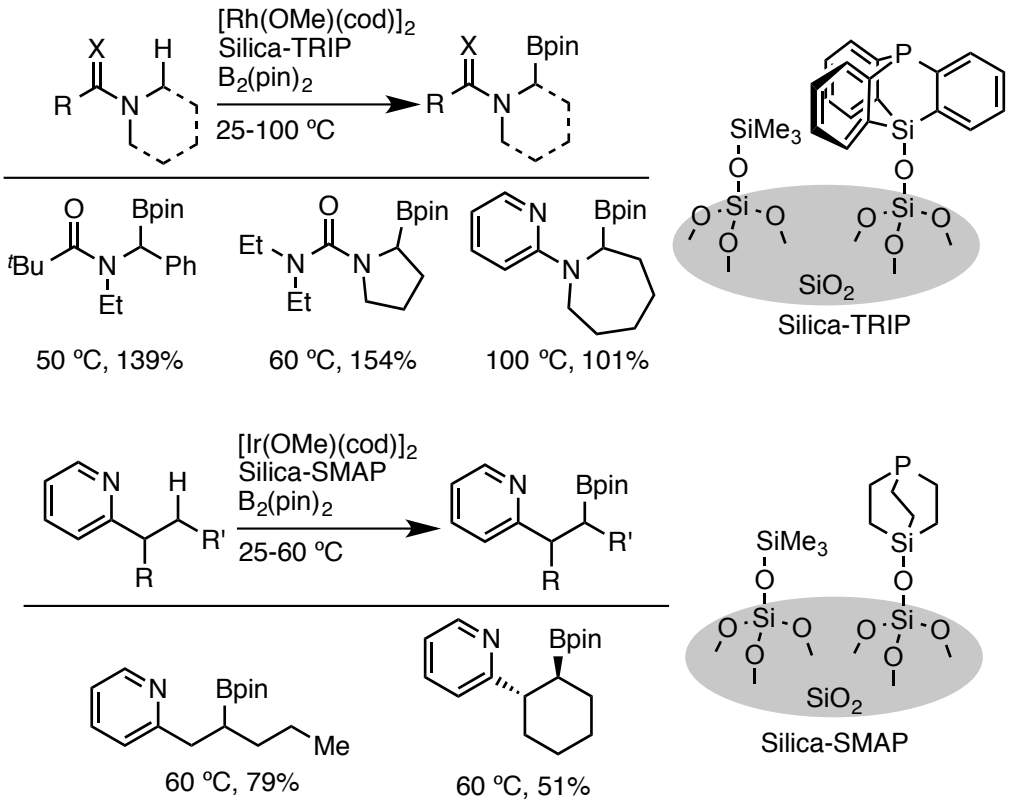




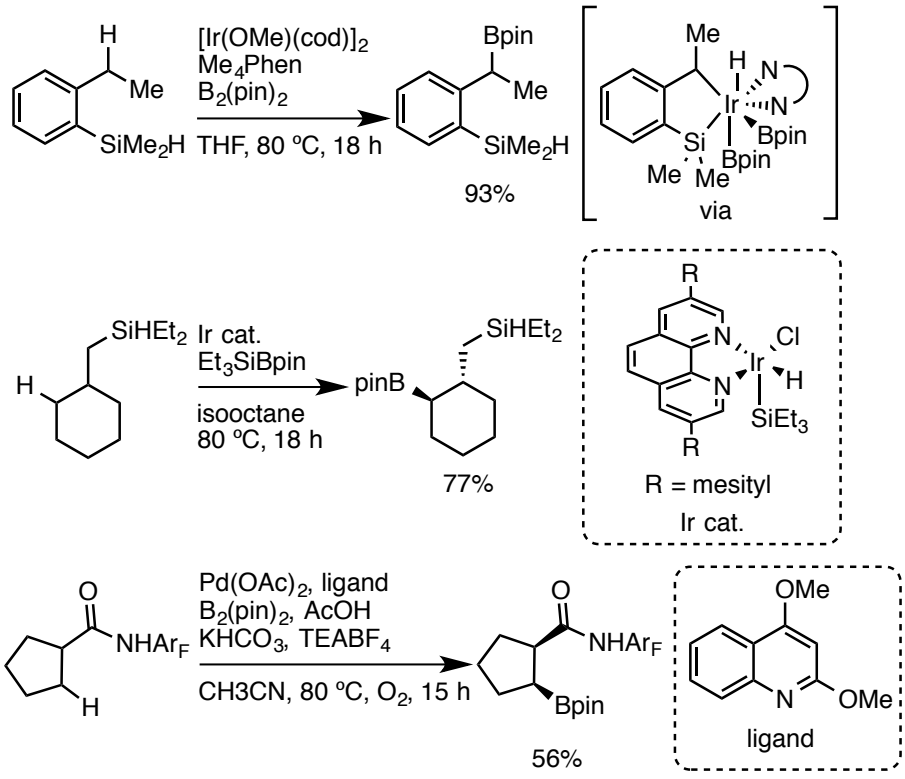
2.2.4. Transition metal-catalyzed heteroatom-directed C(sp^3)–H borylation. In general, the selectivity of transition metal-catalyzed C(sp^3)–H borylation favors primary C(sp^3)–H bonds, avoiding the steric hindrance of the substrate. Therefore, the scope of site-selective internal C(sp^3)–H borylation 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(sp^3)–H Borylation: Sawamura Group



Scheme 34. Heteroatom-directed Secondary C(sp^3)–H Borylation: Other Groups



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-alkylazaarenes. In chapter 3, the author describes the Pd-catalyzed linear selective allylation of 2-alkylazaarenes 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

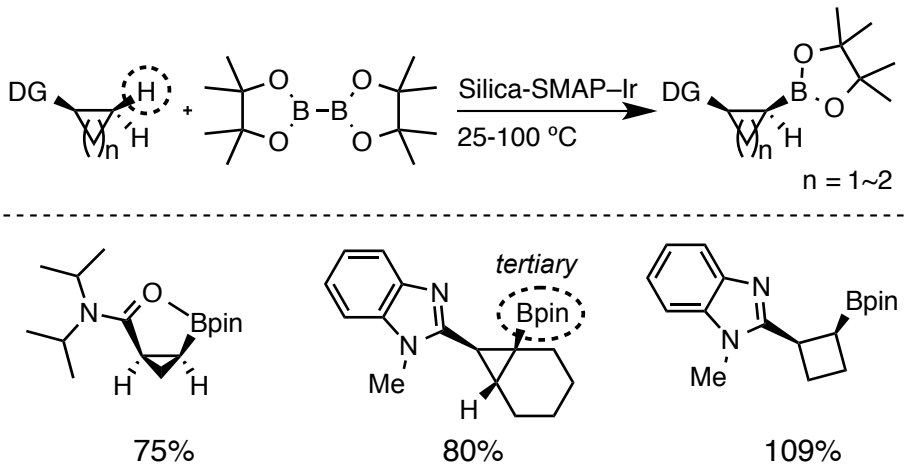
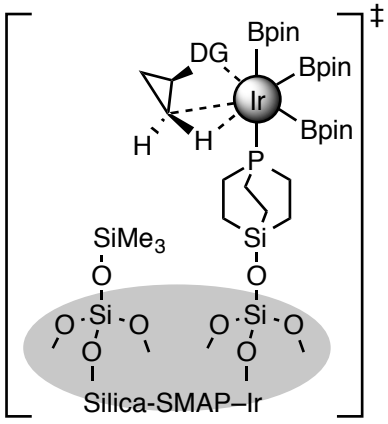


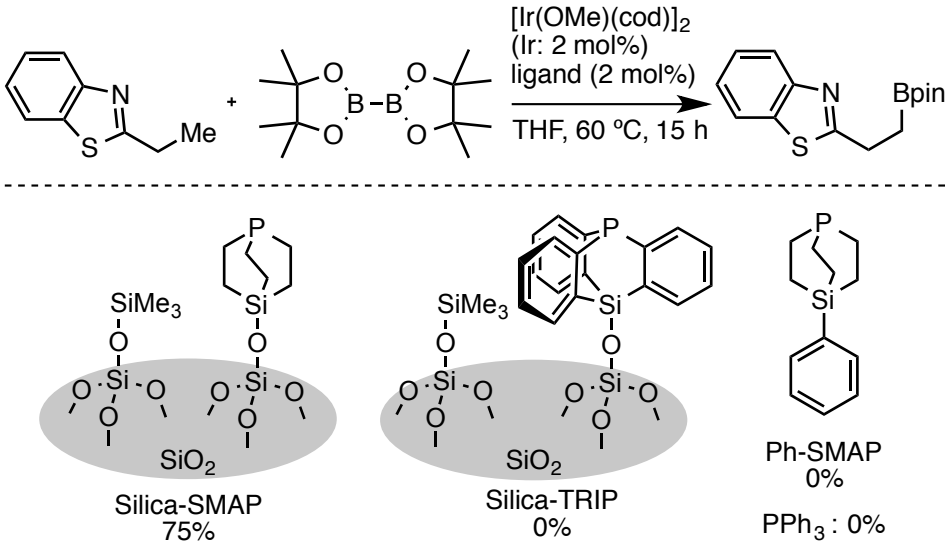
Figure 1. The Origin of Regio- and Stereoselectivities



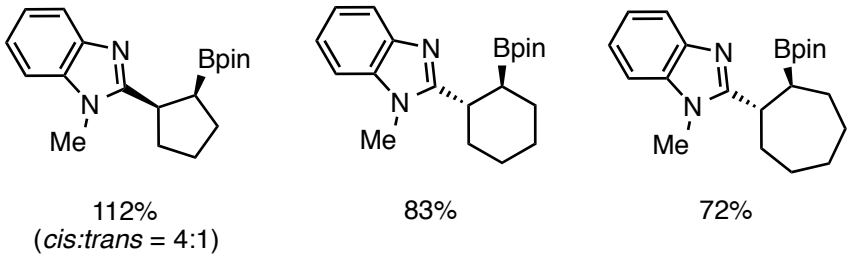
3.2. Site-selective and Stereoselective C(sp^3)–H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Ir Catalyst (Chapter 2)

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 γ 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



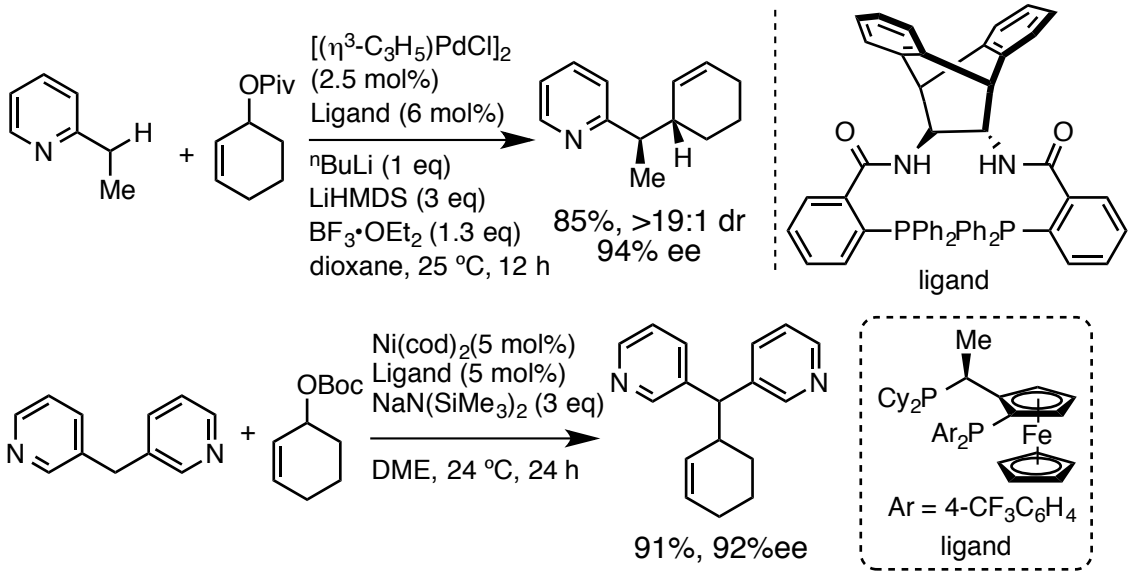
Scheme 37. Stereoselective C(sp^3)–H Borylation



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 $BF_3 \cdot OEt_2$ 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.

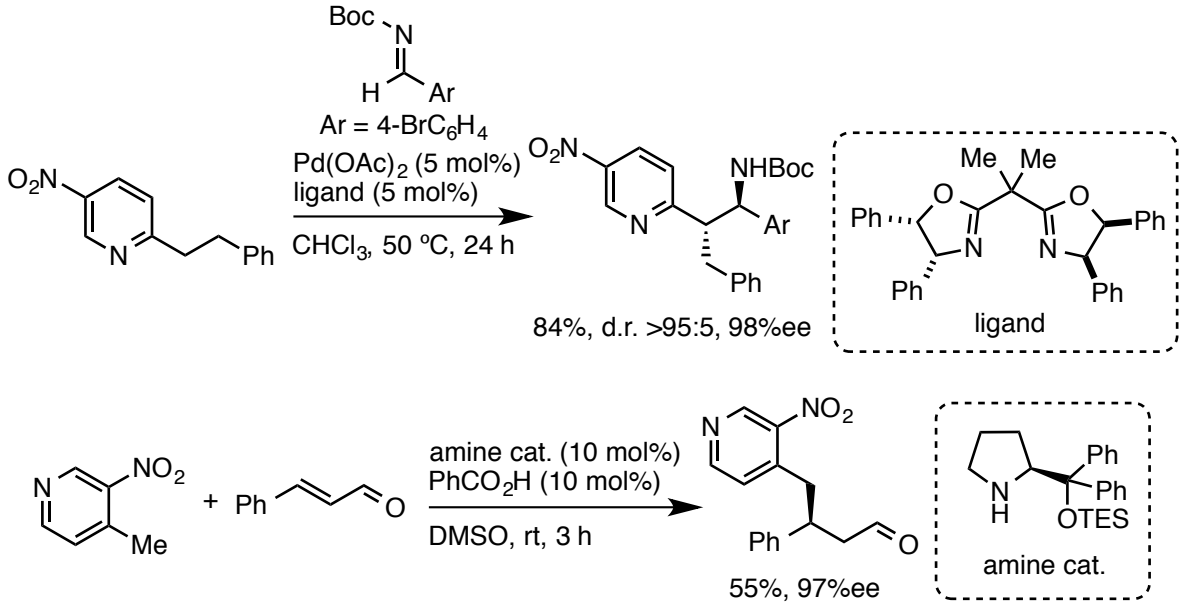
Scheme 38. Transition Metal-catalyzed Enantioselective Allylation of 2-Alkylazaarenes

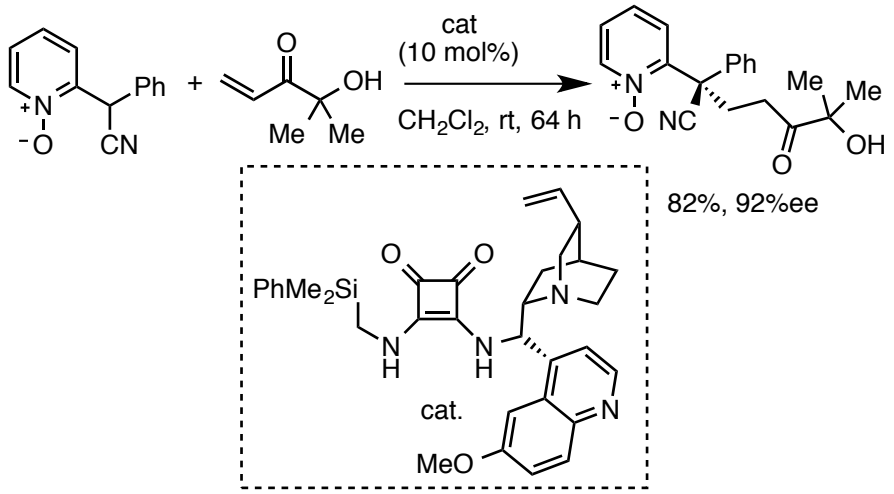


Recently, the α-deprotonation-functionalization of preactivated 2-alkylazaarenes with electron-withdrawing groups in the aromatic ring, such as *p*-nitroazaarenes and

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)[62]. 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[63]. 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[64]. However, these reactions required the use of preactivated 2-alkylpyridine substrates.

Scheme 39. Substrate-controlled Functionalization of 2-Alkylazaarenes

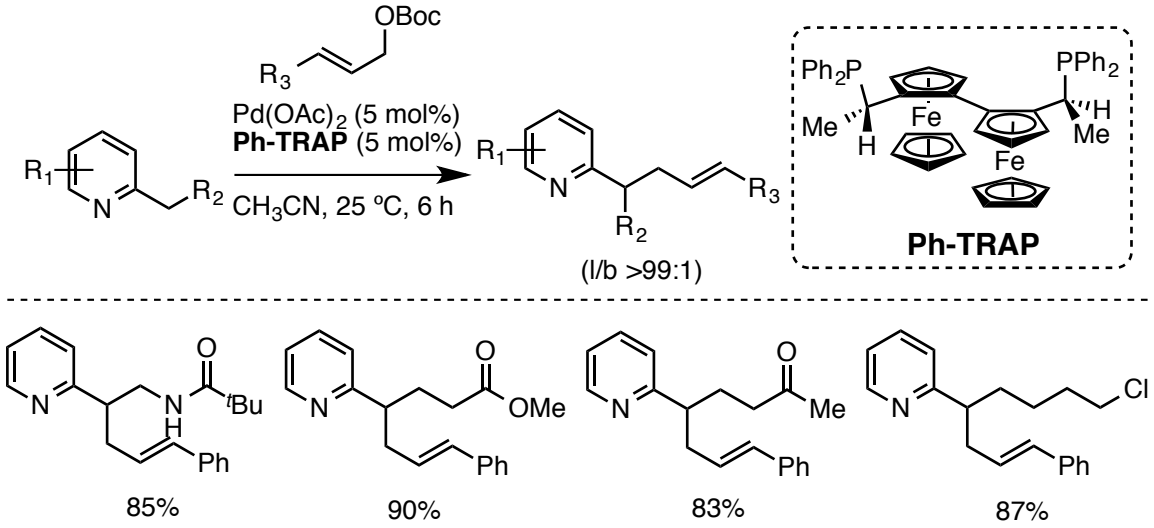




3.4. Pd-catalyzed Side Chain C(α) Allylation of 2-Alkylazaarenes without the Use of External Bases (Chapter 3)

Chapter 3 describes Pd-catalyzed side chain C(α) allylation of 2-alkylazaarenes 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).

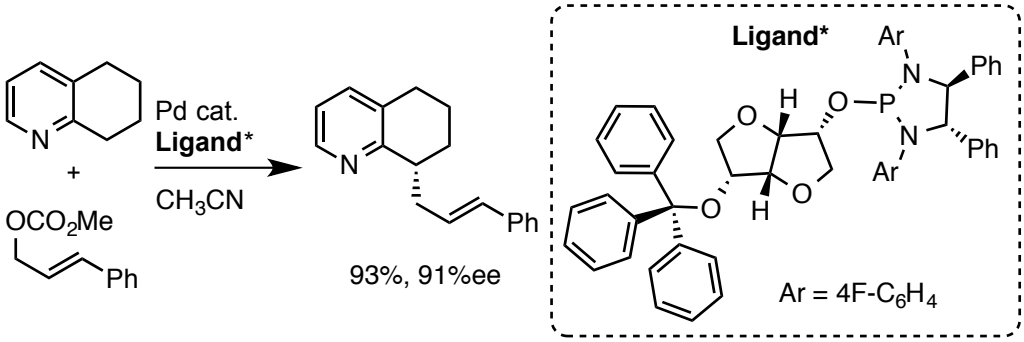
Scheme 40. Ph-TRAP-Pd-catalytic System: Substrate Scope



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



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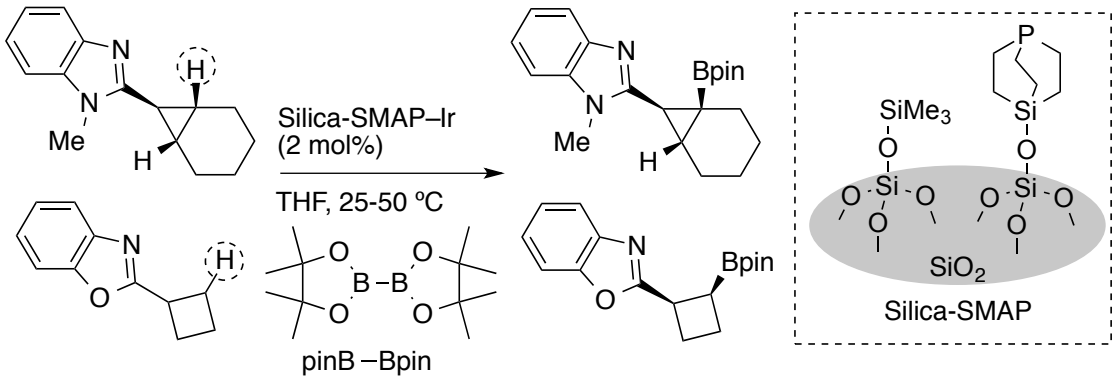
Chapter 1

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.[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.[3–6] Among these reactions, C–H borylation reactions are attractive because borylated small-ring compounds can act as "handles" for diverse molecular transformations.[7–11] Recently, Hartwig and co-workers reported the *trans*-selective borylation of substituted cyclopropanes using Ir-phenanthroline catalyst systems.[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^3)–H bonds of *N*-alkylated amides, ureas, and aminopyridines[10b] and 2-alkylpyridines[10c] catalyzed by Ir- or Rh-catalyst systems based on immobilized monophosphine ligands such as Silica-SMAP[12] and Silica-TRIP[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.

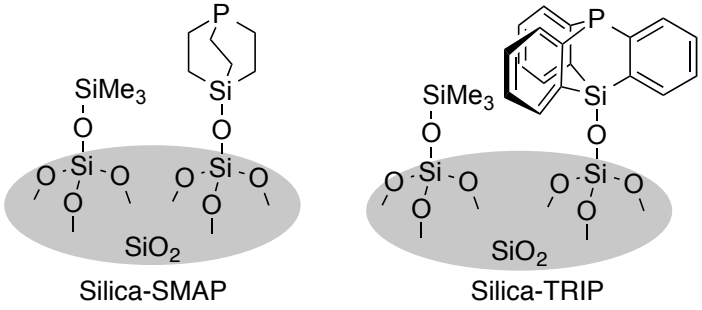


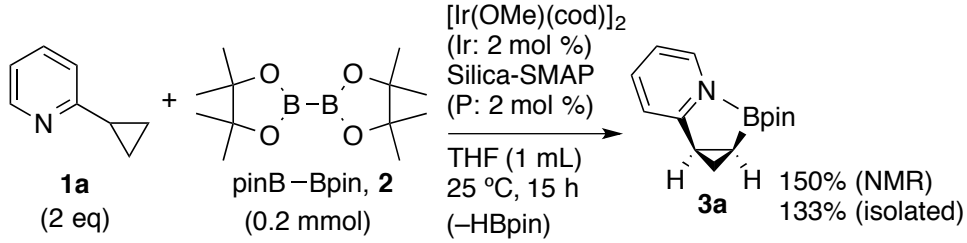
Figure 1. Silica-supported Monophosphines.

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.[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

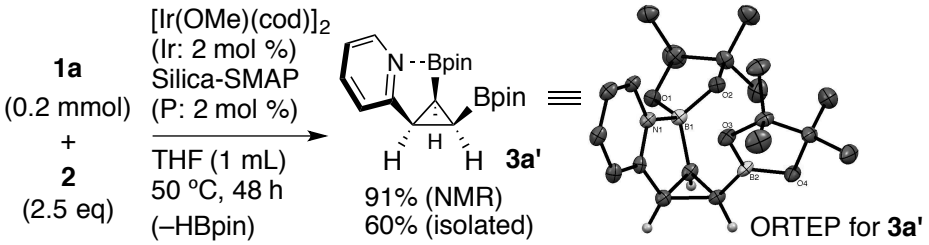
Initially, Ir and Rh catalyst systems based on various ligands {[M(OMe)(cod)]$_2$ (M = Ir or Rh, 2 mol % M)} were evaluated for catalytic activity toward borylation of 2-cyclopropylpyridine (**1a**, 0.4 mmol) with bis(pinacolato)diboron (**2**, 0.2 mmol) in THF. As a result, the Ir complex coordinated 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%, *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 *γ* to the pyridine N atom in favor of the *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-*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). $C_{23}H_{37}B_2NO_5$, 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 ($I>2\sigma(I)$), wR_2 = 0.2907.

Homogeneous Ir catalyst systems with Ph-SMAP,[14] PPh_3, PMe_3, PCy_3 or P*t*Bu$_3$ 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$_2$phen), 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.

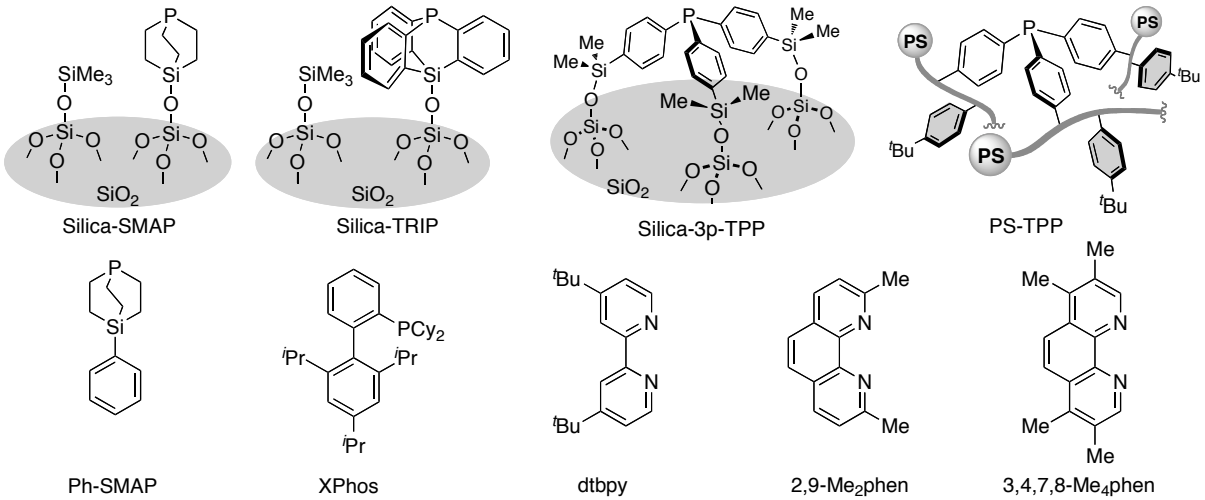
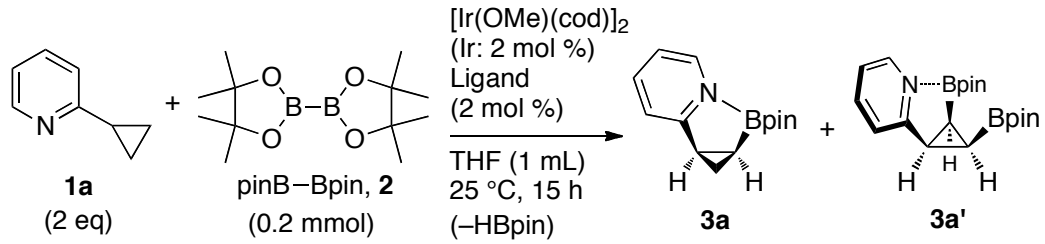


Table 1. Ligand Effects in the Ir-catalyzed Borylation of **1a** at 25 °C.[a]

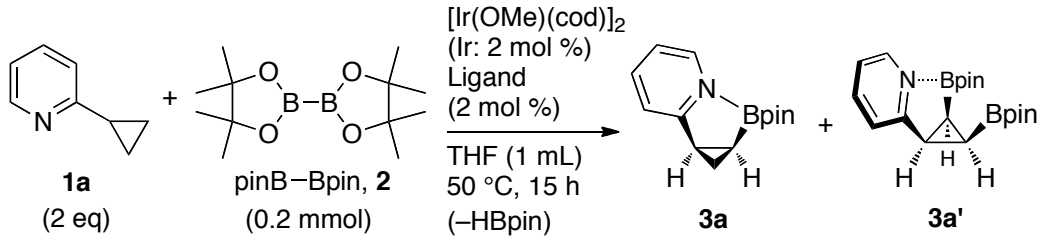


1a (2 eq) + pinB–Bpin, **2** (0.2 mmol) → **3a** + **3a'**

Entry	Ligand	Yield of **3a** (%)[b]	Yield of **3a'** (%)[b]
1	Silica-SMAP	150 (133)	6
2[c]	Silica-SMAP	0	0
3	Silica-TRIP	0	0
4	Silica-3p-TPP	0	0
5	PS-TPP	0	0
6	Ph-SMAP	0	0
7	PMe_3	0	0
8	PCy_3	0	0
9	P^tBu_3	0	0
10	PPh_3	0	0
11	XPhos	0	0
12[d]	dtbpy	0	0
13[d]	2,9-Me_2Phen	0	0
14[d]	3,4,7,8-Me_4Phen	0	0
15	none	0	0

[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 ^1H 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]



Entry	Ligand	Yield of **3a** [%][b]	Yield of **3a'** [%][b]
1	Silica-SMAP	138	7
2 [c]	Silica-SMAP	0	0
3	Silica-TRIP	121	0
4	Silica-3p-TPP	102	21
5	PS-TPP	67	0
6	Ph-SMAP	12	0
7	PMe_3	54	6
8	PCy_3	12	0
9	P^tBu_3	0	0
10	PPh_3	15	0
11	XPhos	0	0
12 [d]	dtbpy	0	0
13 [d]	2,9-Me_2Phen	0	0
14 [d]	3,4,7,8-Me_4Phen	0	0
15	none	43	0

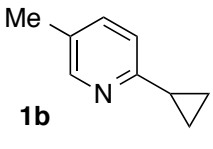
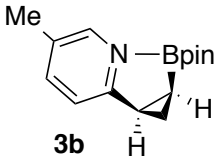
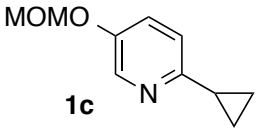
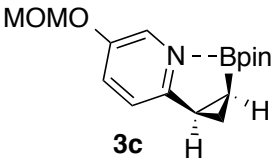
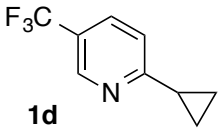
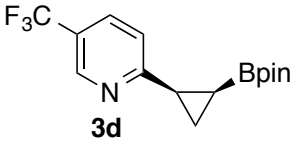
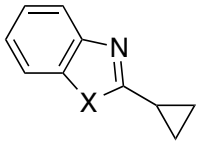
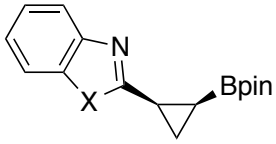
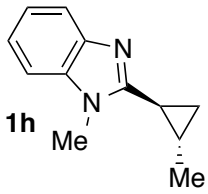
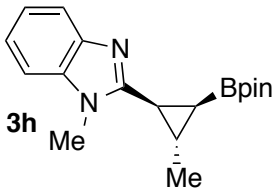
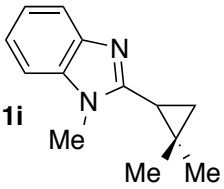
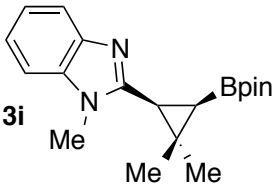
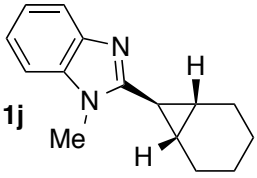
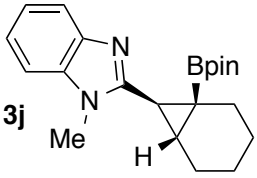
[a] Conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (0.004 mmol Ir), ligand (0.004 mmol), THF (1 mL), 50 °C, 15 h. [b] Yields based on **2** were determined by ^1H NMR spectroscopy. Yield in excess of 100% indicates that HBpin also worked as a borylating reagent (theoretical maximum 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, benzooxazole, 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-1*H*-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. Benzooxazole (in **1f**) also functioned as a directing group, but C(sp^2)–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 ^{11}B 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-1*H*-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]

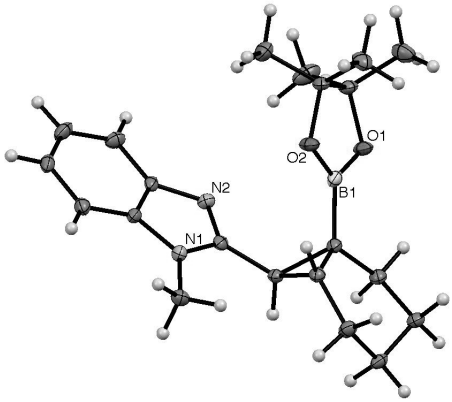
Table 3. Silica-SMAP-Ir catalyzed C–H borylation of cyclopropane derivatives (**1**) with diboron (**2**). [a]

Enter	Substrate **1**	Product **3**	Temp. (°C)	Yield [b] (%)
1 [c]	 **1b**	 **3b**	25	168 [d] (150)
2 [c]	 **1c**	 **3c**	25	108 [e,f] (82)
3 [c]	 **1d**	 **3d**	25	164 [d] (158)
				
4	**1e** (X = NMe)	**3e** (X = NMe)	25	148 [g] (133)
5	**1f** (X = O)	**3f** (X = O)	40	98 (87) [h]
6	**1g** (X = S	**3g** (X = S)	70	156 (130)
7	 **1h**	 **3h**	30	137 [g] (123) [i]
8	 **1i**	 **3i**	40	86 [g] (61)
9	 **1j**	 **3j**	50	91 [g] (80)

[a] Conditions: **1** (0.4 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (0.004 mmol Ir), Silica-SMAP

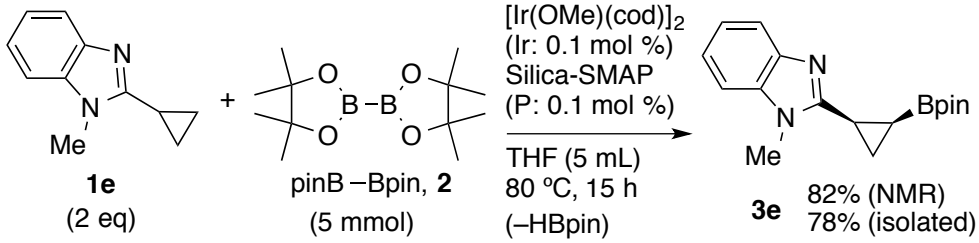
(0.004 mmol P), THF (2 mL), 15 h. [b] Yields based on **2** were determined by ^{1}H NMR spectroscopy. Isolated yields are in parentheses. Yield in excess of 100% indicates that HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield is 200%). [c] THF (1 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_2Cl_2/hexane): $C_{21}H_{29}BN_2O_2$, 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, β = 95.519(7)°, 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.

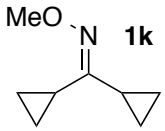
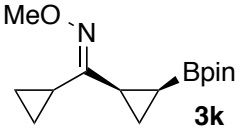
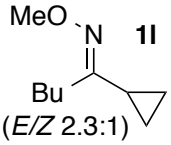
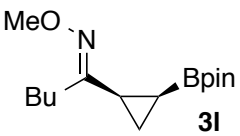
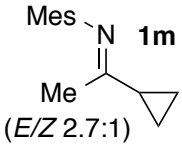
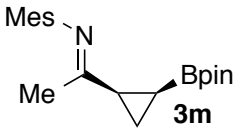
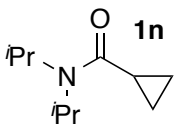
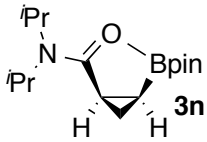
Scheme 3. Gram-scale borylation of **1e.**



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 (**1l**) 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 [a]

Entry	Substrate **1**	Product **3**	Ligand	Temp. (°C)	Yield [b] (%)
1	 **1k**	 **3k**	Silica-SMAP	25	107 (66)
2			Silica-TRIP	25	88
3	 **1l** (*E*/*Z* 2.3:1)	 **3l**	Silica-SMAP	25	115 [c] (64)
4			Silica-TRIP	25	104 [c]
5 [d]	 **1m** (*E*/*Z* 2.7:1)	 **3m**	Silica-SMAP	100	85 [c,e]
6 [d]			Silica-TRIP	100	113 [c,e] (98)
7 [f]	 **1n**	 **3n**	Silica-SMAP	80	77 (75)
8 [f]			Silica-TRIP	80	0

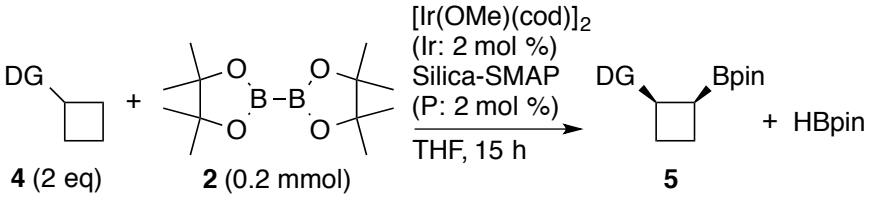
[a] Conditions: **1** (0.4 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (0.004 mmol Ir), ligand (0.004 mmol P), THF (1 mL), 24 h. [b] Yields based on **2** were determined by ^{1}H NMR spectroscopy. Isolated yield is in parentheses. Yield in excess of 100% indicates that HBpin also worked as a borylating 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).

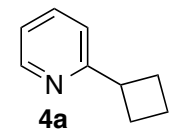
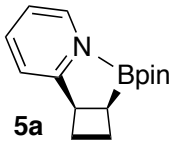
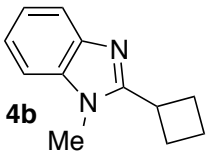
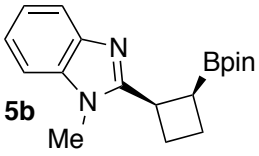
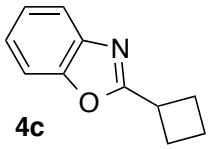
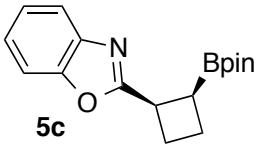
Substrate Scope with C–H Borylation of Cyclobutanes

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).

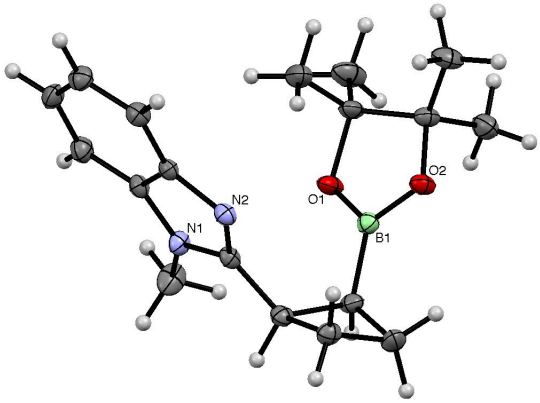
Table 5. Silica-SMAP-Ir catalyzed C–H borylation of cyclobutane derivatives (**4**) with diboron (**2**). [a]



Entry	Substrate **4**	Product **5**	Temp. (°C)	Yield [b] (%)
1 [c]	 **4a**	 **5a**	25	105 (85) [d]
2	 **4b**	 **5b**	40	109[e] (99) [f]
3	 **4c**	 **5c**	50	99 (94) [f]

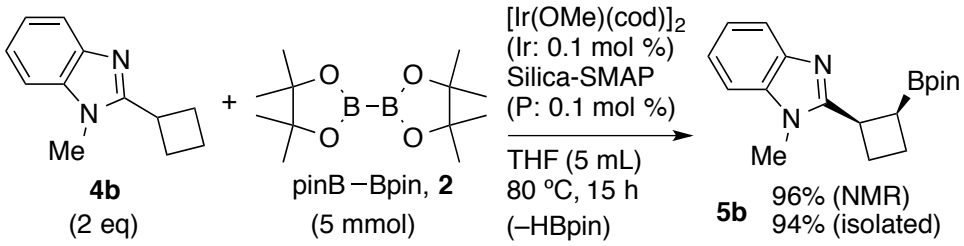
[a] Conditions: **4** (0.4 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (0.004 mmol Ir), ligand (0.004 mmol P), THF (2 mL), 15 h. [b] Yields based on **2** were determined by ^{1}H NMR spectroscopy. Isolated yield is in parentheses. Yield in excess of 100% indicates that HBpin also worked as a borylating 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 CH_2Cl_2/hexane). $C_{18}H_{25}BN_2O_2$, M = 312.22, orthorhombic, space group $Pna2_1$ (#33), a = 20.315(10) Å, b = 9.222(5) Å, c = 9.401(5) Å, V = 1761.2(16) Å^3, Z = 4, density (calc.) = 1.177, total reflections collected = 10688, unique reflections = 2907 (R_{int} = 0.0685), GOF = 0.987, R_1 = 0.0515 ($I>2\sigma(I)$), wR_2 = 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,[11a] one-carbon-homologation/oxidation sequence,[17] and Pd-catalyzed Suzuki–Miyaura coupling with aryl or alkenyl bromides.[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.[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.

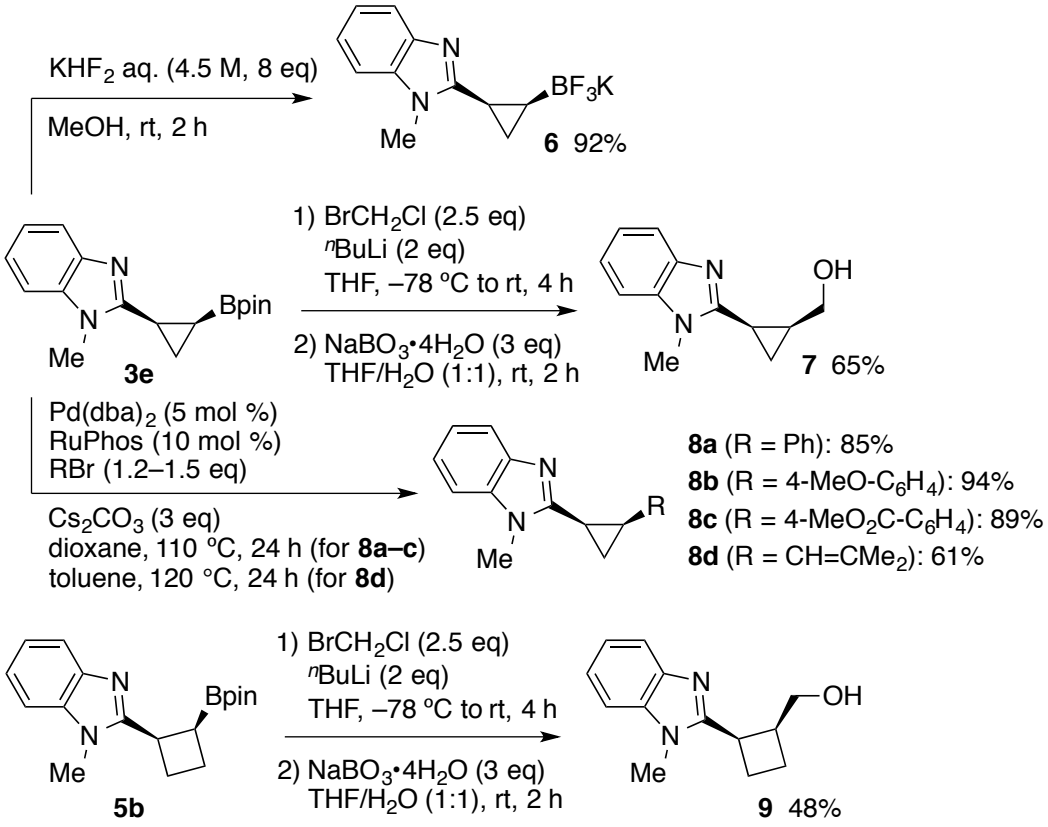
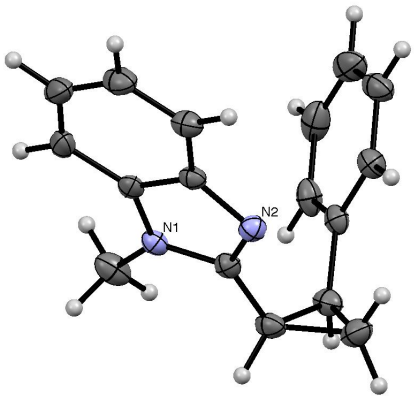


Figure 4. Molecular structure of the cross-coupling product **8a**.



Crystal data for **8a** (CCDC 1005183; recrystallization from CH_2Cl_2/hexane). $C_{17}H_{16}N_2$, M = 248.33, triclinic, space group $P\bar{1}$ (#2), a = 6.418(4) Å, b = 9.102(5) Å, c = 12.253(6) Å, α = 94.716(7), β = 103.510(6), γ = 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.

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_4Si, 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 fleshly 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 ^{1}H 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 ^{1}H 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 ^{1}H 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-1*H*-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 ^{1}H NMR (82%). The crude material was then purified by Kugelrohr distillation (1 mmHg, 150 °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,

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 dicyclopropylmethanone *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 ^{1}H 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).

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 2-cyclobutylpyridine (**4a**) (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 **5a** was determined by ^{1}H NMR (105%). The crude material was then purified by Kugelrohr distillation (1 mmHg, 85 °C), to give the corresponding product **5a** (43.8 mg, 0.17 mmol, 85% 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-1*H*-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}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-(2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclopropyl)-1*H*-benzo[*d*]imidazole was determined by ^{1}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 $NaBO_3$•$4H_2O$ (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

Cs_2CO_3 (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 Et_2O. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/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 Cs_2CO_3 (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 Et_2O. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/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).

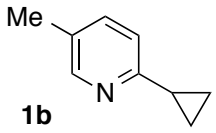
Procedure for the One-Carbon Homologation Following Oxidation of 5b (Scheme 5). Under Ar atmosphere, the boronate **5b** (31.2 mg, 0.1 mmol), bromochloromethane (32.3 mg, 0.25 mmol), and anhydrous THF (1 mL) were placed in a 10-mL glass tube containing a magnetic stirring bar. The tube was sealed with 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)-1*H*-benzo[*d*] imidazole was determined by ^{1}H 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 $NaBO_3$•$4H_2O$ (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 **9** (10.3 mg, 0.048 mmol, 48% yield in two steps).

Preparation of Substrates.

The substrates for borylation **1a**,[24] **1f**,[25] **1g**,[26] **1n**[27] and **4c**[28] are reported in the literatures.

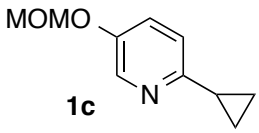
Preparation of 2-Cyclopropyl-5-methylpyridine (1b). The title compound (**1b**) was synthesized via the reaction of 2-chloro-5-methylpyridine and cyclopropyl magnesium bromide with a $ZnBr_2$/PEPPSI catalyst system (22%).[29]



1b

Isolated by silica gel chromatography (hexane/EtOAc 80:20) followed by Kugelrohr distillation (10 mmHg, 75 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) 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}C NMR** ($CDCl_3$) δ 9.32 (2C), 16.58, 17.87, 120.51, 129.36, 136.39, 149.40, 159.65. **IR** (ATR): 3004, 1604, 1489, 1213, 1022, 818, 803 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_9H_{12}N$, 134.09643; found, 134.09661.

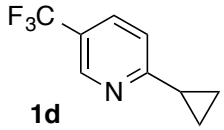
Preparation of 2-Cyclopropyl-5-(methoxymethoxy)pyridine (1c). The title compound (**1c**) was synthesized via the reaction of 2-chloro-5-(methoxymethoxy)pyridine[30] and cyclopropyl magnesium bromide with a $Fe(acac)_3$ catalyst system (50%).[31]



1c

Isolated by silica gel chromatography (hexane/EtOAc 80:20) followed by GPC. Pale yellow oil. **^{1}H NMR** ($CDCl_3$) 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}C NMR** ($CDCl_3$) δ 9.13 (2C), 16.31, 55.96, 94.90, 121.17, 123.57, 138.81, 151.27, 156.03. **IR** (ATR): 3003, 2957, 2902, 1570, 1485, 1200, 1152, 1080, 986, 903, 825 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{10}H_{14}N$, 180.10191; found, 180.10204.

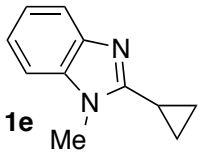
Preparation of 2-Cyclopropyl-5-(trifluoromethyl)pyridine (1d). The title compound (**1d**) was synthesized via the reaction of 2-chloro-5-(trifluoromethyl)pyridine and cyclopropyl magnesium bromide with a $Fe(acac)_3$ catalyst system (42%).[31]



1d

Isolated by silica gel chromatography (hexane/EtOAc 80:20) followed by Kugelrohr distillation (10 mmHg, 70 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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 $C_9H_9NF_3$, 188.06816; found, 188.06861.

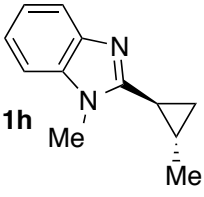
Preparation of 2-Cyclopropyl-1-methyl-1*H*-benzo[*d*]imidazole (1e). The title compound (**1e**) was synthesized via the reaction of 2-cyclopropyl-1*H*-benzo[*d*]imidazole[32] and MeI with NaH (95%).



1e

Isolated by silica gel chromatography ($CHCl_3$/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 100 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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.

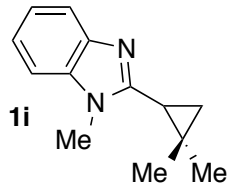
Preparation of 1-Methyl-2-(2-methylcyclopropyl)-1*H*-benzo[*d*]imidazole (1h). The title compound (**1h**) was synthesized via the reaction of 1-methyl-2-(2-methylcyclopropyl)-1*H*-benzo[*d*]imidazole[33] and MeI with NaH (99%).



1h

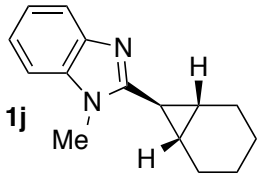
Isolated by silica gel chromatography ($CHCl_3$/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 110 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 0.87–0.94 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.38–1.43 (m, 1H), 1.54–1.62 (m, 1H), 1.66 (td, *J* = 8.8, 4.4 Hz, 1H), 3.80 (s, 3H), 7.19–7.26 (m, 3H), 7.63–7.67 (m, 1H). **^{13}C NMR** ($CDCl_3$) 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, $C_{12}H_{15}N_2$, 187.12298; found, 187.12321.

Preparation of 2-(2,2-Dimethylcyclopropyl)-1-methyl-1*H*-benzo[*d*]imidazole (1i). The title compound (**1i**) was synthesized via the reaction of 2-(2,2-dimethylcyclopropyl)-1*H*-benzo[*d*]imidazole[33] and MeI with NaH (68%).



Isolated by silica gel chromatography ($CHCl_3$/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 115 °C). White solids. **M.p.** 63.3–64.7 °C. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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, $C_{13}H_{17}N_2$, 201.13863; found, 201.13892.

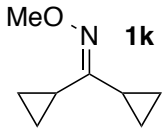
Preparation of 2-(Bicyclo[4.1.0]heptan-7-yl)-1-methyl-1*H*-benzo[*d*]imidazole (1j). The title compound (**1j**) was synthesized via the reaction of bicyclo[4.1.0]heptane-7-carboxylic acid[34] and *o*-phenylenediamine, followed by the methylation with MeI and NaH (82%).



Isolated by silica gel chromatography ($CHCl_3$/EtOAc 90:10) followed by recrystallization from hexane. White solids. **M.p.** 111.7–112.3 °C. **^{1}H NMR** ($CDCl_3$) δ 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). **^{13}C NMR** ($CDCl_3$) δ 20.09, 21.20 (2C), 21.34 (2C), 23.23 (2C),

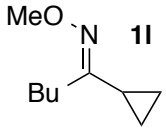
29.63, 108.46, 118.75, 121.50, 121.60, 135.92, 142.46, 157.14. **IR** (ATR): 2929, 2856, 1615, 1509, 1449, 1272, 742 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for, $C_{15}H_{19}N_2$, 227.15428; found, 227.15436.

Preparation of Dicyclopropylmethanone *O*-Methyl Oxime (1k). The title compound (**1k**) was synthesized via the reaction of dicyclopropylmethanone and $MeONH_2 \cdot HCl$ with pyridine (90%).



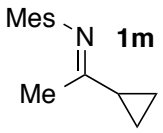
Isolated by silica gel chromatography (hexane/EtOAc 95:5) followed by Kugelrohr distillation (10 mmHg, 75 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 0.57–0.62 (m, 2H), 0.69–0.73 (m, 2H), 0.82–0.87 (m, 2H), 0.90–0.97 (m, 3H), 2.30–2.37 (m, 1H), 3.82 (s, 3H). **^{13}C NMR** ($CDCl_3$) δ 4.83 (2C), 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 $C_8H_{14}ON$, 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 $MeONH_2$•HCl with pyridine (86%).



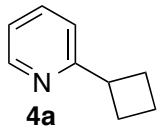
Isolated by silica gel chromatography (hexane/EtOAc 99:1) followed by Kugelrohr distillation (10 mmHg, 80 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 0.68–0.71 (m, 3.4H), 0.80–0.85 (m, 0.6H), 0.88–0.93 (m, 3H), 1.27–1.52 (m, 5H), 1.75–1.79 (m, 0.6H), 2.13–2.23 (m, 1.4H), 3.78 (s, 2.1H), 3.86 (s, 0.9H). **^{13}C NMR** ($CDCl_3$) **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 $C_9H_{18}ON$, 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%).



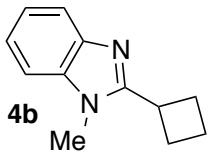
Isolated by Kugelrohr distillation (1 mmHg, 115 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 0.66–0.71 (m, 0.3H), 0.83–0.89 (m, 2H), 1.02–1.06 (m, 1.7H), 1.35–1.41 (m, 0.3H), 1.63 (s, 2.1H), 1.72–1.79 (m, 0.7H), 1.84 (s, 0.9H), 1.92 (s, 4.2H), 2.02 (s, 1.8 H), 2.23 (s, 2.1H), 2.25 (s, 0.9H), 6.79 (s, 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 $ZnBr_2/Pd(OAc)_2/P^tBu_3$ catalyst system (60%).[29]



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, 1568, 1473, 1433, 1148, 745 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_9H_{12}N$, 134.09643; found, 134.09665.

Preparation of 2-Cyclobutyl-1-methyl-1*H*-benzo[*d*]imidazole (4b). The title compound (**4b**) was synthesized via the reaction of 2-cyclobutyl-1*H*-benzo[*d*]imidazole[33] and MeI with NaH (89%).

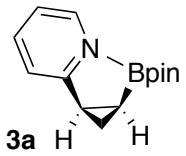


Isolated by silica gel chromatography ($CHCl_3$/MeOH 95:5) followed by Kugelrohr distillation (1 mmHg, 110 °C). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.98–2.07 (m, 1H), 2.09–

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), 7.74–7.79 (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

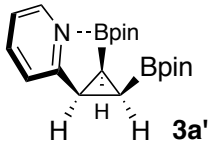
2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyridine (3a)



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 $C_{14}H_{21}O_2N^{10}B$, 245.16962; found, 245.17007.

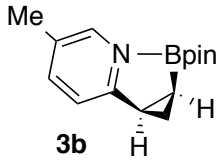
2-[2,3-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyridine (3a')



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 $C_{20}H_{32}O_4N^{10}B_2$, 370.25846; found, 370.25868.

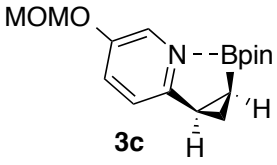
5-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)pyridine (3b)



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 $C_{15}H_{23}O_2N^{10}B$, 259.18527; found, 259.18576.

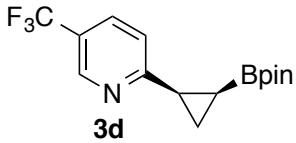
5-(Methoxymethoxy)-2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyridine (3c)



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 $C_{16}H_{25}O_4N^{10}B$, 305.19075; found, 305.19094.

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

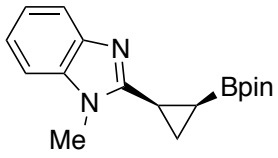


3d

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,

6H), 1.20–1.30 (m, 2H), 2.43 (ddd, *J* = 9.6, 8.0, 5.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 8.65 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ 5.7 (br), 13.64, 22.82, 24.70 (2C), 25.05 (2C), 82.90 (2C), 122.40, 123.69 (q, *J* = 33.4 Hz), 123.76 (q, *J* = 270.8 Hz), 132.95 (q, *J* = 3.8 Hz), 144.97 (q, *J* = 3.8 Hz), 166.02. **^{11}B NMR** ($CDCl_3$) δ 30.2. **IR** (ATR): 3000, 1607, 1403, 1327, 1299, 1134, 1119, 1087, 966 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{20}O_2N^{10}BF_3$, 313.15700; found, 313.15700.

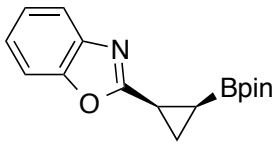
1-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)-1*H*-benzo[*d*]imidazole (3e)



3e

Isolated by Kugelrohr distillation (1 mmHg, 145 °C, 79.8 mg, 133% yield). White solids. **M.p.** 106.9–108.7 °C . **^{1}H NMR** ($CDCl_3$) δ 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), 7.18–7.23 (m, 3H), 7.65–7.69 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 31.1. **IR** (ATR): 2976, 1615, 1522, 1398, 1323, 1220, 1143 cm^{-1}. **HRMS–EI** (*m/z*): $[M]^+$ Calcd for, $C_{17}H_{23}{}^{11}BN_2O_2$, 298.18526; found, 298.18498.

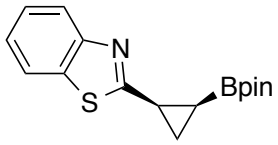
2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]benzo[*d*]oxazole (3f)



3f

Isolated by Kugelrohr distillation (1 mmHg, 95 °C, 49.6 mg, 87% yield, contaminated with arylboronates (10%)). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 31.2. **IR** (ATR): 2978, 1617, 1571, 1411, 1328, 1141, 1223, 857, 742 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{16}H_{21}O_3N^{10}B$, 285.16453; found, 285.16530.

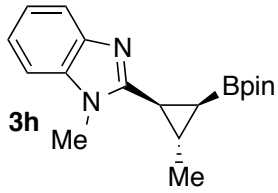
2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)benzo[*d*]thiazole (3g)



3g

Isolated by Kugelrohr distillation (1 mmHg, 120 °C, 78.2 mg, 130% yield). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 31.2. **IR** (ATR): 2977, 1522, 1408, 1326, 1224, 1142, 853, 757 cm^{-1}. **HRMS–APCI** (*m/z*): $[M+H]^+$ Calcd for $C_{16}H_{21}O_2N^{10}BS$, 301.14169; found, 301.14163.

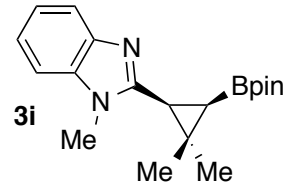
1-Methyl-2-[2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-1*H*-benzo[*d*]imidazole (3h)



3h

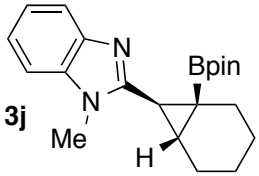
Isolated by Kugelrohr distillation (1 mmHg, 150 °C, 76.8 mg, 123% yield, contaminated with regioisomers (8%)). White solids. **M.p.** 125.1–126.6 °C. **^{1}H NMR** ($CDCl_3$) δ 0.42 (t, *J* = 7.6 Hz, 1H), 0.87 (s, 6H), 1.03 (s, 6H), 1.27–1.34 (m, 4H), 1.95–1.99 (m, 1H), 3.77 (s, 3H), 7.17–7.23 (m, 3H), 7.63–7.68 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 30.6 (br). **IR** (ATR): 2980, 2942, 1616, 1469, 1372, 1315, 1141, 853, 751 cm^{-1}. **HRMS–EI** (*m/z*): $[M]^+$ Calcd for $C_{18}H_{25}O_2N_2{}^{11}B$, 312.20091; found, 312.20080.

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



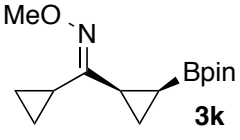
Isolated by Kugelrohr distillation (1 mmHg, 155 °C) followed by washing with a small amount of hexane (40.1 mg, 61% yield). White solids. **M.p.** 139.9–141.8 °C. **^{1}H NMR** ($CDCl_3$) δ 0.56 (d, *J* = 10.0 Hz, 1H), 1.14 (s, 3H), 1.27 (s, 6H), 1.30 (s, 6H), 1.36 (s, 3H), 2.08 (d, *J* = 10.0 Hz, 1H), 3.74 (s, 3H), 7.17–7.24 (m, 3H), 7.62 (d, *J* = 8.4, Hz, 1H). **^{13}C NMR** ($CDCl_3$) 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. **^{11}B NMR** ($CDCl_3$) δ 30.1. **IR** (ATR): 2975, 1616, 1523, 1397, 1317, 1143, 862, 741 cm^{-1}. **HRMS–EI** (*m/z*): $[M]^+$ Calcd for $C_{19}H_{27}O_2N_2{}^{11}B$, 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]-1*H*-benzo[*d*]imidazole (3j)



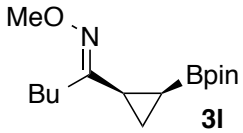
Isolated by Kugelrohr distillation (1 mmHg, 200 °C) followed by recrystallization from hexane. (56.3 mg, 80% yield). White solids. **M.p.** 161.9–163.0 °C. **^{1}H NMR** ($CDCl_3$) δ 0.80 (s, 6H), 0.99 (s, 6H), 1.22–1.47 (m, 4H), 1.81–1.90 (m, 1H), 1.94 (d, *J* = 5.6 Hz, 1H), 2.04–2.10 (m, 2H), 2.14–2.19 (m, 2H), 3.76 (s, 3H), 7.16–7.22 (m, 3H), 7.66 (dd, *J* = 8.8, 3.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) 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. **^{11}B NMR** ($CDCl_3$) δ 30.8. **IR** (ATR): 2926, 1615, 1466, 1394, 1318, 1141, 856, 737 cm^{-1}. **HRMS–EI** (*m/z*): $[M]^+$ Calcd for $C_{21}H_{29}O_2N_2{}^{11}B$, 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 31.3. **IR** (ATR): 2979, 1614, 1409, 1324, 1221, 1144, 1055, 857, 736 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{14}H_{25}O_3N^{10}B$, 265.19583; found, 265.19586.

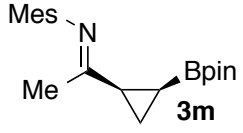
(*E*)-1-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pentan-1-one *O*-Methyl Oxime (3l)



3l

Isolated by Kugelrohr distillation (1 mmHg, 100 °C, 36.0 mg, 64% yield). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 31.6. **IR** (ATR): 2978, 2959, 2933, 1627, 1409, 1323, 1222, 1144, 1053, 858 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{29}O_3N^{10}B$, 281.22713; found, 281.22720.

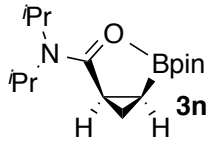
(*E*)-2,4,6-Trimethyl-*N*-[1-{2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl}ethylidene]aniline (3m)



3m

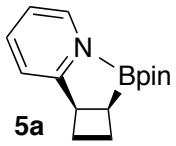
Isolated by Kugelrohr distillation (1 mmHg, 100 °C) followed by recrystallization from hexane. (64.1 mg, 98% yield). White solids. M.p. 152.5–154.2 °C. **^{1}H NMR** ($CDCl_3$) δ 0.71 (td, *J* = 9.2, 6.4 Hz, 1H), 0.83 (s, 6H), 0.92–0.96 (m, 1H), 0.97 (s, 6H), 1.23 (td, *J* = 8.6, 2.8 Hz, 1H), 1.91 (s, 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 14.5. **IR** (ATR): 2964, 1632, 1381, 1359, 1293, 1165, 1084, 877, 774 cm^{-1}. **HRMS–APCI** (*m/z*): $[M+H]^+$ Calcd for $C_{20}H_{31}O_2N^{10}B$, 327.24787; found, 327.24795.

***N*,*N*-Diisopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropanecarboxamide (3n)**



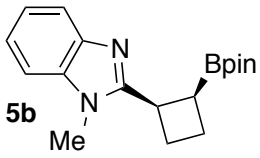
Isolated by Kugelrohr distillation (1 mmHg, 85 °C, 44.3 mg, 75% yield, contaminated with traces of impurities). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 0.56 (td, *J* = 9.6, 6.8 Hz, 1H), 0.84–0.87 (m, 1H), 1.02–1.07 (m, 1H), 1.23 (s, 12H), 1.28 (d, *J* = 6.4 Hz, 6H), 1.33–1.37 (m, 6H), 1.95 (td, *J* = 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 16.1. **IR** (ATR): 2971, 1595, 1371, 1312, 1143, 1110, 751, 730 cm^{-1}. **HRMS–APCI** (*m/z*): $[M+H]^+$ Calcd for $C_{16}H_{31}O_3N^{10}B$, 295.24728; found, 295.24364.

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



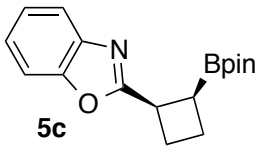
Isolated by Kugelrohr distillation (1 mmHg, 85 °C, 43.8 mg, 85% yield, contaminated with traces of impurities). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.21 (s, 6H), 1.24 (s, 6H), 1.85–2.00 (m, 2H), 2.01–2.14 (m, 2H), 2.60–2.68 (m, 1H), 3.75–3.81 (m, 1H), 7.31–7.37 (m, 2H), 7.85 (td, *J* = 8.0, 1.2 Hz, 1H), 8.64 (d, *J* = 5.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ 19.11, 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** ($CDCl_3$) δ 16.9. **IR** (ATR): 2973, 2931, 1617, 1476, 1379, 1143, 1080, 772 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ $C_{15}H_{23}O_2N^{10}B$, 259.18527; found, 259.18549.

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



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 $C_{18}H_{25}O_2N_2{}^{11}B$, 312.20091; found, 312.20028.

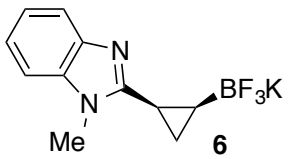
2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl]benzo[*d*]oxazole (5c)



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, 1567, 1456, 1370, 1319, 1141, 853, 742 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{17}H_{23}O_3N^{10}B$, 299.18018; found, 299.18110.

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

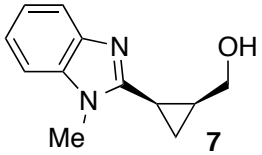


6

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 $C_{11}H_{12}N_2{}^{10}BF_3K$, 278.07135; found, 278.07198.

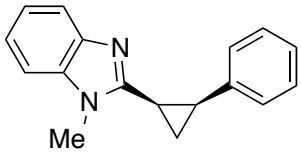
[2-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)cyclopropyl]methanol (7)



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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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.

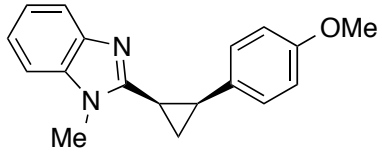
1-Methyl-2-(2-phenylcyclopropyl)-1*H*-benzo[*d*]imidazole (8a)



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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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 $C_{17}H_{17}N_2$, 249.13863; found, 249.13866.

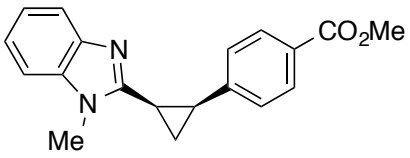
2-[2-(4-Methoxyphenyl)cyclopropyl]-1-methyl-1*H*-benzo[*d*]imidazole (8b)



8b

Isolated by silica gel chromatography ($CHCl_3$/MeOH 95:5, 26.1 mg, 94% yield). White solids. **M.p.** 126.7–127.6 °C. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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 $C_{18}H_{19}ON_2$, 279.14919; found, 279.14977.

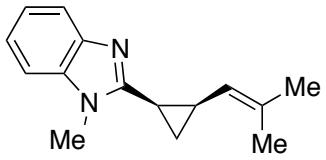
Methyl 4-[2-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)cyclopropyl]benzoate (8c)



8c

Isolated by silica gel chromatography ($CHCl_3$/MeOH 95:5, 27.3 mg, 89% yield). White solids. **M.p.** 175.1–176.5 °C. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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 $C_{19}H_{19}O_2N_2$, 307.14410; found, 307.14445.

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

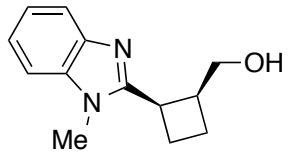


8d

Isolated by silica gel chromatography ($CHCl_3$/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. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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 $C_{15}H_{19}N_2$, 227.15428; found, 227.15444.

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



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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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-Kα radiation (λ = 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.

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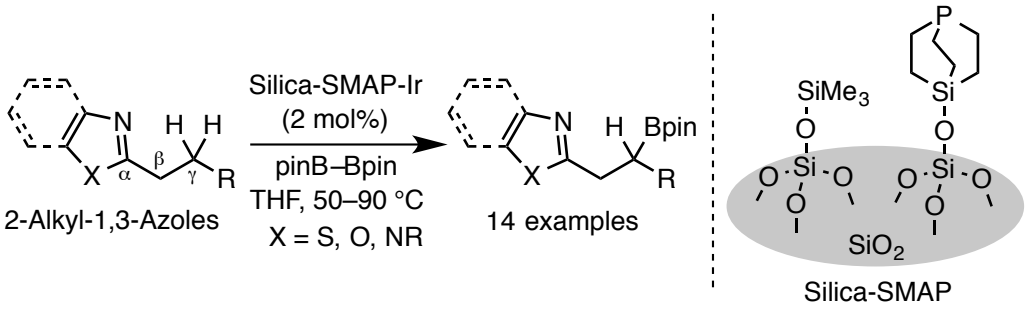
Chapter 2

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

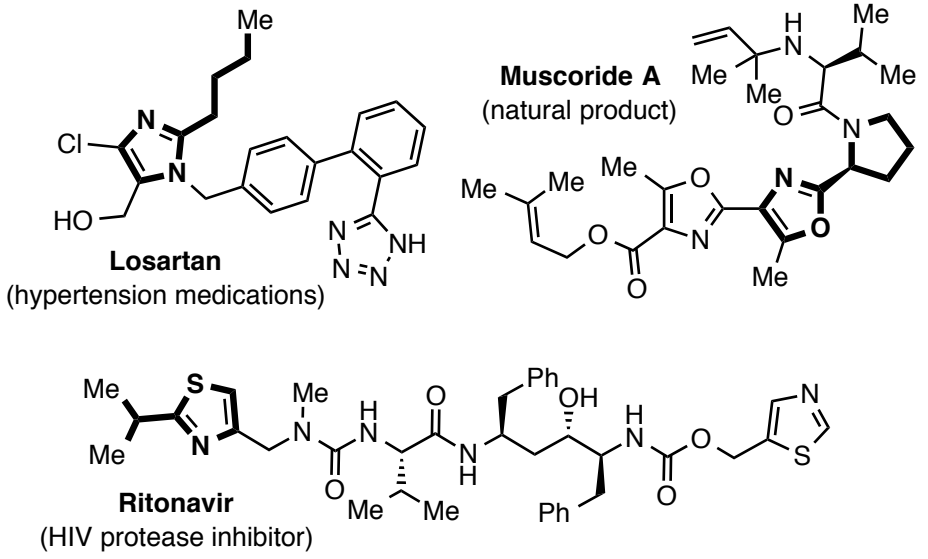


Site-selective and stereoselective C(sp^3)–H borylation of alkyl side chains of 1,3-azoles with bis(pinacolato)diboron was effectively catalyzed by a silica-supported monophosphine-Ir catalyst. The borylation occurred under relatively mild conditions (2 mol% Ir, 50–90 °C), affording the corresponding 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]

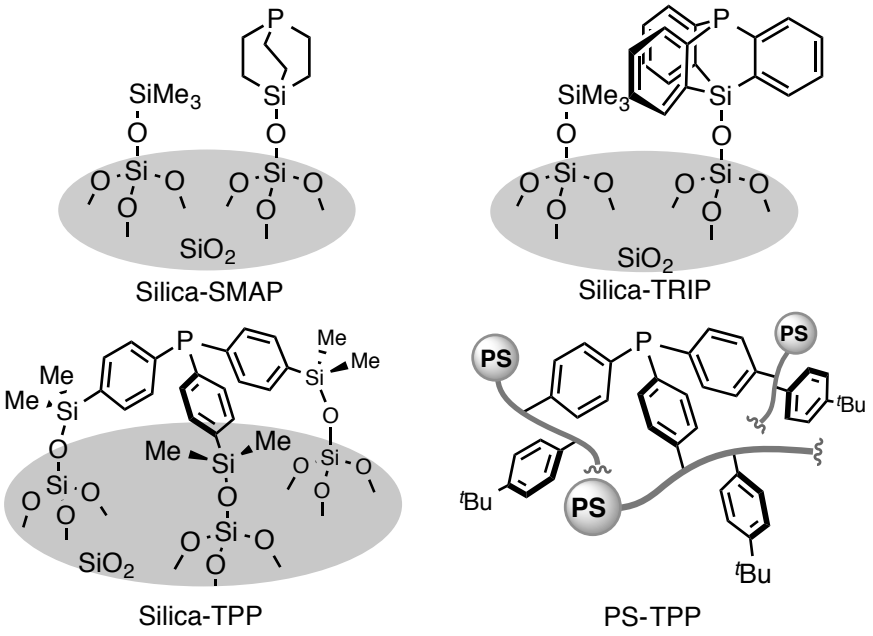
Figure 1. Representative Compounds Containing the 2-Alkyl-1,3-azole Scaffold.



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 γ 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(sp^3)–H boylation of small-ring carbocycles such as cyclopropanes and cyclobutanes.[7b] 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(sp^3)–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(sp^3)–H bonds of linear and cyclic alkyl substituents in 1,3-azoles, including thiazoles, oxazoles, and imidazoles.

Results and Discussion

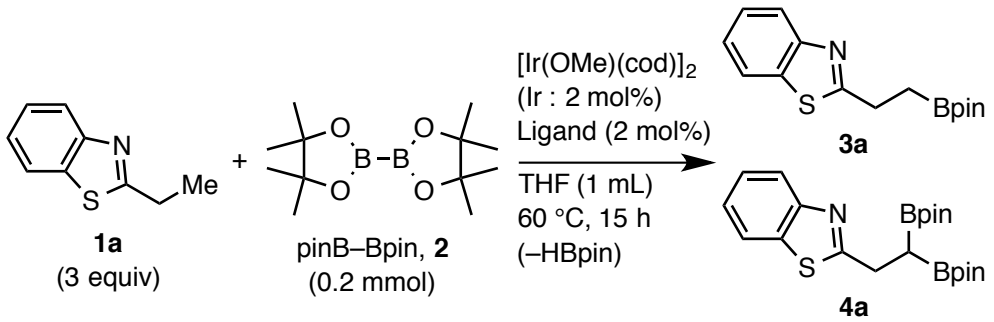
Optimization of reaction conditions. Initially, the borylation reaction between 2-ethylbenzothiazole (**1a**, 0.6 mmol) and bis(pinacolato)diboron (B_2pin_2) (**2**, 0.2 mmol) in THF at 60 °C for 15 h in the presence of various Ir catalysts (2 mol% Ir), which were prepared *in situ* from $[Ir(OMe)(cod)]_2$ and different ligands. The results are summarized in Table 1.

In contrast to the C(sp^3)–H borylation of 2-alkylpyridines reported previously,[10a] for which all solid-supported monophosphines shown in Figure 1 were effective ligands (Silica-SMAP,[10a] Silica-TRIP,[10b] Silica-TPP[10c] and PS-TPP[10d]), the borylation of **1a** was

specifically promoted by commercially available Silica-SMAP, affording the terminal C(sp^3)–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(sp^3)–H borylation with the Silica-SMAP-Ir system at 25 °C,[10a] 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 B_2pin_2 (**2**) indicated that pinacolborane (HBpin), which was a byproduct of the reaction with B_2pin_2, also served as a borylating reagent, although it was less reactive than **2**. The C(sp^2)–H bonds of the benzothiazole ring and the C(sp^3)–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)[12] and PPh_3 did not promote the C(sp^3)–H borylation (entries 5 and 6). Bipyridine-based ligands such as Dtbpy and Me_4Phen (Figure 2) resulted in only aromatic C–H borylation with lower efficiencies (<4% yields of arylboronates, entries 7 and 8).[13] 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]

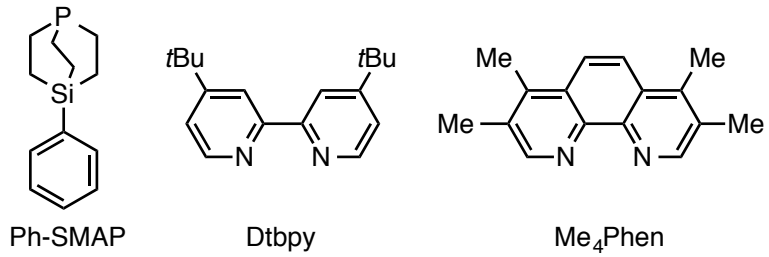


Entry	Ligand	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	Silica-SMAP	82[c] (75)[d]	32
2	Silica-TRIP	0	0

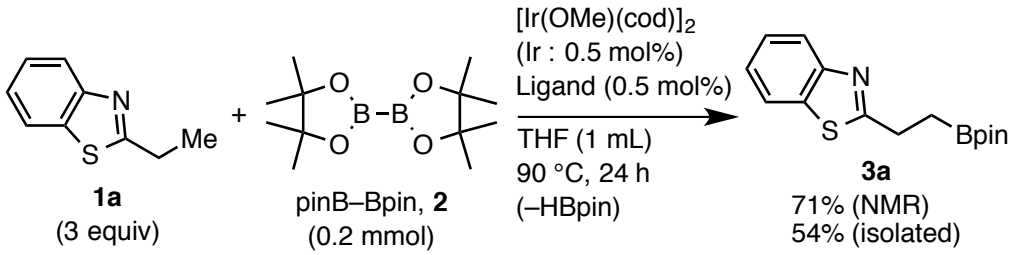
3	Silica-TPP	0	0
4	PS-TPP	0	0
5	Ph-SMAP	0	0
6	PPh_3	0	0
7 [e]	Dtbpy	0	0
8 [e]	Me_4Phen	0	0
9	none	0	0

[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] ^1H 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).

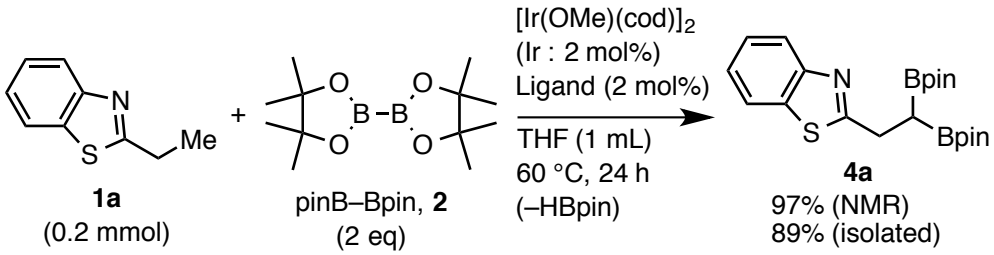
Figure 3. Homogeneous Ligands Used in Table 1.



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



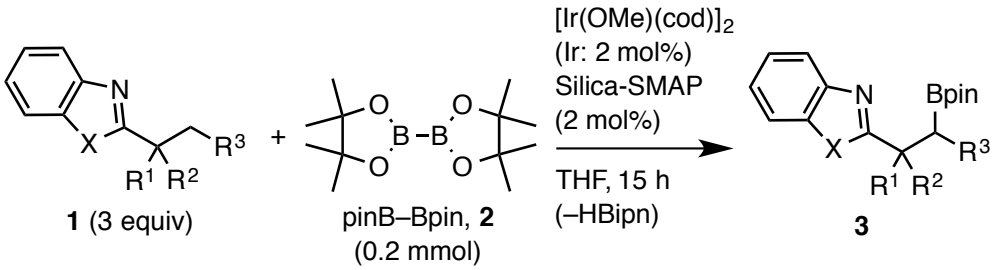
Scheme 2. Geminal diborylation of **1a**.

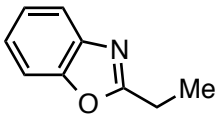
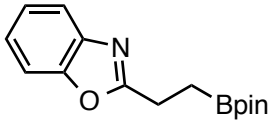
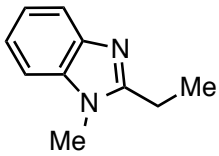
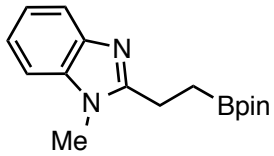
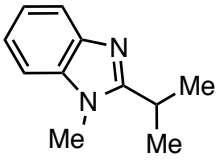
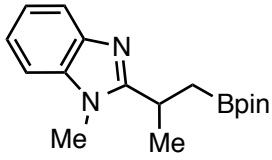
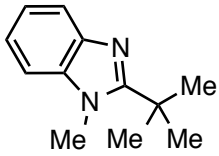
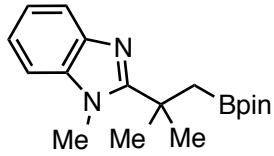
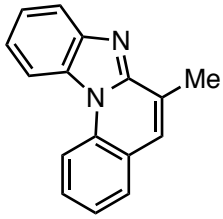
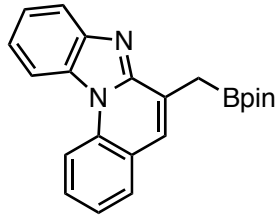


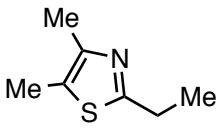
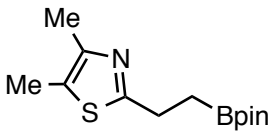
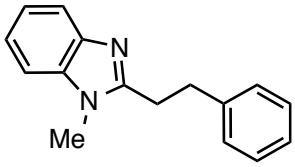
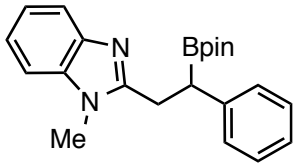
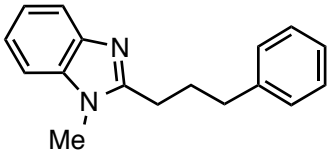
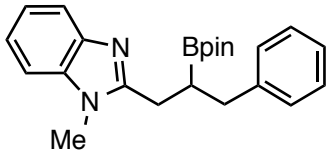
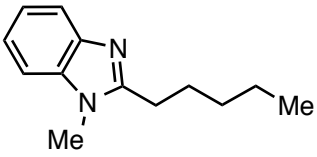
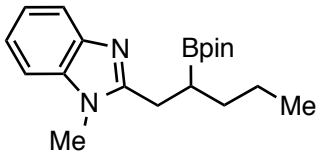
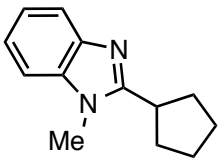
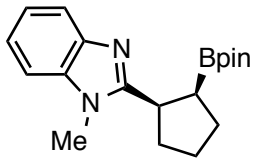
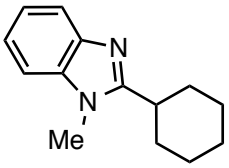
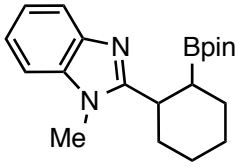
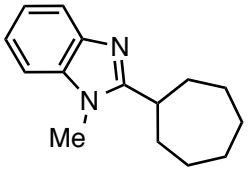
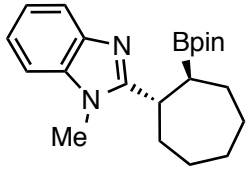
Scope of 1,3-azoles. The Silica-SMAP-Ir system was applicable to various 1,3-(benzo)azoles **1**, including thiazoles, oxazoles, and imidazoles (Table 2). Some of the borylation products **3** obtained in this manner were converted into the corresponding alcohols **5** through subsequent oxidation for 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(sp^2)–H borylation products (5%) (Table 2, entry 1). 2-Ethylbenzimidazole (**1c**) was borylated at 50 °C, 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 ^{1}H 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(sp^3)–H bonds (entries 4 and 5). The methyl C(sp^3)–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(sp^3)–H borylation (entry 7). Internal C(sp^3)–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 °C), 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(sp^3)–H bonds located γ to the directing sp^2-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,[7b] normal-sized ring compounds were also borylated site- and stereoselectively. Specifically, the reaction of 2-cyclopentyl-*N*-methylbenzimidazole (**1k**) at 90 °C 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 °C 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]



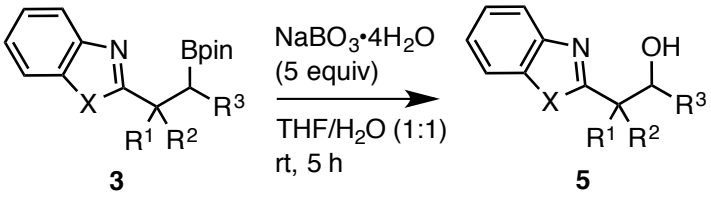
Entry	Substrate **1**	Borylation Product **3**	Temp (°C)	Yield of **3** (%)[b]
1	 **1b**	 **3b**	60	78[c,d,e] (48)[f]
2	 **1c**	 **3c**	50	38 [c,d,g]
3 [h]			50	60[c,d] (54) [f]
4	 **1d**	 **3d**	80	83 [d]
5	 **1e**	 **3e**	80	87
6	 **1f**	 **3f**	70	86

7	 **1g**	 **3g**	60	80 [c] (63)
8	 **1h**	 **3h**	80	81 [d,e]
9	 **1i**	 **3i**	80	89 [d,e]
10	 **1j**	 **3j**	90	89 [d,e]
11	 **1k**	 **3k** (*cis*:*trans* = 4:1)	90	112 [d,e]
12	 **1l**	 **3l**	70	83 [d,e]
13	 **1m**	 **3m**	80	72 [d,e]

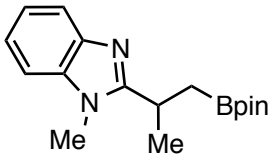
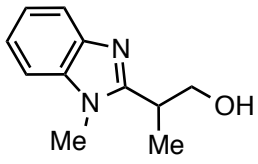
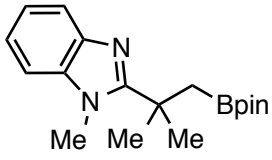
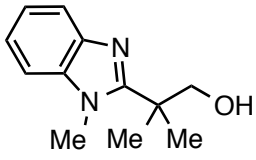
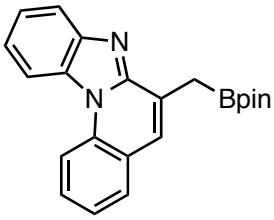
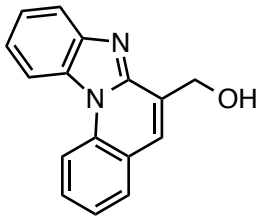
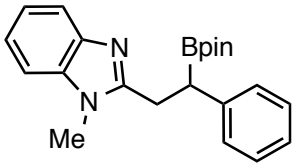
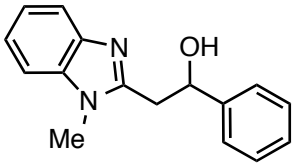
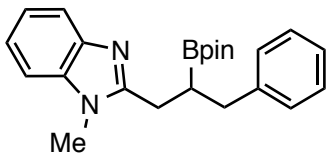
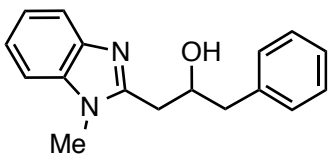
[a] Conditions for C–H borylation: **1a** (0.6 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (2 mol% Ir), Silica-SMAP (2 mol% P), THF (1 mL), 15 h. Conditions for oxidation: $NaBO_3 \cdot 4H_2O$ (1 mmol), THF (1 mL), H_2O (1 mL), rt, 5 h. [b] ^1H NMR yield based on **2**. Isolated yields shown in parentheses. [c] Geminal diborylation products **4** were formed in entries 1, 2, 3 and 7 (26%, 19%, 31%, and 34%, respectively). [d] 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). [e] Arylboronates were formed in entries 1, 8, 9, 10, 11, 12 and 13 (5%, 7%,

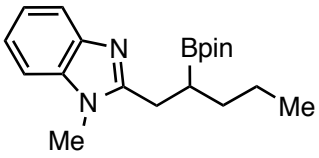
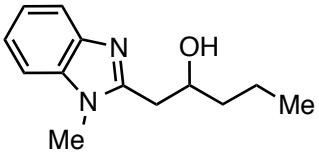
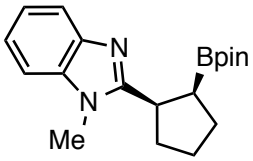
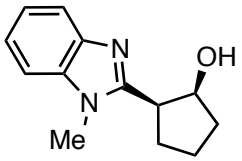
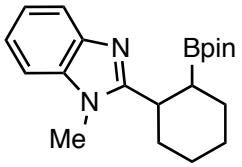
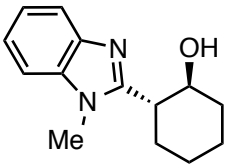
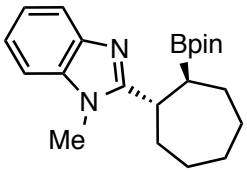
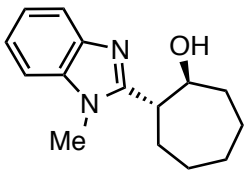
6%, 11%, 4%, 8%, and 2%, respectively). [f] Isolated product was contaminated with arylboronates (9%) and the diborylation product (1%). [g] The C=N reduction product of **3c** (structure not determined, ca. 20%) was formed. [h] Cyclooctene (0.2 mmol) was used as an additive. [i] Isolated product was contaminated with the diborylation product (<1%).

Table 3. Oxidation of borylated 2-Alkyl-1,3-azoles **3**.[a]



3 **5**

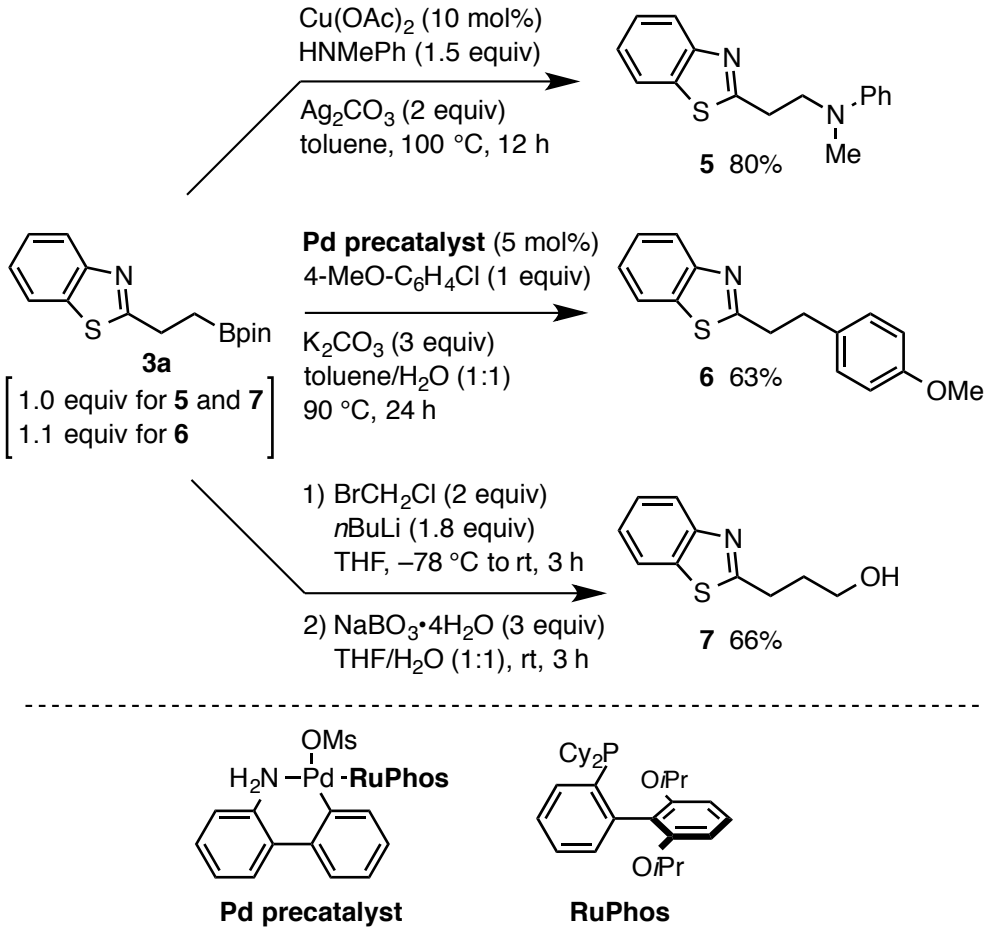
Entry	Borylated compound **3**	Alcohol product **5**	Yield of **5** (%)[a]
1	 **3d**	 **5d**	59
2	 **3e**	 **5e**	68
3	 **3f**	 **5f**	71
4	 **3h**	 **5h**	69
5	 **3i**	 **5i**	70

6	 **3j**	 **5j**	74
7	 **3k** (*cis*:*trans* = 4:1)	 **5k** (*cis*:*trans* = 4:1)	5k (cis): 67 5k' (trans):16 [c]
8	 **3l**	 **5l**	55 [c]
9	 **3m**	 **5m**	43 [c]

[a] Conditions: $NaBO_3 \cdot 4H_2O$ (1 mmol), THF (1 mL), H_2O (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_2CO_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.

^{1}H (400 MHz), ^{13}C (100 MHz) and ^{11}B (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_4Si (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 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 $60F_{254}$.

All reactions were carried out under a nitrogen atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. $[Ir(OMe)(cod)]_2$,[17] 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® 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. 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 ^{1}H 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-ehtylbenzo[*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 ^{1}H 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(sp^2)–H borylation products (5.5 mg, 10% yield), as estimated by ^{1}H 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-1*H*-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 $NaBO_3$•$4H_2O$ (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_2Cl_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_3N 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_2CO_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_2CO_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_2O (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_2O. 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,

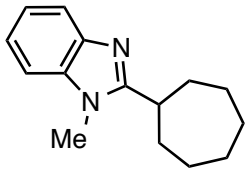
0.30 mmol, 2 equiv), and anhydrous THF (2 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. The tube was sealed with a screw cap with a Teflon-coated silicon rubber septum. After the mixture was cooled to –78 °C, ^{n}BuLi in hexane (1.6 M, 170 μL, 0.27 mmol, 1.8 equiv) was added. 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)-1*H*-benzo[*d*]imidazole was determined by ^{1}H 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 $NaBO_3$•$4H_2O$ (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 $CHCl_3$, 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 (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**,[23] **1b**,[24] **1c**,[25] **1d**,[26] **1e**,[26] **1f**,[27] **1h**,[28] **1i**,[29] **1j**,[30] **1k**[31] and **1l**[26] are reported in the literatures.

2-Cycloheptyl-1-methyl-1*H*-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).

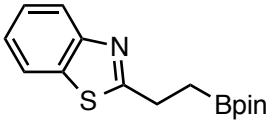


Isolated by silica gel chromatography ($CHCl_3$/MeOH 98:2). White solids. **M.p.** 79.6–80.0 °C. **^{1}H NMR** ($CDCl_3$) δ 1.54–1.73 (m, 6H), 1.87–2.09 (m, 6H), 3.04 (sep, *J* = 4.0 Hz, 1H), 3.72 (s, 3H), 7.20–7.30 (m, 3H), 7.72–7.75 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ 26.81 (2C), 27.96 (2C), 29.59, 33.20 (2C), 38.03, 108.77, 119.20, 121.58, 121.80, 135.60, 142.44, 160.12. **IR** (ATR):

2915, 2856, 1614, 1504, 1454, 1443, 1329, 1254, 1121, 1005, 738 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{21}N_2$, 229.16993; found, 229.16997.

Characterization of Products

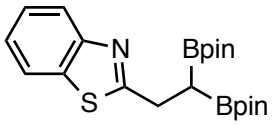
2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzo[*d*]thiazole (3a)



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, 2931, 1519, 1436, 1370, 1313, 1142, 1082, 967, 845, 758 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{21}O_2N^{10}BS$, 289.14169; found, 289.14170.

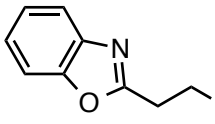
2-(2,2-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzo[*d*]thiazole (4a)



4a

Isolated by Kugelrohr distillation [1 mmHg, 180 °C, 75.5 mg, 89% yield, comtaminated 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 $C_{21}H_{31}O_4N^{11}B_2S$, 415.21599; found, 415.21564.

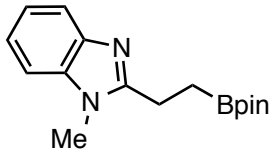
2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzo[*d*]oxazole (3b)



3b

Isolated by Kugelrohr distillation [1 mmHg, 130 °C, 26.7 mng, 49% yield, contaminated with C(sp^2)–H borylation products (4.6 mg, 9% yield) and diborylation product (0.83 mg, 1% yield)]. Colorless oil. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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. **^{11}B NMR** ($CDCl_3$) 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 $C_{15}H_{20}O_3N^{10}B$, 272.15725; found, 272.15662.

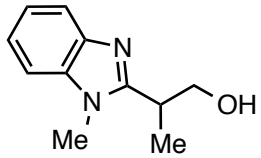
1-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-1*H*-benzo[*d*]imidazole (3c)



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. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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. **^{11}B NMR** ($CDCl_3$) 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 $C_{16}H_{24}O_2N_2{}^{10}B$, 286.19671; found, 286.19747.

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

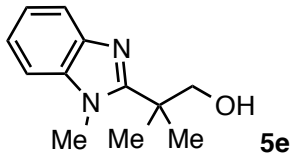


5d

Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 97:2:1) (22.2 mg, 0.117 mmol, 59% yield in two steps). Pale pink solids. **M.p.** 127.4–128.9 °C. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) δ 16.13, 29.68, 33.73, 65.56,

109.07, 119.14, 122.08, 122.31, 135.34, 141.99, 157.57. **IR** (ATR): 3129, 2972, 2832, 1615, 1507, 1472, 1315, 1239, 1075, 1047, 836, 741, 725 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{11}H_{15}ON_2$, 191.11789; found, 191.11802.

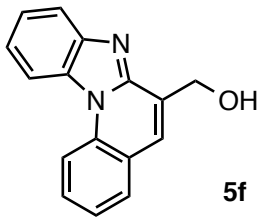
2-Methyl-2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)propan-1-ol (5e)



5e

Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 97:2:1) (27.6 mg, 0.135 mmol, 68% yield in two steps). White solids. **M.p.** 106.8–109.5 °C. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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 $C_{12}H_{17}ON_2$, 205.13354; found, 205.13358

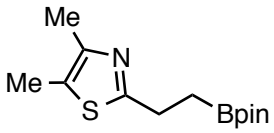
Benzo[4,5]imidazo[1,2-*a*]quinolin-6-ylmethanol (5f)



5f

Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 97:2:1) (35.0 mg, 0.141 mmol, 71% yield in two steps). White solids. **M.p.** 206.7–207.3 °C. **^{1}H NMR** (DMSO-d_6) 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). **^{13}C NMR** (DMSO-d_6) 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 $C_{16}H_{12}ON_2Na$, 271.08418; found, 271.08402.

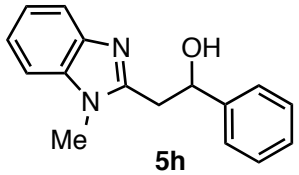
4,5-Dimethyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)thiazole (3g)



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 $C_{13}H_{22}O_2N^{10}BS$, 266.15006; found, 2666.14926.

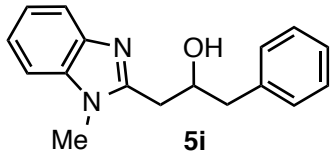
2-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethan-1-ol (5h)[32]



5h

Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 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.

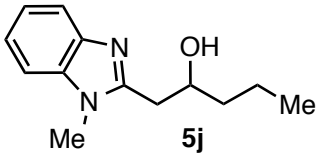
1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-3-phenylpropan-2-ol (5i)



5i

Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 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 (ddd, *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, 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.

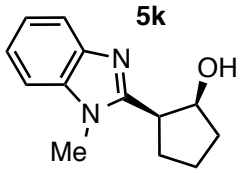
1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)pentan-2-ol (5j)



5j

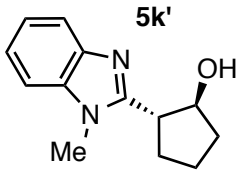
Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 97:2:1) (32.3 mg, 0.148 mmol, 74% yield in two steps). White solids. **M.p.** 125.1–126.8 °C. **^{1}H NMR** ($CDCl_3$) δ 0.98 (t, *J* = 6.8 Hz, 3H), 1.43–1.62 (m, 3H), 1.63–1.76 (m, 1H), 2.83 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.96 (dd, *J* = 16.0, 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). **^{13}C NMR** ($CDCl_3$) 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, 1065, 1056, 741 cm^{-1}. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{13}H_{19}ON_2$, 219.14919; found, 219.14918.

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



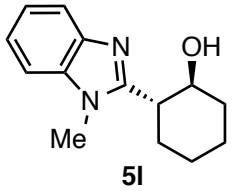
Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 97:2:1) (29.2 mg, 0.135 mmol, 67% yield in two steps). White solids. **M.p.** 114.0–116.9 °C. **^{1}H NMR** ($CDCl_3$) δ 1.79–1.91 (m, 2H), 1.98–2.08 (m, 2H), 2.10–2.21 (m, 2H), 3.10 (ddd, *J* = 11.2, 7.6, 3.6 Hz, 1H), 3.76 (s, 3H), 4.65 (t, *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). **^{13}C NMR** ($CDCl_3$) 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 $C_{13}H_{17}ON_2$, 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-1*H*-benzo[*d*]imidazol-2-yl)cyclopentan-1-ol (5k')**



Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 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. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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 $C_{13}H_{17}ON_2$, 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-1*H*-benzo[*d*]imidazol-2-yl)cyclohexan-1-ol (5l)**

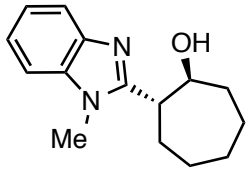


5l

Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 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. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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 $C_{14}H_{19}ON_2$, 231.14919; found, 231.14912. The ^{1}H 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 α to the alcohol group (4.28 ppm) and the proton at the position α to the azole group (2.83 ppm) is also indicative of *trans* configuration for **5l**.

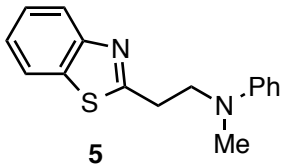
***trans*-2-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)cycloheptan-1-ol (5m)**



5m

Isolated by silica gel chromatography ($CHCl_3$/MeOH/Et_3N 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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 α to the alcohol group (4.44 ppm) is a triplet of doublets (J = 8.8, 3.6 Hz). The coupling constant is assignable to *trans* configuration for **5m**. In the NOESY NMR analysis, no correlation peak between the proton at the position α to the alcohol group (4.44 ppm) and the proton at the position α to the azole group (3.03 ppm) is also indicative of *trans* configuration for **5m**.

***N*-(2-(Benzo[*d*]thiazol-2-yl)ethyl)-*N*-methylaniline (5)**

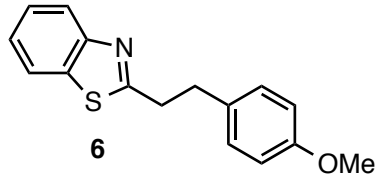


5

Isolated by silica gel chromatography (EtOAc/hexane 70:30) (32.2 mg, 0.120 mmol, 80% yield). Pale yellow oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 31.34, 38.55, 52.44, 112.61 (2C), 116.92, 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 $C_{16}H_{17}N_2S$, 269.11070; found, 269.11052.

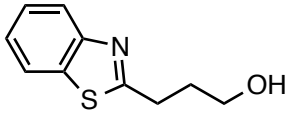
2-(4-Methoxyphenethyl)benzo[*d*]thiazole (6)



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. **^{1}H 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). **^{13}C 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)



7

Isolated by silica gel chromatography (EtOAc/hexane 70:30) (19.1 mg, 0.099 mmol, 66% yield in two steps). Pale yellow oil. **^{1}H 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). **^{13}C 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.

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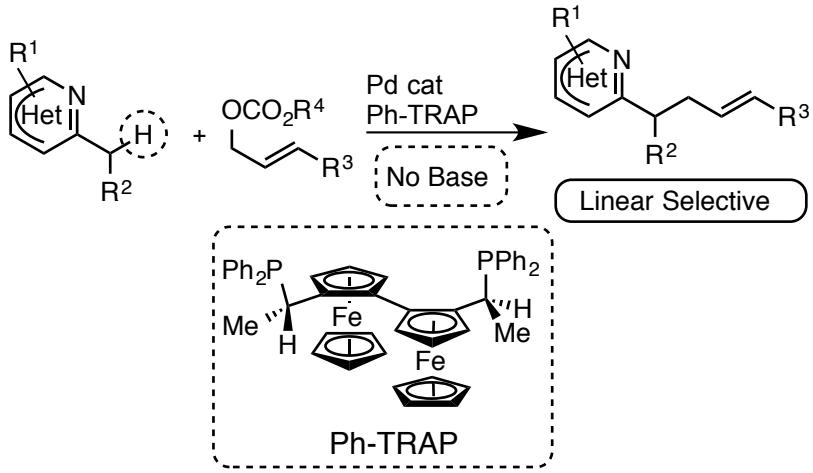
Chapter 3

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

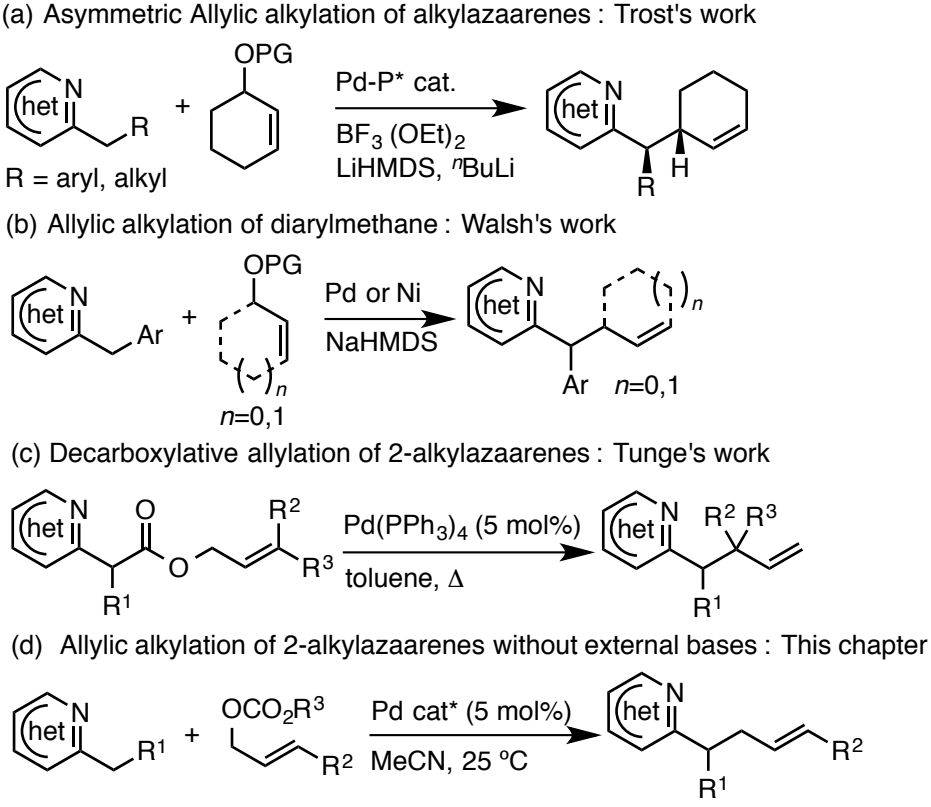


Palladium-catalyzed side chain C(α) allylation of 2-alkylazaarenes with allylic carbonates proceeded in the absence of external bases. This reaction occurred with exceptional linear selectivity under relatively mild conditions. Acid- or base-sensitive functional groups were compatibile in this allylation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

Introduction

Alkyl-substituted azaarenes are ubiquitos 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(α)–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. Transtion-metal catalyzed side chain C(α) allylation of 2-alkylazaarenes



This chapter describes the Pd-catalyzed side chain C(α) allylation of 2-alkylazaarenes

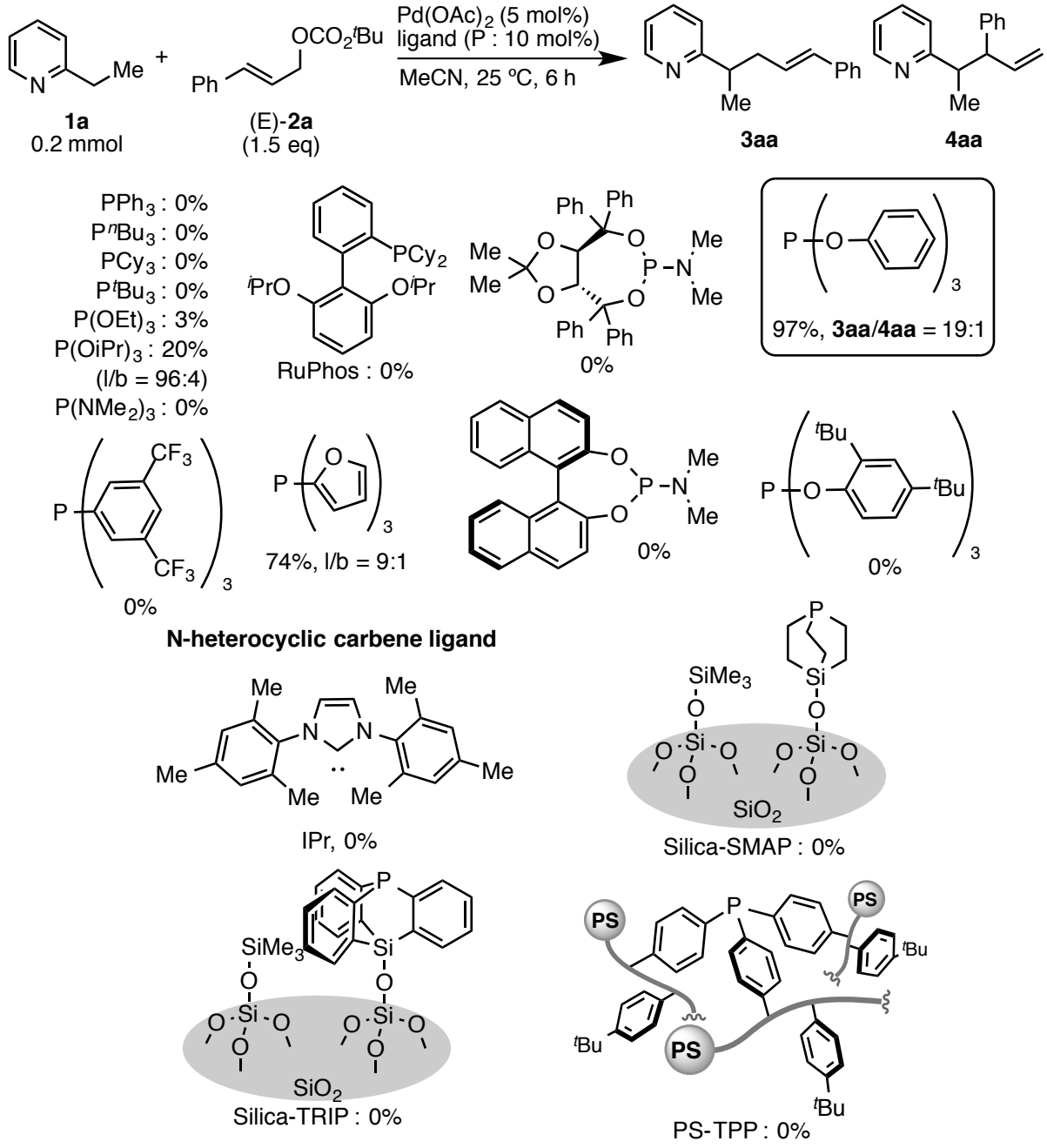
with allyl carbonates without using external bases (Scheme 1d). This reaction occurred with exceptional regioselectivity to give the linear allylation products with a tertiary carbon at the C(α) position of 2-alkylazaarenes. Owing to the neutral and mild conditions, base-sensitive functional groups were tolerable. The present Pd catslysis 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 CH_3CN 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 $P(2\text{-furyl})_3$ 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-SMAP[7], Silica-TRIP[8] and PS-TPP[9] 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.

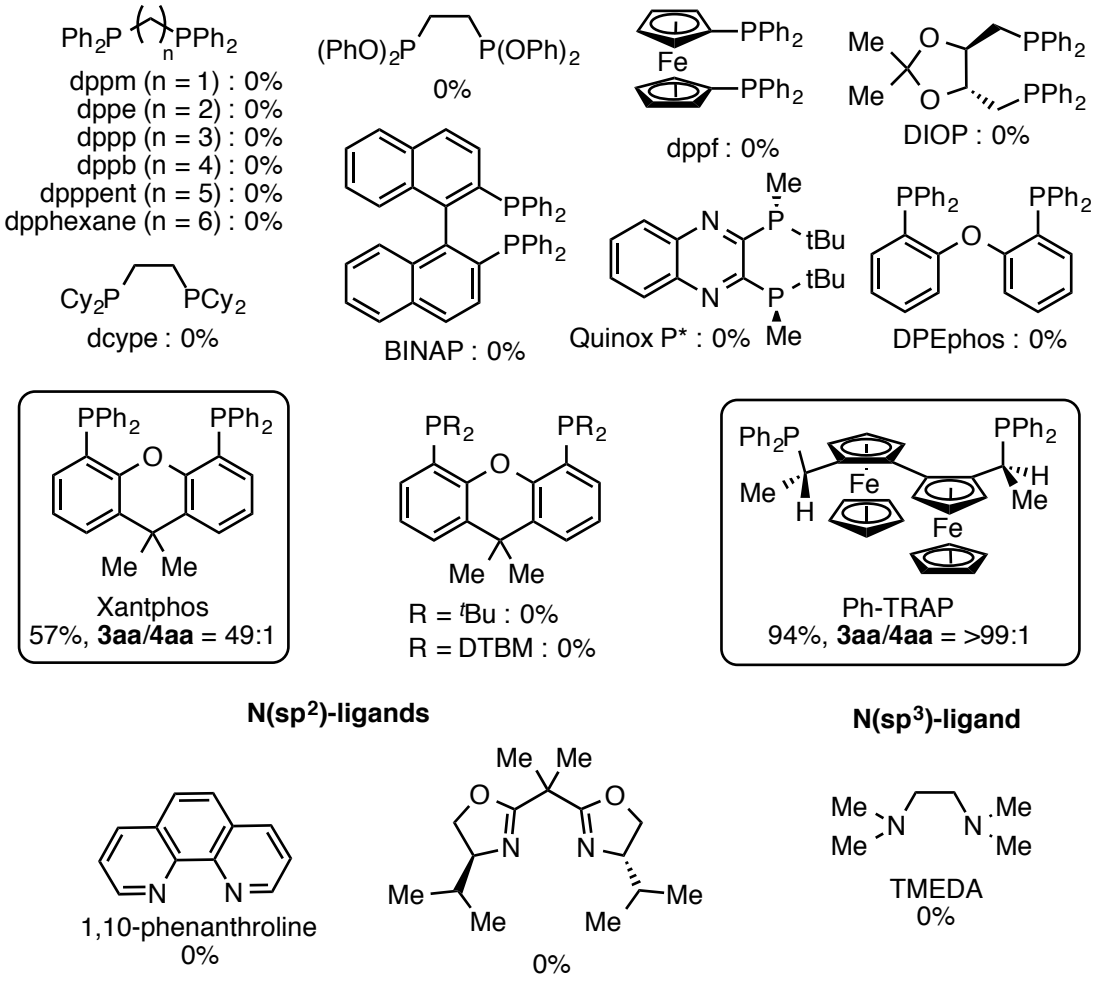
The results with various bidentate ligands are summarized in Figure 2. A large bite-angle bisphosphine Xantphos was effective for this transfomrtaion, giving **3a** with the high linear selectivity in a moderate yield (57%). However, the Xantphos derivatives *t*Bu-Xantphos and DTBM-Xantphos, which have aromatic substituents with increased steric demands on the phosphorus atoms, caused no reaction. During further bisphosphine screening, it was revealed that Ph-TRAP[10], 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-phenanthrolin and TMEDA were not effective.

Figure 1. Screening of monodentate ligands. Reaction conditions:



$Pd(OAc)_2$ (5 mol%), ligand (P: 10 mol%), **1a** (0.2 mmol), **2a** (0.3 mmol), CH_3CN (1 mL), 25 ºC, 6 h. Product yields and constitutional isomer ratio were determined by ^1H NMR.

Figure 2. Screening of Bidentate ligands. Conditions are indentical with those in Figure 1.



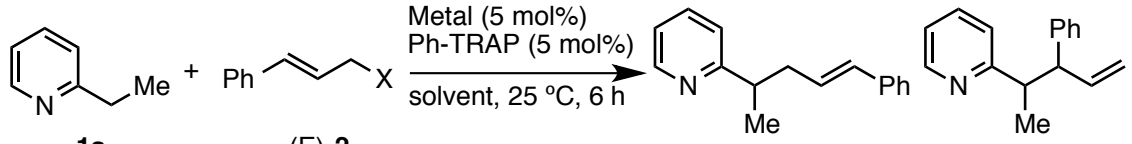
Optimization of palladium-catalyzed allylation with 2-alkylazaarenes. Ph-TRAP ligand (5 mol% M. Pd/ligand 1:1), various conditions and parameters in the reaction of **1a** as a representative 2-alkylazaarene substrate were investigated (Table 1). The reaction between **1a** and allylic carbonate (**2a**) 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 $PdCl_2(CH_3CN)_2$ and $[PdCl(allyl)]_2$ could be applied in allylic alkylation reaction (entry 3-4). Other transition metal precursors such as $Ni(cod)_2$, $[RuCl_2(p\text{-cymene})]_2$, $[RhCl(cod)]_2$, $[IrCl(cod)]_2$ 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). Thses 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_2Cl_2, THF and toluene (entries 14-17). The allylation reaction proceeded in polar solvent such as CH_3CN and DMF and allylation product was moderate yield (entry 1 and 14). The allylation reaction proceeded in CH_2Cl_2 solvent resuting in allylation product was moderate yield and linear selectivity of allylation product was slighly 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 alkyltion between 1a and 2a under various conditions[a]



1a 0.2 mmol (E)-**2** (1.5 eq) **3aa** **4aa**

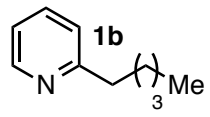
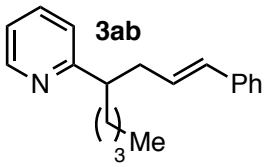
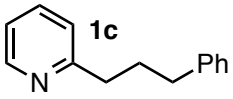
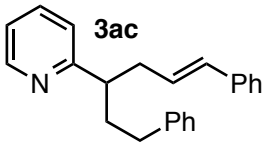
Entry	Metal	LG	Solvent	NMR Yield of **3aa** (%)[b]	**3aa**/**4aa**[b]
1	$Pd(OAc)_2$	$OCO_2{}^tBu$	CH_3CN	94 (91)[d]	>99:1
2	$Pd(dba)_2$	$OCO_2{}^tBu$	CH_3CN	93	>99:1
3	$PdCl_2(CH_3CN)_2$	$OCO_2{}^tBu$	CH_3CN	78	99:1
4	$[PdCl(allyl)]_2$	$OCO_2{}^tBu$	CH_3CN	90	>99:1
5	$Ni(cod)_2$	$OCO_2{}^tBu$	CH_3CN	0	
6	$[RuCl_2(p\text{-cymene})]_2$	$OCO_2{}^tBu$	CH_3CN	0	
7	$[RhCl(cod)]_2$	$OCO_2{}^tBu$	CH_3CN	0	
8	$[IrCl(cod)]_2$	$OCO_2{}^tBu$	CH_3CN	0	
9	$Pd(OAc)_2$	OCO_2Me	CH_3CN	95	>99:1
10	$Pd(OAc)_2$	$OC(O)NMe_2$	CH_3CN	0	
11	$Pd(OAc)_2$	OAc	CH_3CN	0	
12	$Pd(OAc)_2$	Cl	CH_3CN	0	

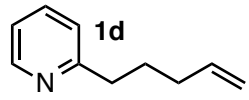
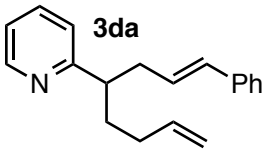
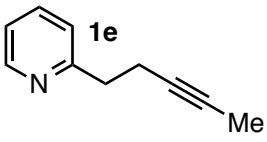
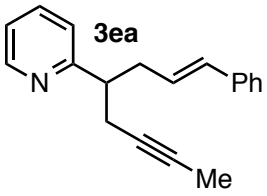
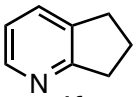
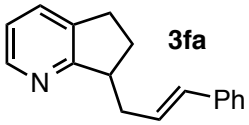
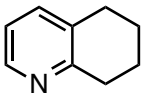
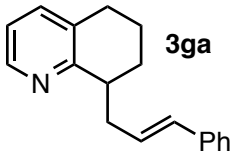
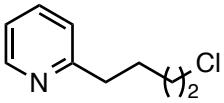
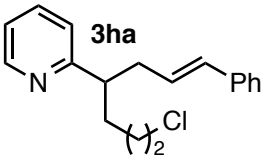
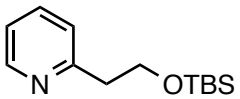
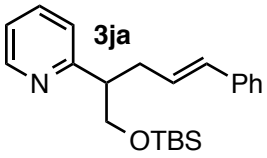
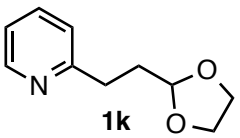
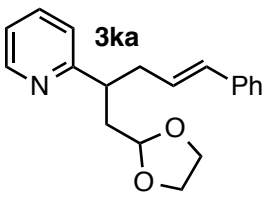
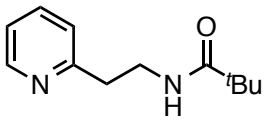
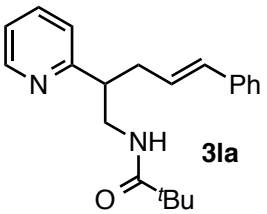
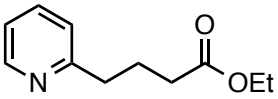
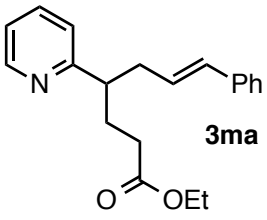
13	$Pd(OAc)_2$	$OP(O)(OEt)_2$	CH_3CN	0	
14	$Pd(OAc)_2$	$OCO_2{}^tBu$	DMF	76	>99:1
15	$Pd(OAc)_2$	$OCO_2{}^tBu$	CH_2Cl_2	69	98:2
16	$Pd(OAc)_2$	$OCO_2{}^tBu$	THF	0	
17	$Pd(OAc)_2$	$OCO_2{}^tBu$	Toluene	0	

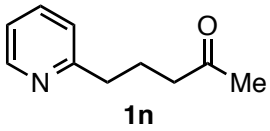
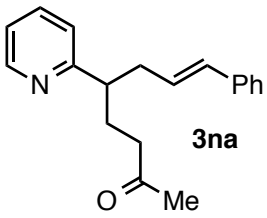
[a] Reaction conditions: Metal (5 mol%), Ph-TRAP (5 mol%), **1a** (0.2 mmol), allylic alcohol derivative **2** (0.3 mmol), solvent (1 mL), 25 ºC, 6 h. [b] Determined by ^{1}H NMR. [c] Constitutional isomer ratio determined by ^{1}H-NMR analysis of crude reaction [d] The yield of isolated product was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

Scope of 2-alkylpyridines. Various 2-alkylpyridines with different substituents at the side chain C(α) 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 substartes (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(α) allylation products were obtained in high yields (entry 11-12).

Table 2. Pd catalyzed allylation of various 2-alkylpyridines with **2a** [a]

Entry	2-alkylpyridines	Product	Yield (%)[b]
1			88
2			91

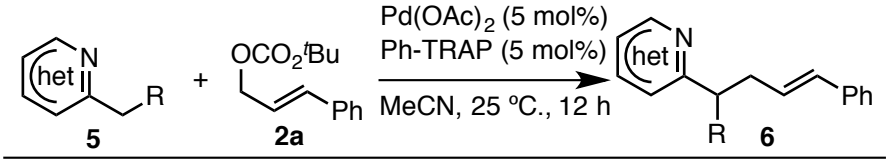
3	 **1d**	 **3da**	90
4	 **1e**	 **3ea**	82
5	 **1f**	 **3fa**	94
6	 **1g**	 **3ga**	97
7	 **1h**	 **3ha**	87
8	 **1j**	 **3ja**	90
9	 **1k**	 **3ka**	96
10	 **1l**	 **3la**	85
11	 **1m**	 **3ma**	90

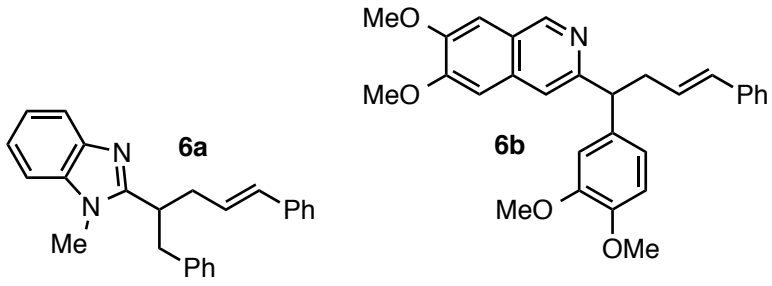
12	 **1n**	 **3na**	83

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), Ph-TRAP (5 mol%), **1** (0.2 mmol), cinnamyl tert-butyl carbonate **2a** (0.3 mmol), CH_3CN (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-alkylazaarenes. In addition to pyridine, benzimidazole and isoquinoline were suitable for the side chain C(α) 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 selectiveity. 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-alkylazaarenes with **2a**

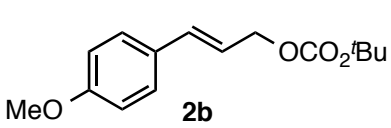
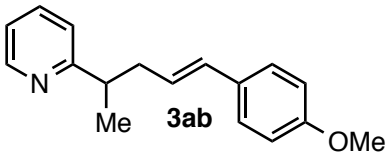
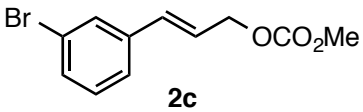
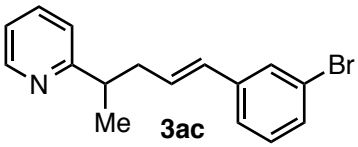
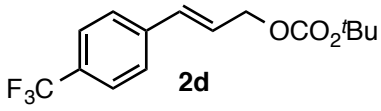
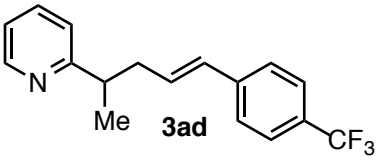
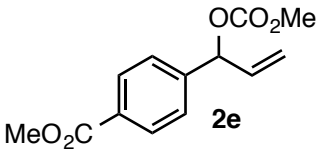
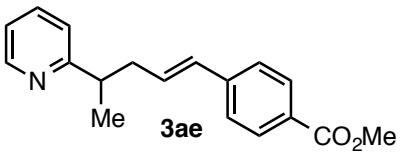
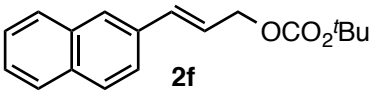
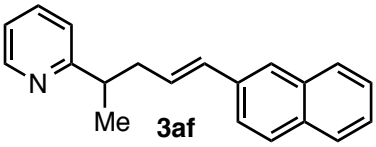
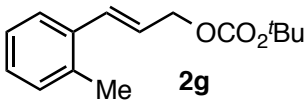
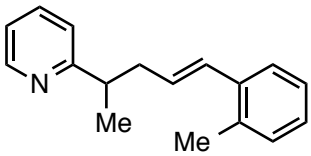


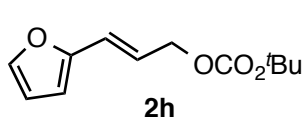
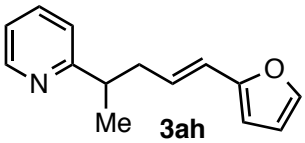
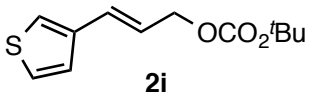
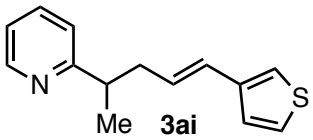
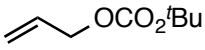
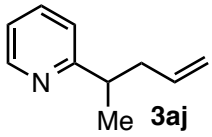
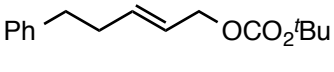
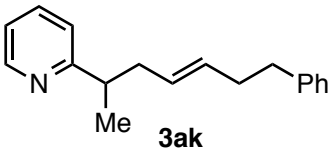
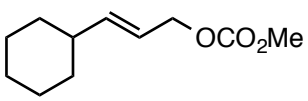
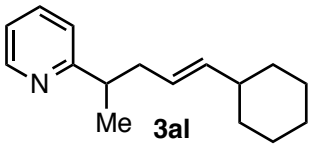
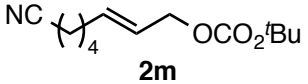
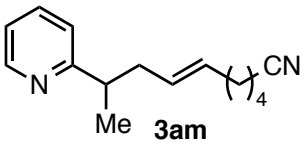
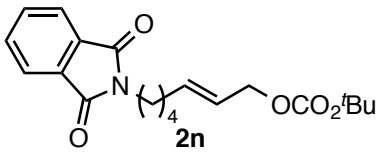
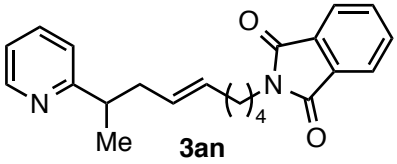


Scope of allylic carbonates. The reaction of cinnamyl carbonate derivatives with electronically and positionally diverse substituents including *p*-OMe, *m*-Br, *p*-CF_3, *p*-CO_2Me, 2-naphtyl, *o*-Me groups were compatible with the reaction conditions to afford the corresponding products in high yields (entry 1-6). The electron-donating group (OMe) on the meta-position of aromatic ring **2b** reacted with **1a** albeit with decreased linear selectivity

(entry 1). 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 acylic 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** [a]

Entry	2-alkylpyridines	Product	Yield (%)[b]	l/b [c]
1	 **2b**	 **3ab**	95	15:1
2	 **2c**	 **3ac**	80	99:1
3	 **2d**	 **3ad**	95	99:1
4	 **2e**	 **3ae**	87	99:1
5	 **2f**	 **3af**	95	99:1
6	 **2g**	 **3ag**	92	99:1

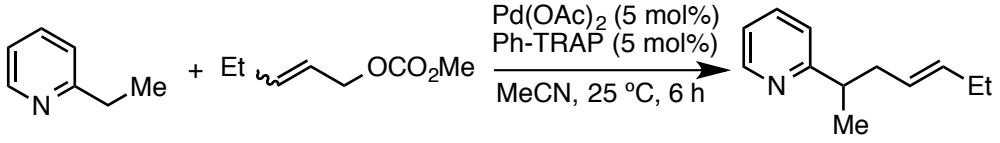
7	 **2h**	 **3ah**	86	20:1
8	 **2i**	 **3ai**	80	99:1
9	 **2j**	 **3aj**	80	
10 [d]	 **2k**	 **3ak**	77	99:1
11	 **2l**	 **3al**	80	99:1
12 [d]	 **2m**	 **3am**	81	99:1
13 [d]	 **2n**	 **3an**	70	99:1

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), Ph-TRAP (5 mol%), **1** (0.2 mmol), cinnamyl tert-butyl carbonate **2a** (0.3 mmol), CH_3CN (1 mL), 25 ºC, 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 ºC.

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 occured on the less hindered site of the allyl moiety.

Figure 2. Effect of alkene geometries of allylic carbonates.



1a (E or Z)-**(2p)** **3**

Entry	(E or Z)-(**2p**)	Product Yield [a] (%)	l/b [b]
1	*E*	93	93:7
2	*Z*	91	96:4

[a] Yield of isolated yield. [b] Constitutional isomer ratio: Determined by ^{1}H-NMR analysis of crude reaction.

Conclusion

The author have developed a palladium-catalyzed linear selective allylation reaction of 2-alkylazaarenes 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-alkylaaarenes. 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 fucntional groups were tolerable. For further detailed reaction mechanism is discussed with the chapter 4.

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_4Si (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. 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. $Pd(OAc)_2$ from Aldrich Chemical Co. All solvents for catalytic reactions were degassed via three freeze–pump–thaw cycles before use.

Experimental Procedures

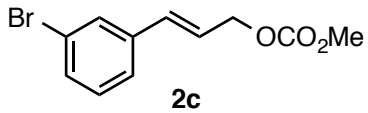
Procedure for Allylic alkylation of 2-ethylpyridine (1a) with cinnamyl tert-butyl carbonate (2a) (Table 1, Entry 6). In grove box, (8.6 mg, 0.01 mmol), $Pd(OAc)_2$ (2.4 mg, 0.01 mmol), and anhydrous, degassed MeCN (1.0 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. 2-Ethylpyridine (**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 grove 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 chromatogramphy on silica-gel (hexane/EtOAc) to give (E)-**3a** (40.6 mg, 0.182 mmol) in 91 %yield.

Preparation of Substrates

The starting material **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).

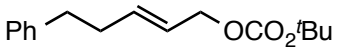


2c

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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) carboate (2k)

The title compound (**2k**) was synthesized via the Boc protection of allylic alcohol with Boc_2O and DMAP (92% yield).

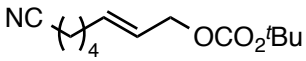


2k

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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_2O and DMAP (85% yield).

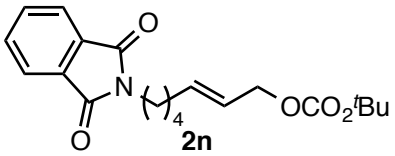


2m

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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-dioxoisoindolin-2-yl)hept-2-en-1-yl) carbonate (2n)

The title compound (**2n**) was synthesized via the Boc protection of allylic alcohol with Boc_2O and DMAP (87% yield).

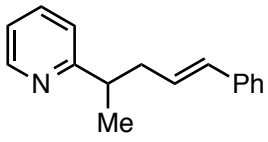


2n

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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

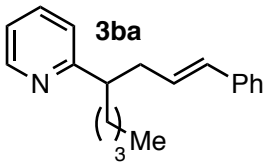
(*E*)-2-(5-phenylpent-4-en-2-yl)pyridine（3aa）



3aa

Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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-phenyloct-1-en-4-yl)pyridine (3ba)

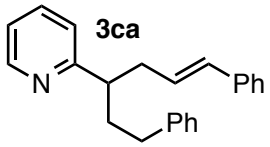


3ba

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil.**^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 14.02, 12.75, 29.73, 34.65, 39.21,

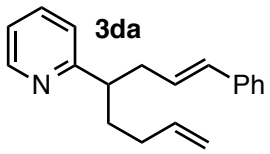
48.11, 121.14, 122.80, 125.93 (2C), 126.80, 128.37 (2C), 128.90, 131.14, 136.01, 137.71, 149.38, 164.57. **HRMS–EI** (*m/z*): [M] Calcd for $C_{19}H_{23}O_2N$, 265.18305; found, 265.18219.

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



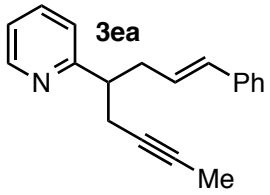
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 2.02–2.21 (m, 2H), 2.48 (t, *J* = 8.4 Hz, 2H), 2.54–2.64 (m, 1H), 2.63–2.71 (m, 1H), 2.89–2.96 (m, 1H), 6.06 (dt, *J* = 11.8, 7.6 Hz, 1H), 6.30 (d, *J* = 15.6 Hz, 1H), 7.09–7.16 (m, 6H), 7.22–7.26 (m, 6H), 7.58 (td, *J* = 7.2, 1.6 Hz, 1H), 8.61 (d, *J* = 4.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) 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.

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



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 31.60, 33.92, 39.17, 47.38, 114.60, 121.26, 123.03, 125.93, 126.85, 128.37, 128.63, 131.29, 136.05, 137.63, 138.49, 149.47, 164.02. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{19}H_{22}N$, 264.17468; found, 264.17467.

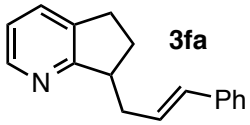
(*E*)-2-(1-phenylocta-1,7-dien-4-yl)pyridine（3ea）



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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),

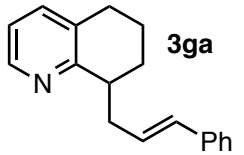
6.08 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.36 (d, *J* = 15.4 Hz, 1H), 7.10–7.14 (m, 1H), 7.16–7.18 (m, 2H), 7.23–7.27 (m, 4H), 7.59 (td, *J* = 7.6, 2.0 Hz, 1H), 8.59 (dt, *J* = 2.8, 0.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ 3.51, 24.28, 37.60, 47.21, 121.53, 122.90, 125.96 (2C), 126.90, 128.12, 128.37 (2C), 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.

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



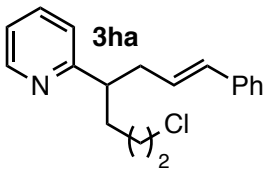
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.82-1.91 (m, 1H), 2.28–2.36 (m, 1H), 2.38–2.46 (m, 1H), 2.80–2.99 (m, 3H), 3.28–3.35 (m, 1H), 6.26 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 7.04 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.17–7.21 (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). **^{13}C NMR** ($CDCl_3$) 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, 137.63, 147.61, 166.80. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{17}H_{18}N$, 236.14338; found, 236.14336.

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



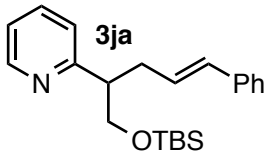
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.69–2.00 (m, 4H), 2.48 (dt, *J* = 10.8, 8.0 Hz, 1H), 2.70–2.82 (m, 2H), 2.96–3.08 (m, 2H), 6.25–6.31 (m, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 7.03–7.05 (m, 1H), 7.17–7.23 (m, 1H), 7.29 (t, *J* = 7.6 Hz, 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 $C_{18}H_{20}N$, 250.15903; found, 250.15913.

(*E*)-2-(7-chloro-1-phenylhept-1-en-4-yl)pyridine（3ha）



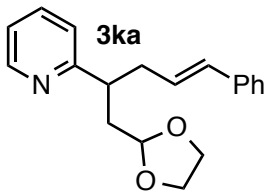
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.19–1.43 (m, 2H), 1.67–1.85 (m, 4H), 2.52–2.68 (m, 2H), 2.88 (dquint, *J* = 6.8, 0.8 Hz, 1H), 3.41–3.49 (m, 2H), 6.07 (dt, *J* = 14.4, 7.6 Hz, 1H), 6.32 (d, *J* = 15.6 Hz, 1H), 7.11 (td, *J* = 6.0, 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ -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** ($CDCl_3$) δ -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.

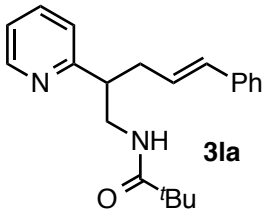
(*E*)-2-(1-(1,3-dioxolan-2-yl)-5-phenylpent-4-en-2-yl)pyridine（3ka）



Isolated by silica gel chromatography (hexane/EtOAc 70:30). White solid. **^{1}H NMR** ($CDCl_3$) 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, 137.58, 149.46, 163.43. **HRMS–EI** (*m/z*): [M] Calcd for $C_{19}H_{21}NO_2$, 295.15723; found, 295.15648.

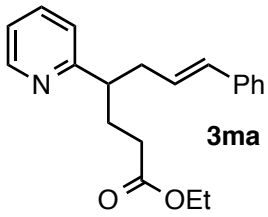
(*E*)-*N*-(5-phenyl-2-(pyridin-2-yl)pent-4-en-1-yl)pivalamide（3la）



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 $C_{21}H_{26}N_2O$, 322.20451; found, 322.20361.

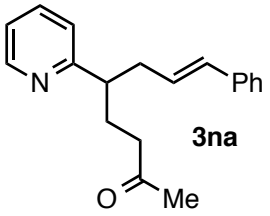
ethyl (*E*)-7-phenyl-4-(pyridin-2-yl)hept-6-enoate（3ma）



3ma

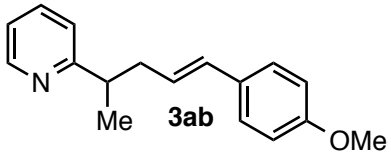
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.21 (t, *J* = 7.6 Hz, 3H), 2.06–2.20 (m, 4H), 2.54–2.61 (m, 1H), 2.63–2.71 (m, 1H), 2.92 (quint, *J* = 8.0 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 6.07 (dt, *J* = 14.4, 7.6 Hz, 1H), 6.33 (d, *J* = 16.0 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）



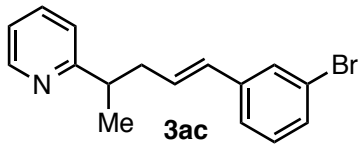
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.98–2.13 (m, 2H), 2.05 (s, 3H), 2.23–2.37 (m, 2H), 2.56 (quint, *J* = 6.8 Hz, 1H), 2.66 (quint, *J* = 6.8 Hz, 1H), 2.86–2.93 (m, 1H), 6.07 (dt, *J* = 14.4, 7.6 Hz, 1H), 6.33 (d, *J* = 15.2 Hz, 1H), 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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–EI** (*m/z*): [M] Calcd for $C_{15}H_{17}NO$, 253.14666; found, 253.14608.

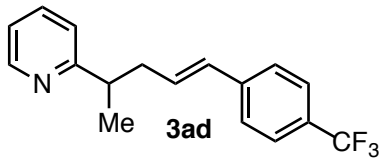
(*E*)-2-(5-(3-bromophenyl)pent-4-en-2-yl)pyridine（3ac）



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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**

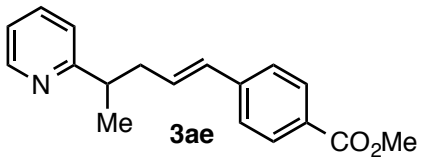
NMR ($CDCl_3$) δ 20.22, 40.33, 41.97, 121.28, 121.63, 122.61, 124.64, 128.79, 129.71, 129.90, 130.02, 130.49, 136.35, 139.81, 149.26, 165.35. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{16}H_{17}NBr$, 302.05389; found, 302.05405.

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



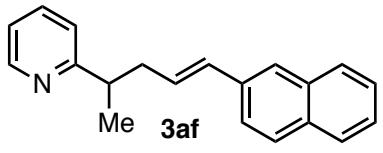
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.35 (d, *J* = 7.2 Hz, 3H), 2.49–2.56 (m, 1H), 2.66–2.75 (m, 1H), 3.08 (sext, *J* = 6.8 Hz, 1H), 6.20–6.28 (m, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 7.11–7.17 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *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** ($CDCl_3$) δ 20.20, 40.37, 41.88, 121.34, 121.63, 125.32 (q, *J* = 3.8 Hz, 2C), 126.05 (2C), 128.63 (q, *J* = 32.4 Hz), 129.70, 130.18, 131.63, 136.45, 141.06, 149.17, 165.21. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{17}H_{17}NF_3$, 292.13076; found, 292.13077.

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



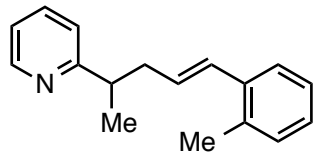
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.35 (d, *J* = 6.8 Hz, 3H), 2.49–2.56 (m, 1H), 2.69–2.75 (m, 1H), 3.07 (sext, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 6.27 (dt, *J* = 14.4, 6.8 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 7.10–7.16 (m, 2H), 7.33 (d, *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** ($CDCl_3$) δ 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.

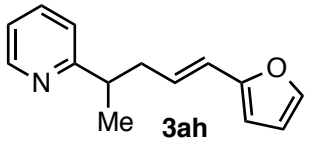
(*E*)-2-(5-(*o*-tolyl)pent-4-en-2-yl)pyridine（3ag）



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.

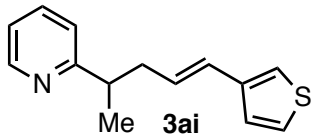
(*E*)-2-(5-(furan-2-yl)pent-4-en-2-yl)pyridine（3ah）



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–EI** (*m/z*): [M] Calcd for $C_{14}H_{15}NO$, 213.11536; found, 213.11576.

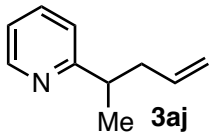
(*E*)-2-(5-(thiophen-3-yl)pent-4-en-2-yl)pyridine（3ai）



3ai

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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.

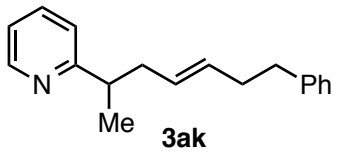
2-(pent-4-en-2-yl)pyridine（3aj）[34]



3aj

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 20.09, 41.26, 41.71, 116.07, 121.12, 121.58, 136.23, 136.86, 149.17, 165.71.

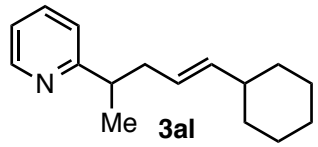
(*E*)-2-(7-phenylhept-4-en-2-yl)pyridine（3ak）



3ak

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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.

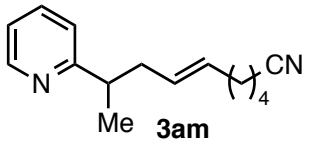
(*E*)-2-(5-cyclohexylpent-4-en-2-yl)pyridine（3al）



3al

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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 NMR** ($CDCl_3$) δ 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. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{16}H_{24}N$, 230.19033; found, 230.19061.

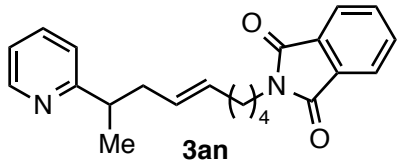
(*E*)-9-(pyridin-2-yl)dec-6-enenitrile（3am）



3am

Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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 NMR** ($CDCl_3$) δ 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. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{21}N_2$, 229.16993; found, 229.17006.

***(E)-2-(8-(pyridin-2-yl)non-5-en-1-yl)isoindoline-1,3-dione*（3an）**

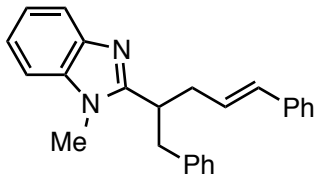


3an

Isolated by silica gel chromatography (hexane/EtOAc 80:20). Colorless oil. Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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 NMR** ($CDCl_3$) δ 20.03, 26.62, 27.93, 31.99, 37.84, 40.03, 42.00, 121.07, 121.69, 123.12 (2C),

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 $C_{22}H_{25}N_2O_2$, 349.19105; found, 349.19107.

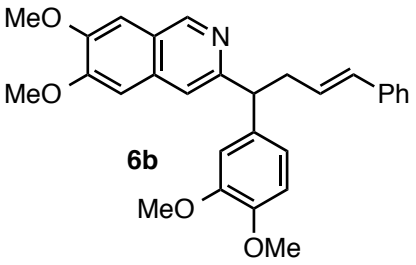
(*E*)-2-(1,5-diphenylpent-4-en-2-yl)-1-methyl-1*H*-benzo[*d*]imidazole（6a）



6a

Isolated by silica gel chromatography (hexane/EtOAc 70:30). White Solid. **^{1}H NMR** ($CDCl_3$) δ2.77-2.84 (m, 1H), 2.95-3.04 (m, 1H), 3.18-3.21 (m, 2H), 3.21 (s, 3H), 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). **^{13}C NMR** ($CDCl_3$) δ 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 $C_{25}H_{25}N_2$, 353.20123; found, 353.20133.

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



6b

Isolated by silica gel chromatography (hexane/EtOAc 70:30). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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). **^{13}C NMR** ($CDCl_3$) δ 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 $C_{29}H_{30}N_2O_4$, 456.21693; found, 456.21713.

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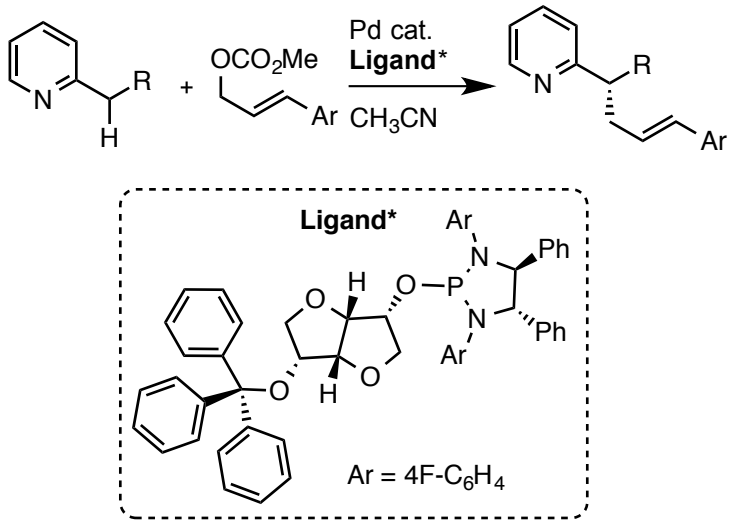
Chapter 4

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 occured 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-alkylazaarenes 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-alkylazaarenes.

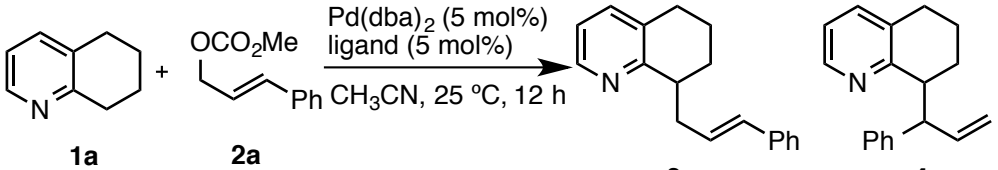
Results and Discussion

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 $Pd(dba)_2$ 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 $BF_3 \cdot OEt_2$ and LHMDS, 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, diamidophophite-type ligands were good candidates for the present asymmetric side chain C(α) allylation. The diamidophosphite ligand can be synthesized for versatile structural modification (Scheme 1). 1,3-propanediol-based bis(diamidophosphite) 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(diamidophosphite) ligand (entry 13-16). Accordingly, (2S,5S)-2,5-hexanediol-based bis(diamidophophite) ligand **L14** increased enantioselectivity to 62% (entry 14), albeit the Ph-DPEN-based bis(diamidophophite) 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(diamidophophite) 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]

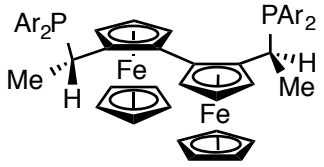


1a 0.2 mmol + **2a** 1.5 eq → **3a** + **4a**

Entry	Ligand	Yield (%)[b]	Ee, % [c]	**3a**/**4a**[d]
1	**L1**	97	11	>99:1
2	**L2**	94	56	>99:1
3	**L3**	0		
4	**L4**	0		
5	**L5**	0		
6	**L6**	0		
7	**L7**	0		
8	**L8**	99	–42	97:3
9	**L9**	94	53	99:1
10	**L10**	87	60	>99:1
11	**L11**	91	61	>99:1
12	**L12**	96	64	>99:1

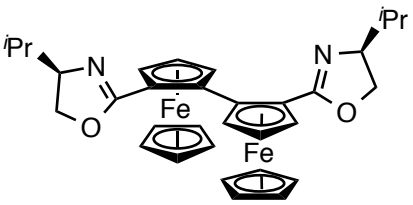
13	**L13**	0		
14	**L14**	34	62	>99:1
15	**L15**	96	53	>99:1
16	**L16**	99	66	>99:1

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), ligand (P: 10 mol%), **1a** (0.2 mmol), **2a** (0.3 mmol), CH_3CN (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.

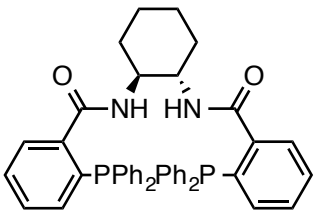


TRAP derivatives

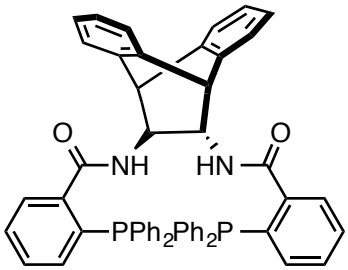
L1 : Ar = C_6H_5
L2 : Ar = 3,5-PhC_6H_3



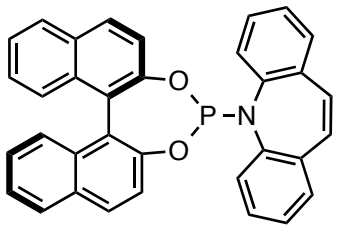
L3



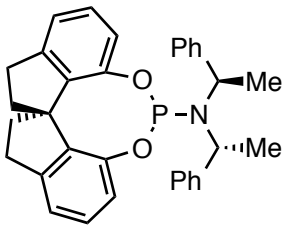
L4



L5



L6



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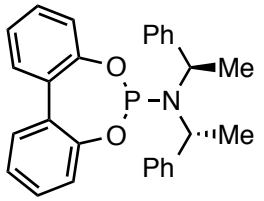
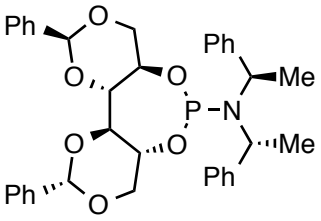
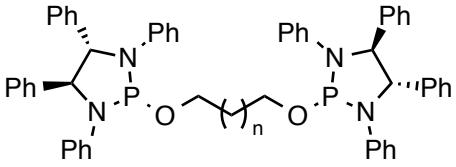


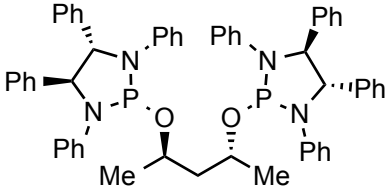
L8



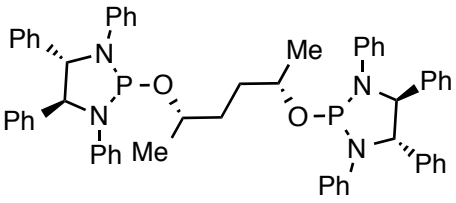
L9



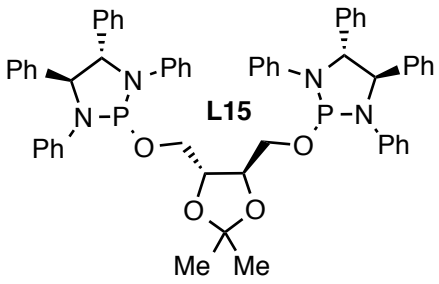
n = 1 : **L10**
n = 2 : **L11**
n = 3 : **L12**



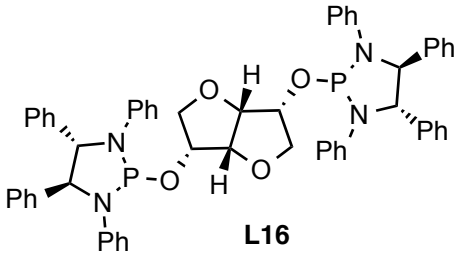
L13



L14

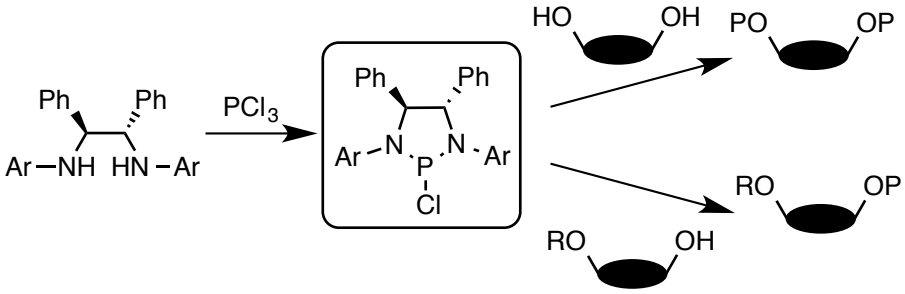


L15



L16

Scheme 1. Synthesis of chiral diamidophophite 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.

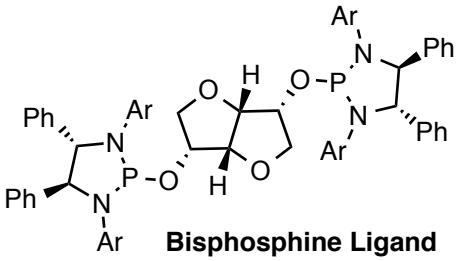
During this study, it revealed that an isomannide-based monodentate diamidophophite[10] ligand showed high performance (entry 7-12). **L24**, introducing a benzoyl protected alcohol group, was effective for enantioselective allylation (entry 7). From this result, it found that the second phosphorus atom was not required necessarily for expression of enantioselectivity. **L24**, having a benzyl-proteced alcohol moiety, showed higher ligand performance than bis(diamidophophite) 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).

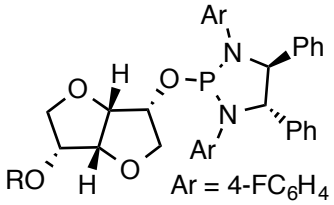
Table 2. Modification of ligand for the enantioselective reaction between **1a** and **2a** [a]

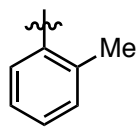
Entry	Ligand	Yield (%)[b]	Ee (%)[c]	**3a/4a**[d]
1	**L17**	0		
2	**L18**	0		
3	**L19**	0		
4	**L20**	98	38	>99:1

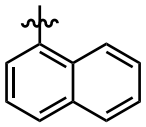
5	**L21**	99	69	>99:1
6	**L22**	98	17	>99:1
7	**L23**	97	64	>99:1
8	**L24**	99	75	>99:1
9	**L25**	96	75	>99:1
10	**L26**	95	84	>99:1
11[e]	**L26**	93	91	>99:1

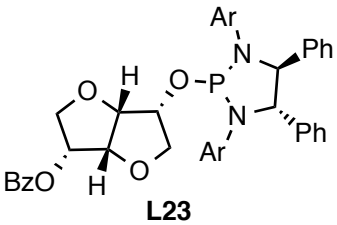
[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), ligand (P: 10 mol%), **1a** (0.2 mmol), **2a** (0.3 mmol), CH_3CN (1 mL), 25 ºC, 12 h. [b] Yield of isolated yield. [c] Determined by HPLC analysis. [d] Constitutional isomer ratio: Determined by ^{1}H-NMR analysis of crude reaction. [e] The reaction was carried out at -20 ºC for 36 h.

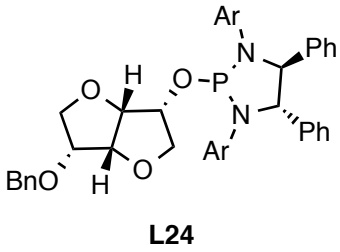


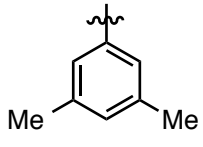


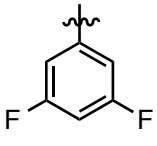


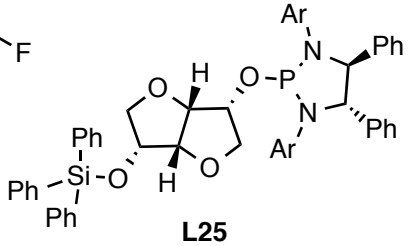


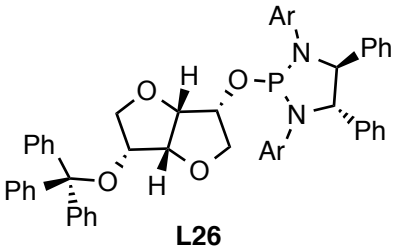


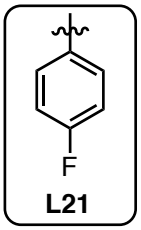


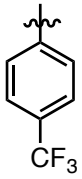






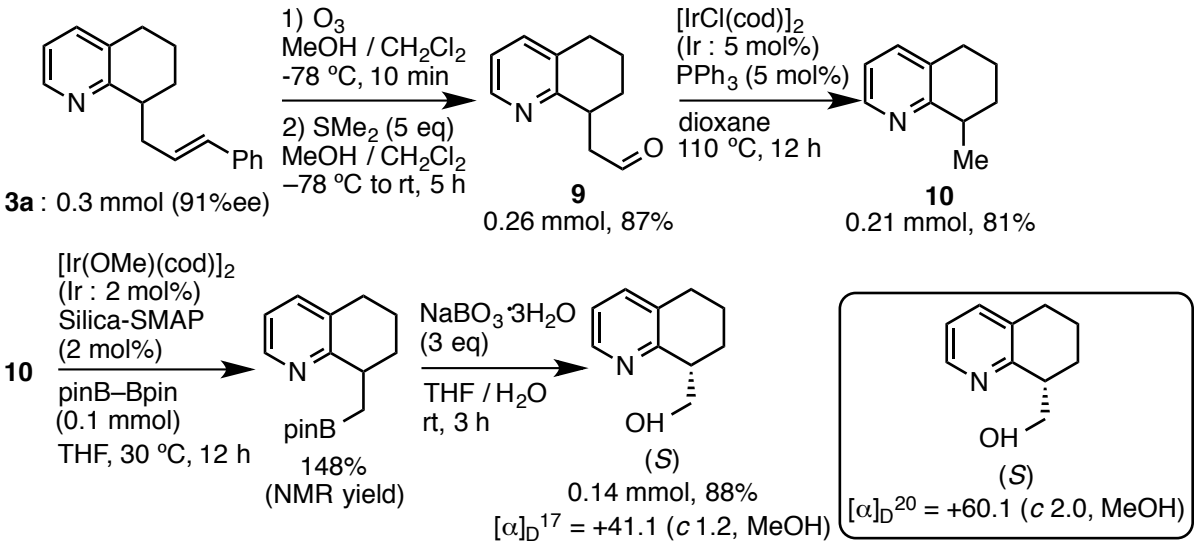






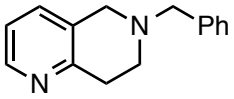
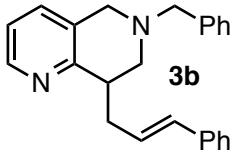
Determination of Absolute Configuration. The title compound **3a** was subjected to ozonolysis and reduction. Ir-catalyzed decarbonylation of aldehyde compound **9** was carried out to afford the compound **10**[11]. Next, Ir-Silica-SMAP-catalyzed C(sp^3)–H borylation of compound **11**[12] was carried out to give the corresponding borylation product **12**, and then desired alcohol product **13**[13] was given by oxidation of alkylboronate **12**. Absolute

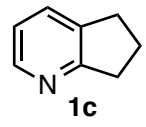
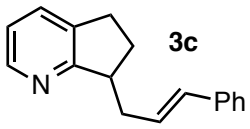
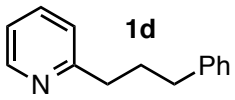
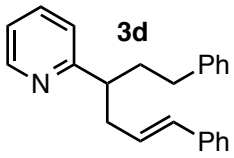
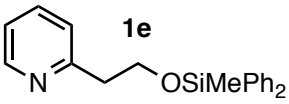
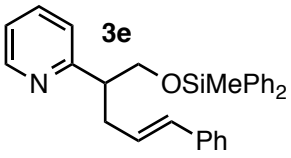
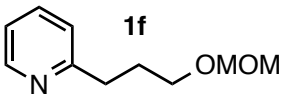
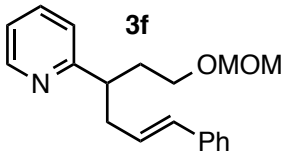
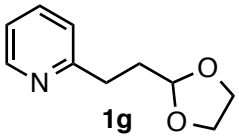
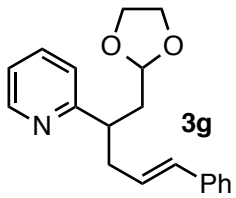
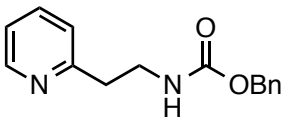
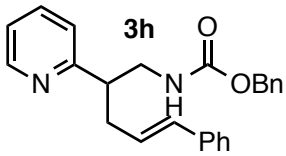
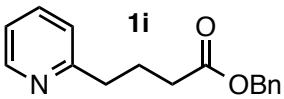
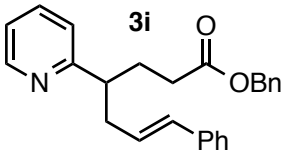
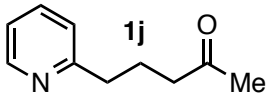
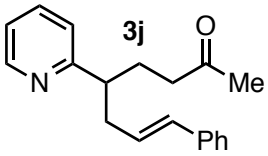
stereochemistry was assigned by optical rotation determination.



Scope of 2-alkylpyridines. With the $Pd(dba)_2$/**L26** catalyst system, the scope of 2-alkylazaarenes was investigated (in CH_3CN 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(α)-allylation product **3c**. Non-fused 2-alkylpyridines were suitable substrates (–10 °C, 36 h), but their enentioselectivities 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 allyation 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 α-carbonyl C–H bonds more acidic than that of azabenzylic positions, were compatible in the allylation, and only side chain C(α) 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]

Entry	2-Alkylpyridine **1**	Product **3**	Yield (%)[b]	Ee (%)[c]
1	 **1b**	 **3b**	95	85

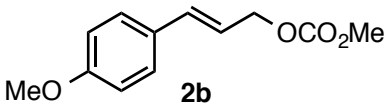
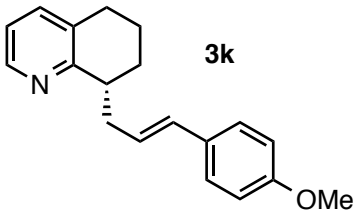
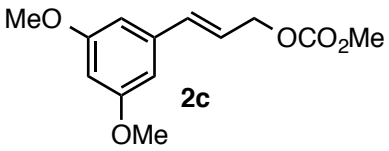
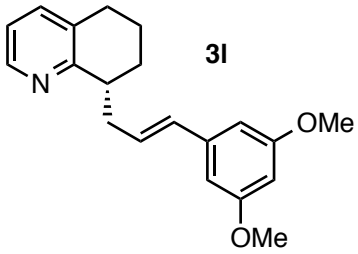
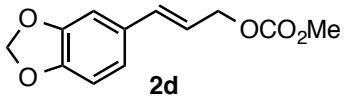
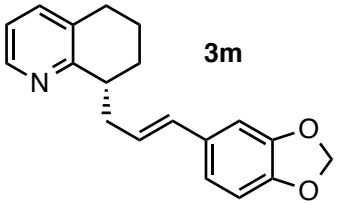
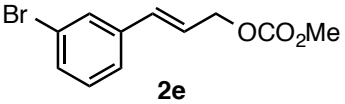
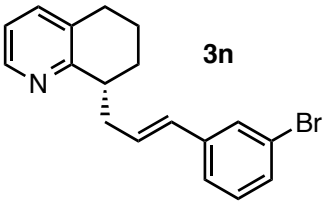
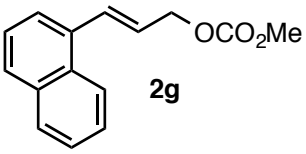
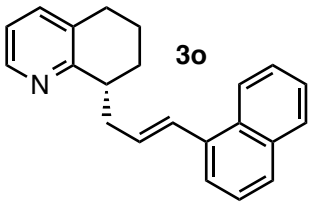
2	 **1c**	 **3c**	96	87
3[d]	 **1d**	 **3d**	76	78
4[d]	 **1e**	 **3e**	91	71
5[d]	 **1f**	 **3f**	83	76
6[d]	 **1g**	 **3g**	99	69
7[d]	 **1h**	 **3h**	83	78
8[d]	 **1i**	 **3i**	88	84
9[d]	 **1j**	 **3j**	92	81

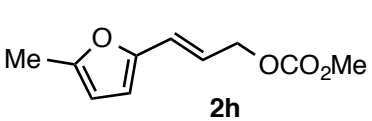
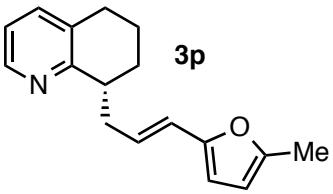
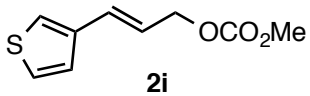
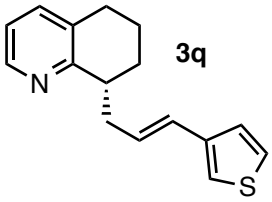
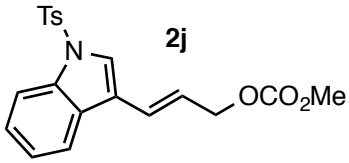
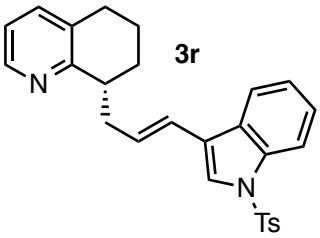
[a] Reaction conditions: $Pd(dba)_2$ (5 mol%), **L26** (5 mol%), **1** (0.2 mmol), **2a** (0.3 mmol), CH_3CN (1 mL), –20 ºC, 36 h. [b] Constitutional isomer ratios (l/b = >99:1, E/Z = >99:1) Determined by ^1H NMR analysis of the crude mixture. Yield of isolated yield. [c] Determined by HPLC analysis. [d] The reaction was carried out at –10 ºC for 36 h.

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 ºC to affod the corresponding allylation product in good yield with high enantioselectivity (entry 2 and 3). On the other hand, the substitution of the armatic 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 substartes (entry 6, 7 and 8).

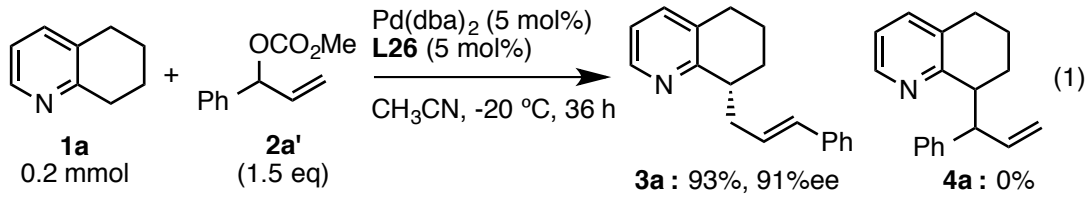
Table 4. Scope of enantioselective allylation reaction with allylic carbonates[a]

entry	Allylic carbonate **2**	Product **3**	Yield (%)[b]	Ee (%)[c]
1	 **2b**	 **3k**	93	94
2	 **2c**	 **3l**	96	93
3	 **2d**	 **3m**	89	92
4	 **2e**	 **3n**	92	90
5	 **2g**	 **3o**	91	86

6	 **2h**	 **3p**	77	87
7	 **2i**	 **3q**	94	91
8 [e]	 **2j**	 **3r**	96	93

[a] Reaction conditions: $Pd(dba)_2$ (5 mol%), **L26** (5 mol%), **1** (0.2 mmol), **2a** (0.3 mmol), CH_3CN (1 mL), –20 ºC, 36 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. [c] Determined by HPLC analysis. [d] The reaction was carried out at –20 ºC for 48 h. [e] The reaction was carried out at –10 ºC for 36 h.

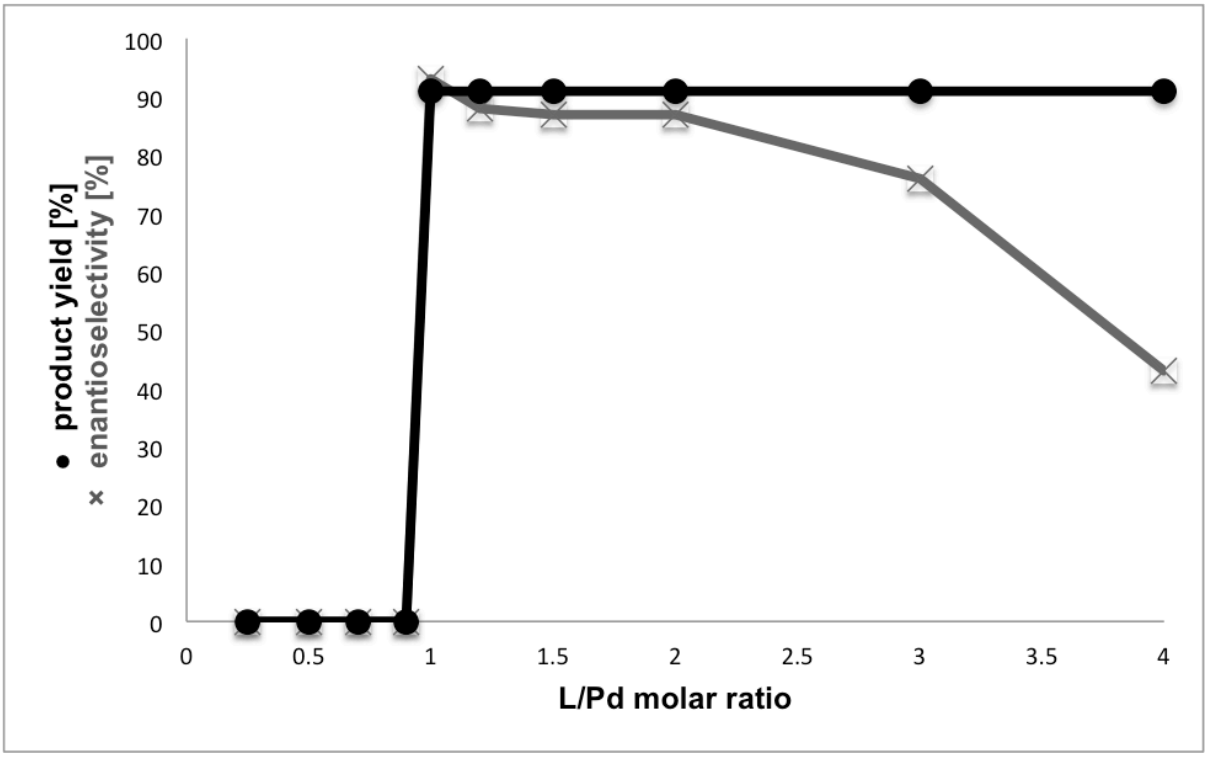
Pd-catalyzed allylation with the secondary allylic carbonate. When the reaction was conducted with secondary allylic carbonate **2a'** instead of **2a**, the same levels of yield, linear selectivity and enantioselectivity as the reaction of the primary allylic carbonate **2a** was obatined. This result indicated that rapid σ-π-σ isomerization of the allyl-palladium species was involed 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 decresed with increasing the loading of **L26** in the range from 1.0 to 4.0, the enantioselectivity (91% ee) was unchanged. Theses 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).



Entry	**L26**/Pd ratio	Yield (%)	Ee (%)
1	0.25	0	
2	0.5	0	
3	0.7	0	
4	0.9	0	
5	1	93	91
6	1.2	88	91
7	1.5	87	91
8	2	87	91
9	3	76	91
10	4	43	91

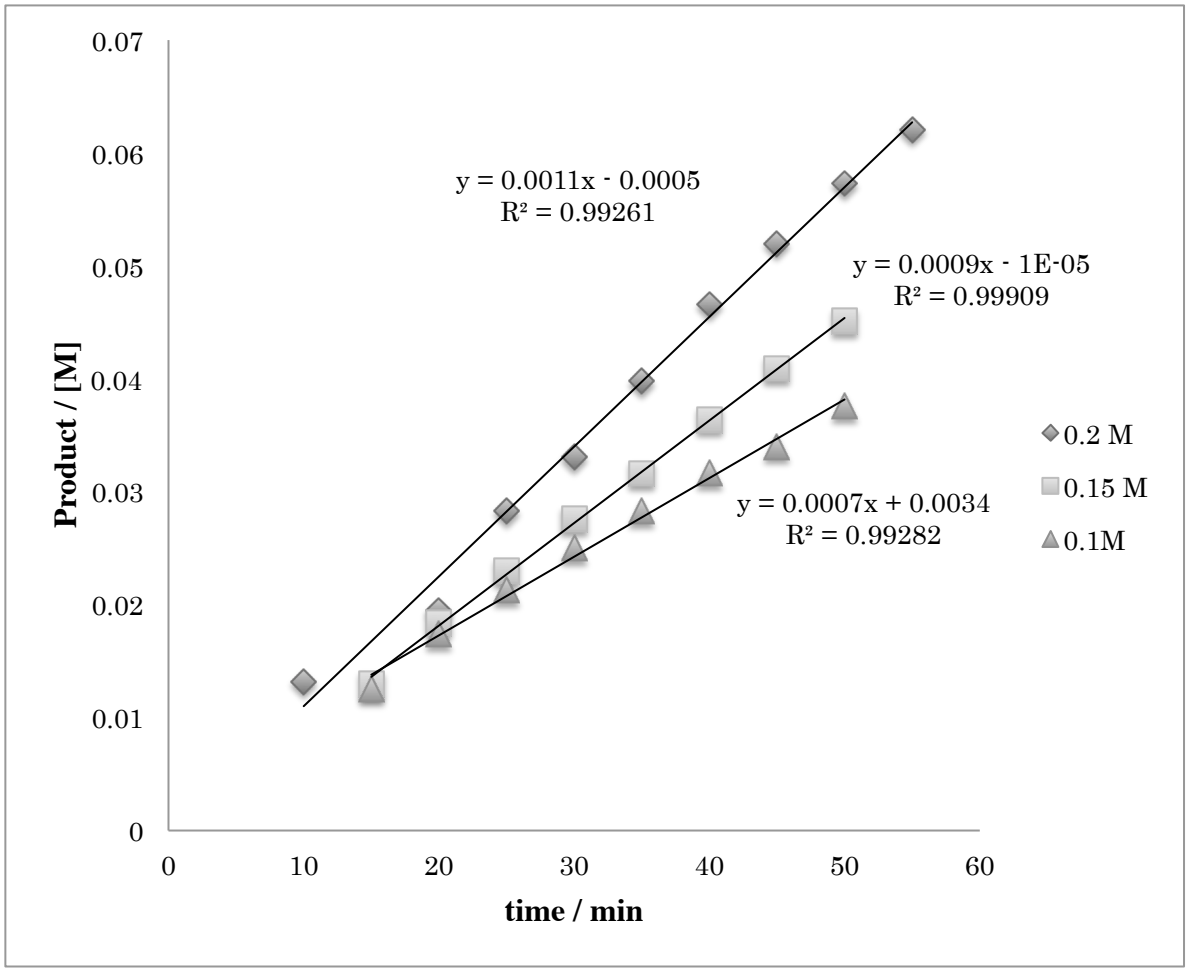
Conditions: $Pd(dba)_2$, 5 mol%, CH_3CN (1 mL); –20 ºC, 36 h

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 ^1H NMR spectroscopy in CD_3CN. 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 concetration 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~~t~~ on concerntration of the palladium catalyst was obserbed (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**

Entry	[**1k**]$_0$ [M]	d[**3s**]/dt [M/min]
1	0.1	0.00813
2	0.15	0.00906
3	0.2	0.00114

Figure 2. (a) Initial rate kinetic experiments for **1k** (b) Plot of (d[**1k**]/dt) versus **1k** (M).



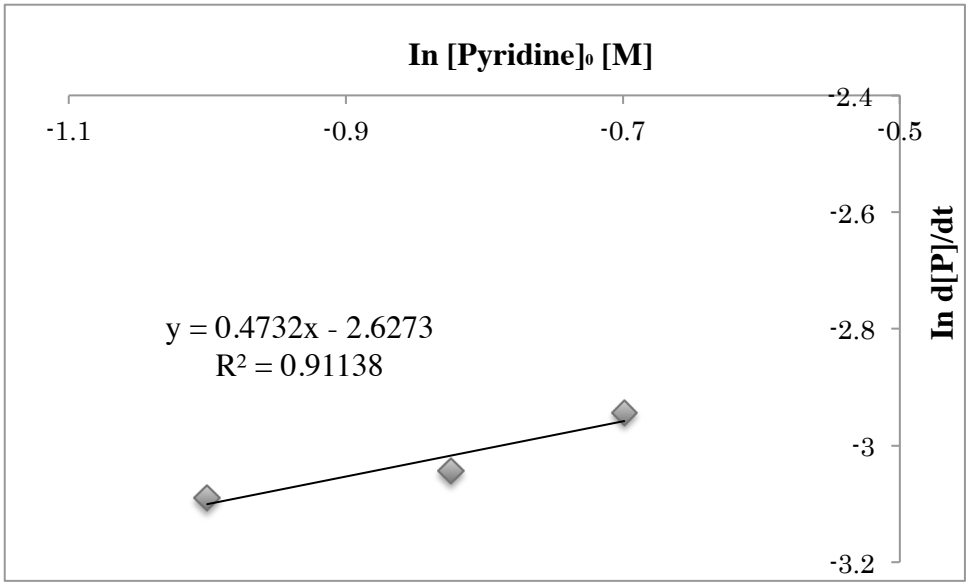


Table 5. Initial rates of varying concentrations of **2a**

Entry	**[2a]$_0$** [M]	d[**3s**]/dt [M/min]
1	0.1	0.00108
2	0.2	0.00110
3	0.3	0.00112

Figure 3. (a) Initial rate kinetic experiments for **1k** (b) Plot of In (d[**3s**]/dt) versus In **1k** [M].

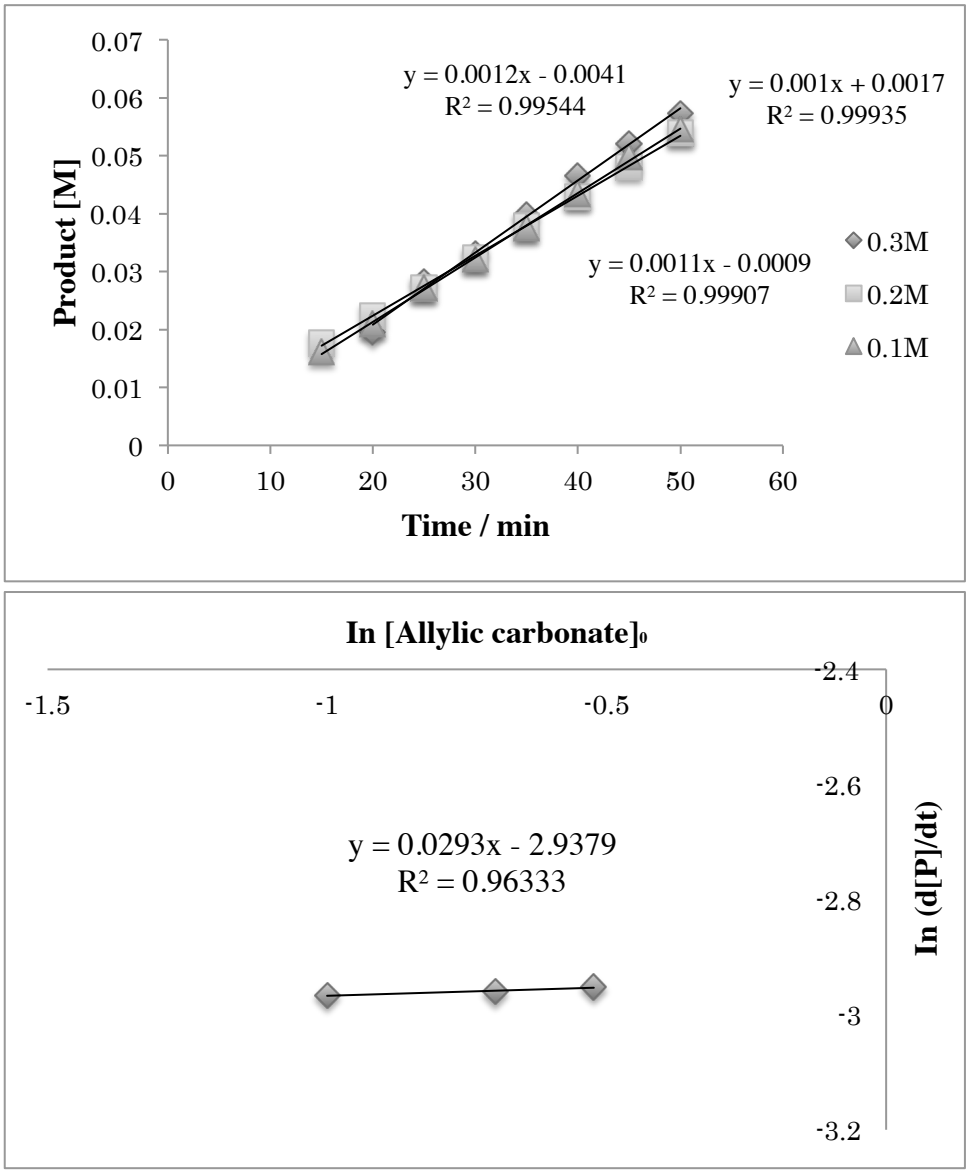
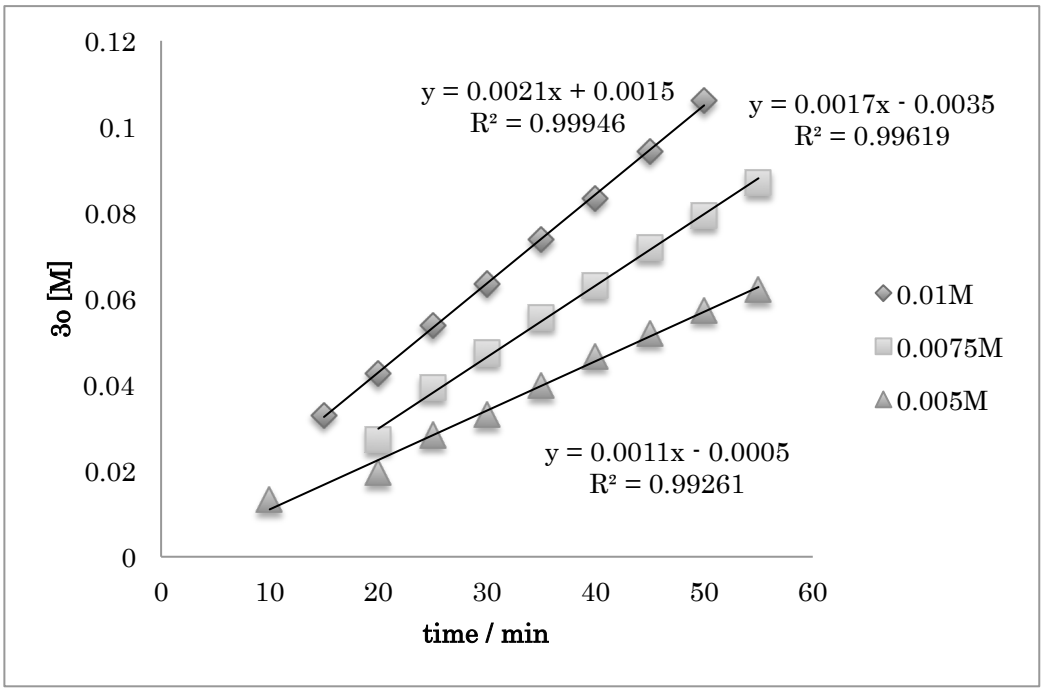


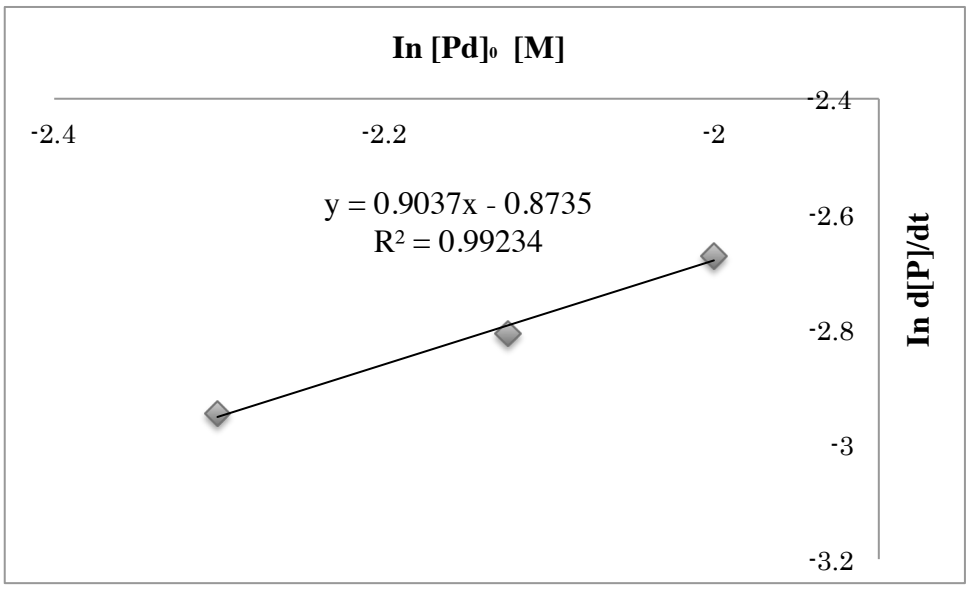
Table 6. Initial rates of varying concentrations of **Pd**

Entry	**[Pd]$_0$** [M]	d[**3s**]/dt [M/min]
1	0.005	0.00113
2	0.0075	0.00156

3	0.01	0.00212

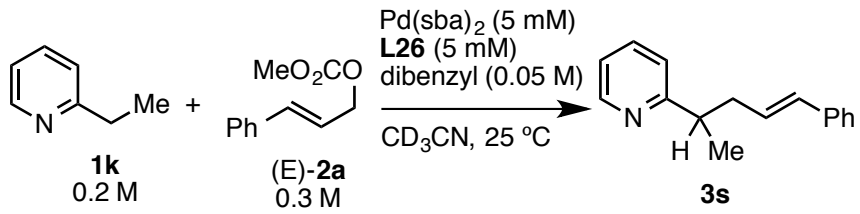
Figure 4. (a) Initial rate kinetic experiments for **Pd** (b) Plot of In (d[**3s**]/dt) versus In **Pd [**M].





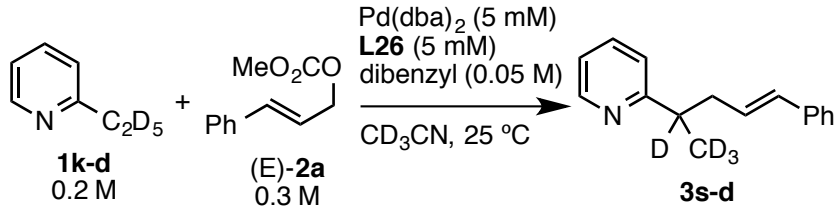
Kinetic isotope effect.[15] To determine whether the side chain C(α)-deprotonation of 2-alkylpyridines is involved in the turnover-limiting step of the catalytic cycle, the kinetic isotope effect was investigated. A large kinetic isotope effect value (k_H/k_D = 4.1) measured in the reactions of **1k** and **1k-d** (Tables 7 and 8; Figure 5) revealed that the C(α)-deprotonation was involed in the turnover-limiting step.

Table 7. Initial rate of **1k**



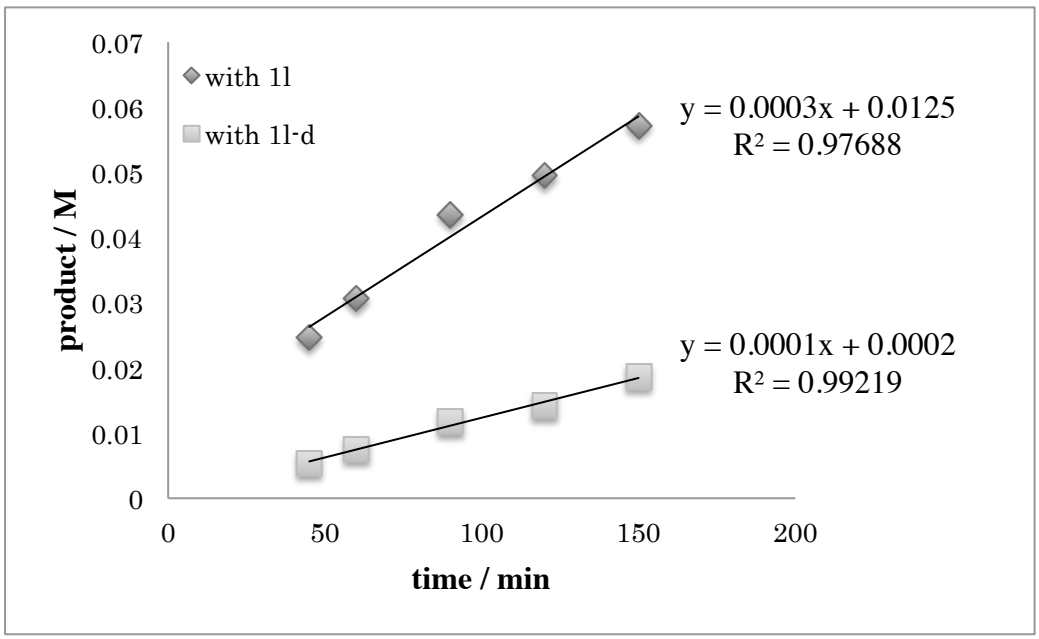
Entry	Time [min]	**3s** [M]	Rate [M/min]
1	45	0.0246	0.000547
2	60	0.0306	0.00051
3	90	0.0435	0.000483
4	120	0.0495	0.000413
5	150	0.0571	0.000381

Table 8. Initial rate of **1k-d**



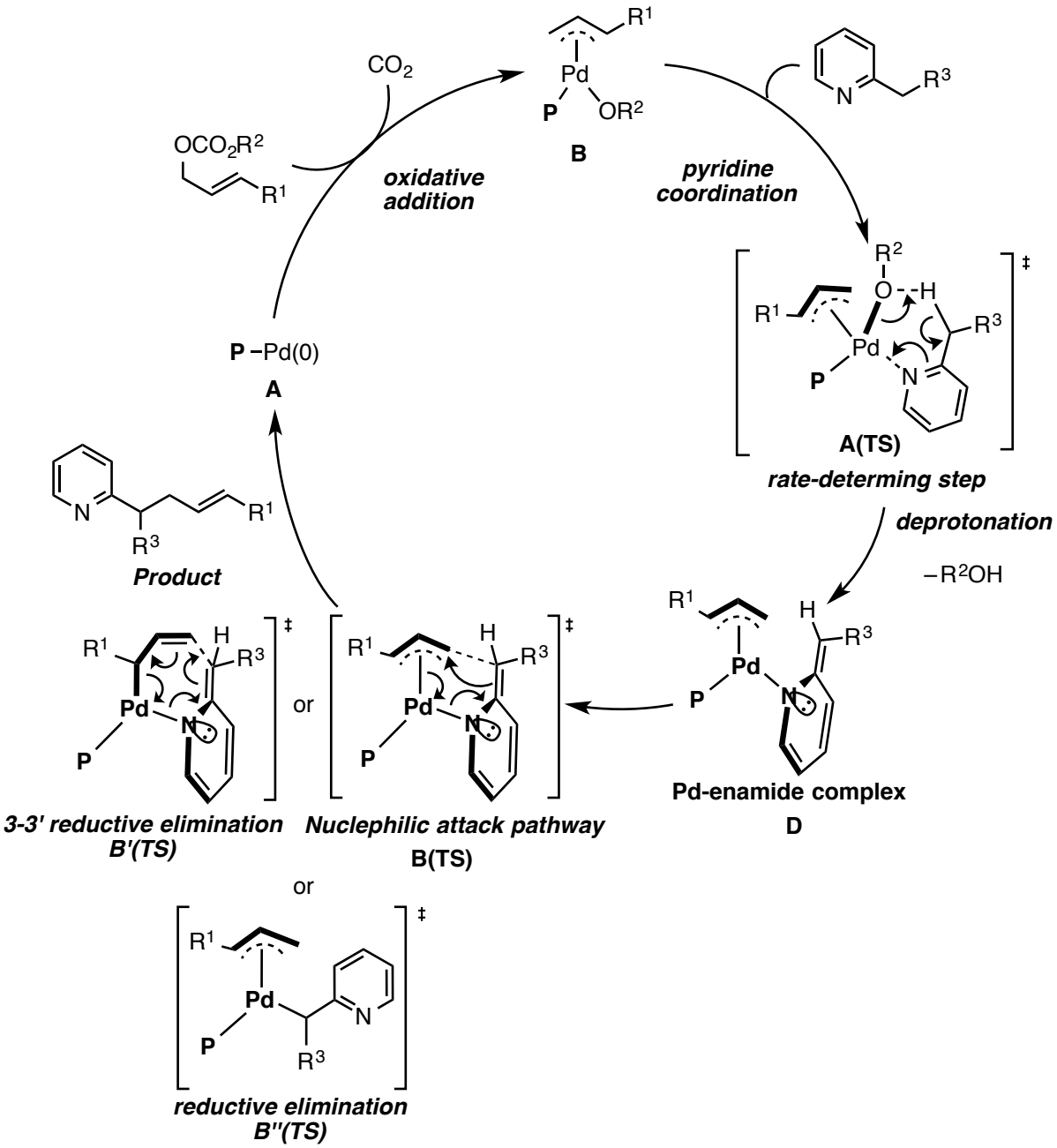
Entry	Time [min]	**3s-d** [M]	Rate [M/min]
1	45	0.00543	0.000121
2	60	0.0075	0.000125
3	90	0.0118	0.000131
4	120	0.0142	0.000118
5	150	0.0186	0.000124

Figure 5. Kinetic isotope effects. Conditions: reaction between **1k** or **1k-d** (0.2 M) and **2a** (0.3 M). Conditions: $Pd(dba)_2$, 5.0 mM, **L26,** 5.0mM, dibenzyl, 0.05 M, CH_3CN (1 mL); 25 ºC.



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 CO_2. 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-determing 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 spiecies 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 rearrangent proposed by Stolts and Morken[16], through a transition state **B'(TS)**. The third is allyl-benzyl reductive elimination. Finaly, 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 diamidophophite **L17** was effective for the enanitoselective allylation. The comparative experiment of regioisomeric allylic carbonates showed that rapid σ-π-σ isomerization of the allyl-palladium species was involed in this catalytic process. The kinetic experiments found that rate-determing step was C–H deprotonation. From thses 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_4Si (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. $Pd(dba)_2$, **L4**, **L5**, **L7** from Aldrich Chemical Co. All solvents for catalytic reactions were degassed via three freeze–pump–thaw cycles before use. Chiral phosphine ligand **L6**[6], **L8**[17], **L9**[18], **L10**[19] and **L13**[8d] were found in the literture.

Experimental Procedures

Procedure for allylation of tetrahydroquinoline (1a) with cinnamyl methyl carbonate (2a) (Table 2, Entry 12). In grove box, **L26** (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 ºC. After 36 h of stirring at –20 ºC, 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

chromatogramphy 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), **L26** (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_3CN (1 mL) in a grove 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.

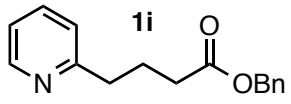
Kinetic Experiment : Kinetic Isotope Effect. To an NMR sample tube were added a $Pd(dba)_2$ (2.6 mg, 0.005 mmol, 0.005 M), **L26** (4.1 mg, 0.005 mmol, 0.005 M), dibenzyl (9.1 mg, 0.05 mmol, 0.05M) , 2-ethylpyridine **1k** (21.7 mg, 0.2 mmol, 0.2 M) and CD_3CN (1 mL) in a grove box. The mixture was stirred 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.

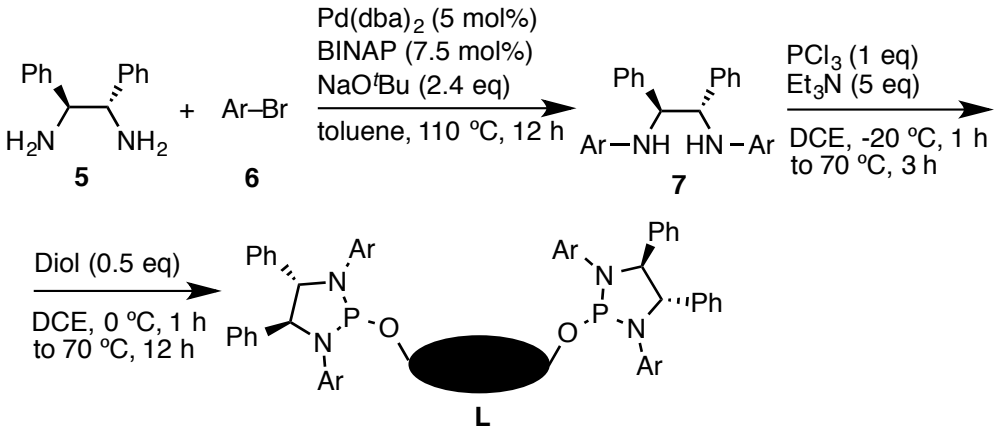
benzyl 4-(pyridin-2-yl)butanoate (1i)

The title compound (**1i**) was synthesized via the reaction of 2-bromopyridine and benzyl 4-bromobutanoate with Ni-dtbpy catalyst system (63%)[32].

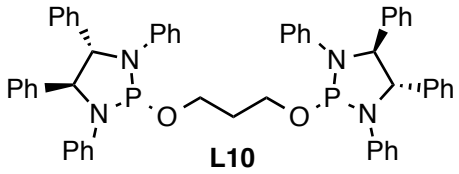


Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 2.10 (quint, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 5.11 (s, 2H), 7.09–7.13 (m, 2H), 7.30–7.38 (m, 5H), 7.58 (td, *J* = 8.0, 2.0 Hz, 1H), 8.52 (d, *J* = 5.2 Hz, 1H). **^{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

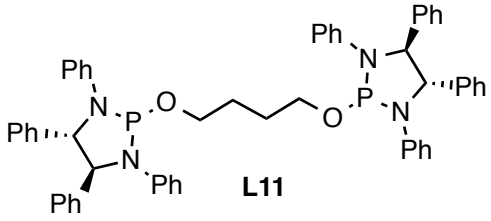


Compound **7**[33]. To solution of $Pd(dba)_2$ (402 mg, 0.7 mmol), rac-BINAP (436 mg, 0.7 mmol) and NaO^tBu (1.75 g, 18.2 mmol) in toluene (20 mL) was added (S,S)-1,2-diphenylenediamine **5** (1.49 g, 7.0 mmol) and Bromobenzene (2.52 g, 16.1 mmol). After being stirred at 110 ºC for 12 h, the reaction 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.



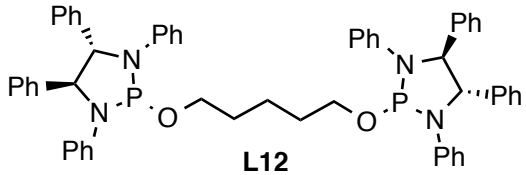
Ligand L10. Distilled phosphorus trichloride (96 mg, 1.0 mmol) was added to dichloroethane (5 mL) under argon at 0 ºC. Triethylamine (710 mg, 5.0 mmol) was added dropwise. **7a** (356 mg, 1.0 mmol) was added at -20 ºC. The reaction was warmed to room temperature over 30 min, then heated to 70 ºC for 3 h. The solution was cooled to 0 ºC 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 ºC 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 128.68. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{55}H_{50}O_2N_4NaP_2$, 883.33012; found, 883.33285. **$[\alpha]_{25}^{D}$** = –71.65 (c 1.0 $CHCl_3$).



L11

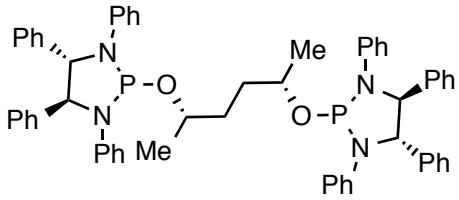
Ligand L11. White Solid. (46% yield). **^{1}H NMR** ($CDCl_3$) δ 1.26-1.46 (m, 4H), 3.72–3.78 (m, 4H), 4.91 (d, *J* = 5.6 Hz, 2H), 5.10 (d, *J* = 7.6 Hz, 2H), 6.75–6.81 (m, 4H), 6.91–6.97 (m, 8H), 7.02–7.14 (m, 12H), 7.20–7.23 (m, 16H). **^{13}C NMR** ($CDCl_3$) δ 27.63, 27.67, 64.60, 64.75, 71.67, 71.75, 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** ($CDCl_3$) δ 127.47. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{56}H_{52}N_4O_2NaP_2$, 897.34577; found, 897.34814. **$[\alpha]_{25}^{D}$** = –124.84 (c 1.00 $CHCl_3$).



L12

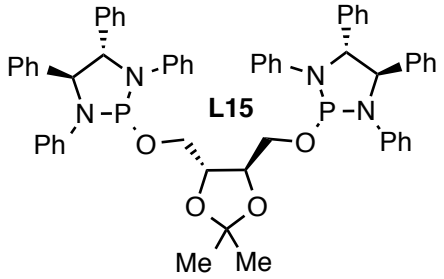
Ligand L12. White Solid. (54% yield). **^{1}H NMR** ($CDCl_3$) δ 1.26-1.35 (m, 6H), 3.72–3.86 (m, 4H), 4.91 (dd, *J* = 7.2, 2.4 Hz, 2H), 5.17 (d, *J* = 7.2 Hz, 2H), 6.74–6.82 (m, 4H), 6.92–6.98 (m, 8H), 7.04–7.15 (m, 12H), 7.19–7.27 (m, 16H). **^{13}C NMR** ($CDCl_3$) δ 21.88, 22.64, 31.00, 31.03, 31.57, 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}P NMR** ($CDCl_3$) δ 127.53. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{57}H_{54}N_4O_2NaP_2$, 911.36142; found, 911.36407. **$[\alpha]_{25}^{D}$** = –70.54 (c 1.1 $CHCl_3$).

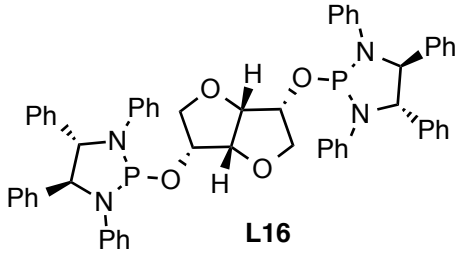


L14

Ligand L14. **^{1}H NMR** ($CDCl_3$) δ 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}C NMR** ($CDCl_3$) δ 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}P NMR** ($CDCl_3$) δ 128.33. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{58}H_{56}O_2N_4NaP_2$, 925.37707; found, 925.37787. **$[\alpha]_{24}^{D}$** = –80.00 (c 1.0 $CHCl_3$).

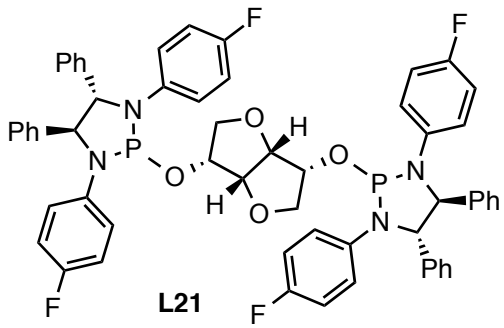


Ligand L15. White Solid. (38% yield). **^{1}H NMR** ($CDCl_3$) δ 1.29 (s, 6H), 3.64 (m, 2H), 3.79-3.80 (m, 4H), 4.94 (dd, *J* = 7.6, 2.4 Hz, 2H), 5.12 (d, *J* = 7.6 Hz, 2H), 6.51 (d, *J* = 7.6 Hz, 2H), 6.79 (dt, *J* = 14.8, 6.8 Hz, 4H), 6.97-7.14 (m, 20 H), 7.22-7.24 (m, 10H), 7.38-7.46 (m, 2H), 7.87-7.90 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ 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}P NMR** ($CDCl_3$) δ 129.00. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{59}H_{56}N_4O_4NaP_2$, 969.36690; found, 969.36856. **$[\alpha]_{25}^{D}$** = –107.87 (c 1.00 $CHCl_3$).



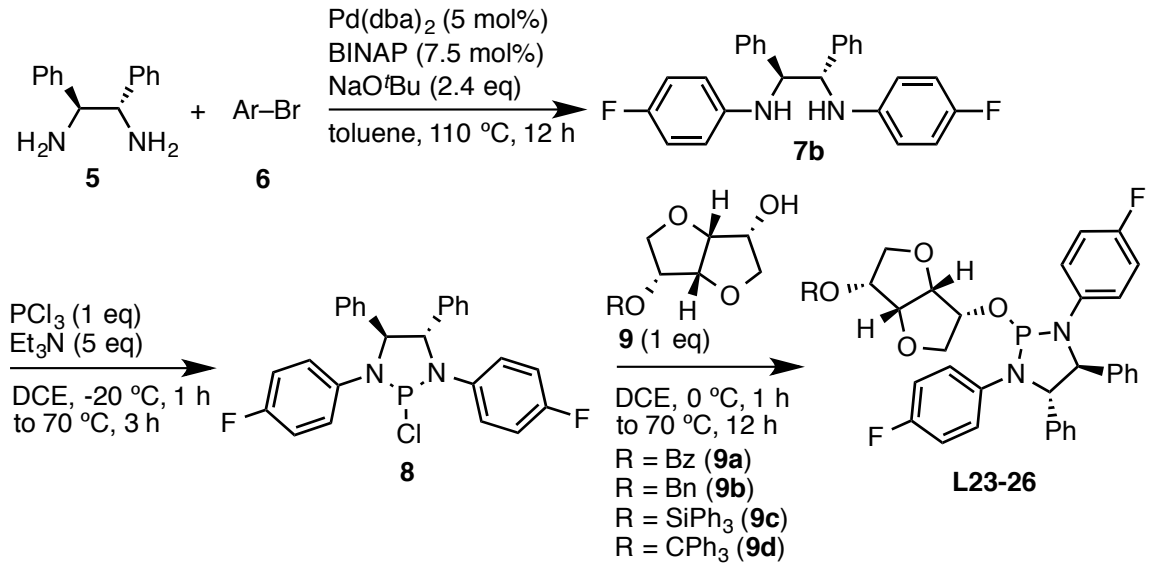
L16

Ligand L16. White Solid. (54% yield). **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 126.64. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{58}H_{52}N_4O_4NaP_2$, 953.33560; found, 953.33838. **$[\alpha]_{24}^{D}$** = –44.69 (c 1.1 $CHCl_3$).

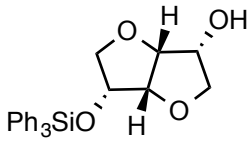


L21

Ligand L21. white solid (65% yield). **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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 (t, *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** ($CDCl_3$) δ –121.00, –123.27. **^{31}P NMR** ($CDCl_3$) δ 127.21. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{58}H_{48}N_4O_4F_4NaP_2$, 1025.29791; found,1025.29858. **$[\alpha]_{24}^{D}$** = –122.45 (c 1.0 $CHCl_3$).



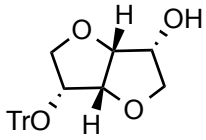
(3*R*,3a*R*,6*R*,6a*S*)-6-((triphenylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ol (9c)



9c

The title compound (**9c**) was synthesized via the triphenylsilyl protection of isomannide with $SiPh_3Cl$ and imidazole (56% yield). Colorless oil. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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). **$[\alpha]_{28}^{D}$** = +45.13 (c 2.4 $CHCl_3$).

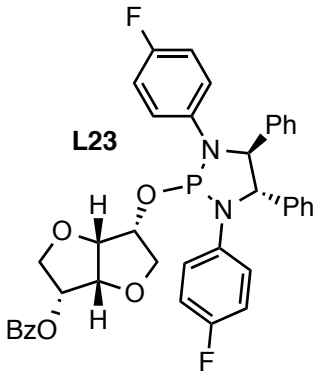
(3*R*,3a*R*,6*R*,6a*R*)-6-(trityloxy)hexahydrofuro[3,2-*b*]furan-3-ol (9d)



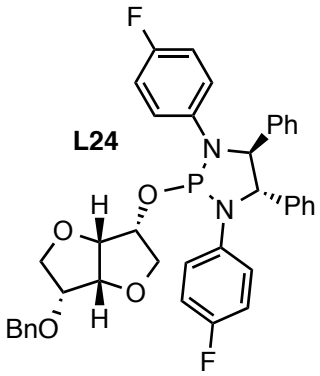
9d

To solution of $ZnCl_2$ (1.36 g, 10 mmol) and **4** (1.46 g, 10 mmol) in CH_3CN (mL) was added trityl chloride (2.78 g, 10 mmol) under argon at 0 ºC. The reaction was allowed to stir to room temperature over 2 h. Then, a solution of Et_3N in the CH_3CN (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 orgainc solvent was evaporated ubder reduced pressure and resulting suspension extracted with dichloromethane. The solvent was concentrated. The

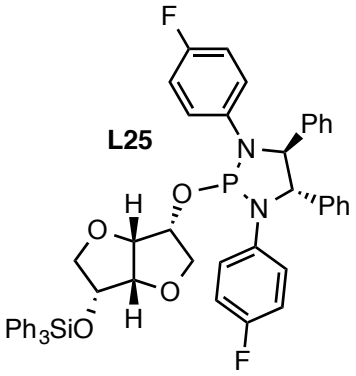
crude product was purified by column chromatography (silica gel, 30-50 EtOAc/hexane) to yield the product 9 (72%) as a white solid. **^{1}H NMR** ($CDCl_3$) δ 2.67 (d, *J* = 7.2 Hz, 1H), 3.00 (t, *J* = 7.6 Hz, 1H), 3.22 (t, *J* = 8.8 Hz, 1H), 3.67 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.94–3.98 (m, 2H), 4.06–4.11 (m, 1H), 4.17–4.24 (m, 2H), 7.22–7.26 (m, 3H), 7.29–7.33 (m, 6H), 7.53–7.54 (m, 6H). **^{13}C NMR** ($CDCl_3$) δ 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 $C_{25}H_{24}O_4Na$, 411.15668; found, 411.15677. **$[\alpha]_{24}^D$** = +107.35 (c 1.0 $CHCl_3$).



Ligand L23. white solid (54% yield). **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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** ($CDCl_3$) δ –120.91, –123.17. **^{31}P NMR** ($CDCl_3$) δ 126.78. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{39}H_{33}N_2O_5F_2NaP$,701.19874; found, 701.19958. **$[\alpha]_{25}^D$** = –4.05 (c 1.0 $CHCl_3$).

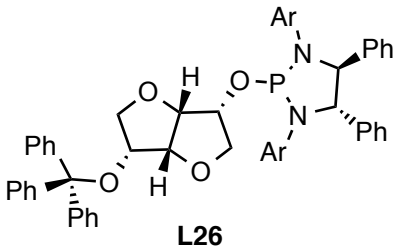


Ligand L24. white solid (75% yield). **^{1}H NMR** ($CDCl_3$) δ 3.59–3.64 (m, 2H), 3.73–3.84 (m, 2H), 3.95–3.98 (m, 3H), 4.43 (t, *J* = 1.6 Hz, 1H), 4.51–4.55 (m, 2H), 4.71–4.75 (m, 1H), 4.85–4.87 (m, 1H), 5.14–5.16 (m, 1H), 6.77–6.86 (m, 6H), 6.97 (m, 2H), 7.07–7.08 (m, 2H), 7.21–7.24 (m, 8H), 7.29–7.36 (m, 5H). **^{13}C NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ –121.07, –123.33. **^{31}P NMR** ($CDCl_3$) δ 127.66. **HRMS–ESI** (*m/z*): $[M+Na]^+$ Calcd for $C_{50}H_{43}N_2O_4F_2NaPSi$, 855.25900; found, 855.25970. **$[\alpha]_{25}^{D}$** = –27.38 (c 1.0 $CHCl_3$).



Ligand L25. white solid (59% yield). **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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), 127.76 (2C), 127.92 (6C), 128.50 (4C), 130.19 (3C),

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 $C_{50}H_{43}N_2O_4F_2NaPSi$, 855.25900; found, 855.25970. **$[\alpha]_{23}^{D}$** = –10.08 (c 1.0 $CHCl_3$).

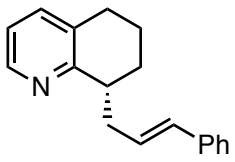


L26

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 $C_{51}H_{43}N_2O_4F_2NaP$, 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)

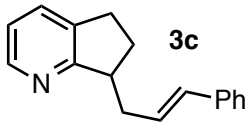


3a

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

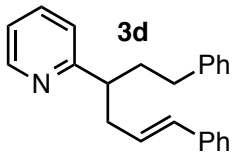
19.76, 27.17, 29.20, 38.72, 40.75, 120.94, 125.97, 126.84, 128.44, 129.47, 131.47, 132.44, 136.74, 137.75, 146.94, 159.61. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{21}N_2$, 229.16993; found, 229.16997. $[\alpha]_{24}^{D}$ = +102.11 (91% ee, c 1.0, $CHCl_3$). The ee value (91% ee) was determined 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-5*H*-cyclopenta[*b*]pyridine (3c)



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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, 137.63, 147.61, 166.80. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{17}H_{18}N$, 236.14338; found, 236.14336. $[\alpha]_{23}^{D}$ = +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.]

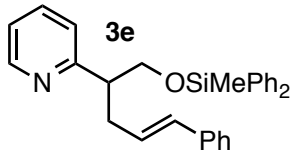
***(E)*-2-(1,6-diphenylhex-5-en-3-yl)pyridine (3d)**



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) 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). **^{13}C NMR** ($CDCl_3$) 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. $[\alpha]_{22}^{D}$ = –46.2 (78% ee, c 1.0,

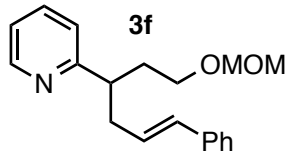
$CHCl_3$). The ee value (78% ee) was determined by chiral HPLC analysis. [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 43.67 min and 48.83 min for isomer.]

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



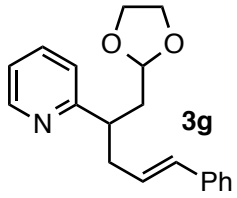
Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 0.51 (s, 3H), 2.63–2.76 (m, 2H), 3.15 (quint, *J* = 6.4 Hz, 1H), 3.96–4.04 (m, 2H), 6.07 (dt, *J* = 14.4, 6.8 Hz, 1H), 6.32 (d, *J* = 15.6 Hz, 1H), 7.10–7.13 (m, 1H), 7.15–7.18 (m, 2H), 7.21–7.26 (m, 4H), 7.29–7.40 (m, 6H), 7.45–7.50 (m, 4H), 7.56 (td, *J* = 8.0, 2.0 Hz, 1H), 8.55 (dd, *J* = 4.8, 0.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ –3.37, 34.62, 50.28, 66.48, 121.53, 123.88, 125.95 (2C), 126.86, 127.76 (2C), 128.36 (2C), 129.73, 131.40, 134.26 (2C), 135.91, 136.00, 137.59, 149.30 (2C), 161.98. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{29}H_{30}NOSi$, 436.20912; found, 436.20917. **$[\alpha]_{23}^{D}$** = –23.21 (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 = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 24.99 min and 29.30 min for isomer.]

(*E*)-2-(1-(methoxymethoxy)-6-phenylhex-5-en-3-yl)pyridine (3f)



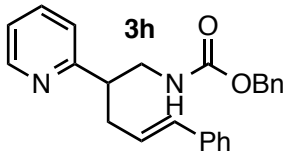
Isolated by silica gel chromatography (hexane/EtOAc 90:10). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 2.03–2.17 (m, 2H), 2.55–2.69 (m, 2H), 3.07–3.13 (m, 1H), 3.30 (S, 2H), 3.32–3.37 (m, 2H), 3.42–3.48 (m, 1H), 6.08 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 7.09–7.19 (m, 3H), 7.24–7.26 (m, 4H), 7.58 (td, *J* = 7.6, 2.0 Hz, 1H), 8.58 (dd, *J* = 4.0, 3.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ 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. **$[\alpha]_{25}^{D}$** = –43.49 (76% ee, c 1.2, $CHCl_3$). 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 ºC, 220 nm UV detector, retension 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)



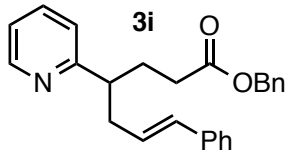
Isolated by silica gel chromatography (hexane/EtOAc 70:30). White solid. **^{1}H NMR** ($CDCl_3$) δ 2.02 (ddd, *J* = 13.8, 6.6, 4.8 Hz, 1H), 2.27–2.34 (m, 1H), 2.56–2.71 (m, 2H), 3.12–3.20 (m, 1H), 3.71–3.81 (m, 2H), 3.89–3.94 (m, 2H), 4.67 (dd, *J* = 7.2, 4.0 Hz, 1H), 6.06 (dt, *J* = 15.6, 8.0 Hz, 1H), 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, 137.58, 149.46, 163.43. **HRMS–EI** (*m/z*): [M] Calcd for $C_{19}H_{21}NO_2$, 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, retension 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)



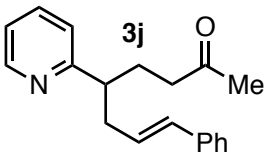
Isolated by silica gel chromatography (hexane/EtOAc 50:50). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 2.55–2.65 (m, 2H), 3.15 (quint, *J* = 6.0 Hz, 1H), 3.57–3.68 (m, 2H), 5.06 (s, 2H), 5.34 (br, 1H), 6.08 (dt, *J* = 15.2, 7.6 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 7.10–7.20 (m, 2H), 7.25–7.26 (m, 4H), 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 $C_{24}H_{25}N_2O_2$, 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, retension time = 28.61 min and 32.47 min for isomer.]

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



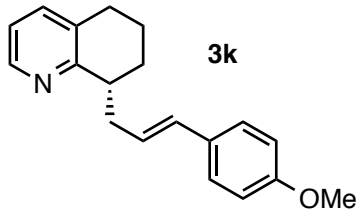
Isolated by silica gel chromatography (hexane/EtOAc 70:30). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 2.10–2.18 (m, 2H), 2.22–2.25 (m, 2H), 2.52–2.59 (m, 1H), 2.62–2.70 (m, 1H), 2.91 (quint, *J* = 8.0 Hz, 1H), 5.06 (s, 2H), 6.05 (dt, *J* = 14.8, 7.2 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 7.04 (d, *J* = 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** ($CDCl_3$) δ 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 $C_{25}H_{26}NO_2$, 372.19581; found, 372.19647. **$[\alpha]_{29}^{D}$** = –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)



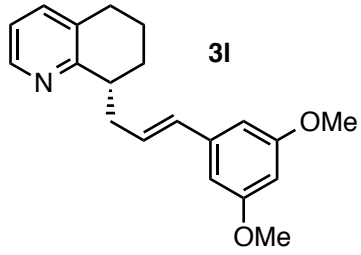
Isolated by silica gel chromatography (hexane/EtOAc 80:20). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.98–2.13 (m, 2H), 2.05 (s, 3H), 2.23–2.37 (m, 2H), 2.56 (quint, *J* = 6.8 Hz, 1H), 2.66 (quint, *J* = 6.8 Hz, 1H), 2.86–2.93 (m, 1H), 6.07 (dt, *J* = 14.4, 7.6 Hz, 1H), 6.33 (d, *J* = 15.2 Hz, 1H), 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** ($CDCl_3$) δ 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. **$[\alpha]_{23}^{D}$** = –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)



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 $C_{19}H_{21}NO$, 279.16231; found, 279.16127. **$[\alpha]_{24}^{D}$** = +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 ºC, 220 nm UV detector, retension time = 13.76 min and 16.93 min for isomer.]

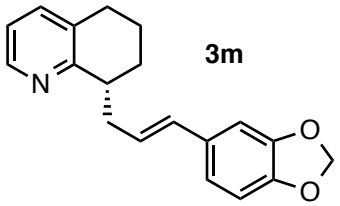
(*E*)-8-(3-(3,5-dimethoxyphenyl)allyl)-5,6,7,8-tetrahydroquinoline (3l)



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. **$[\alpha]_{25}^{D}$** = +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,

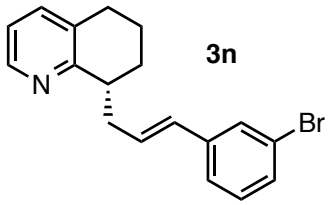
hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 19.86 min and 22.18 min for isomer.]

(*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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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–EI** (*m/z*): [M] Calcd for $C_{19}H_{19}NO_2$, 293.14105; 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® 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 = 15.40 min and 19.52 min for isomer.]

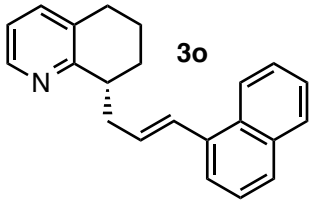
(*E*)-8-(3-(3-bromophenyl)allyl)-5,6,7,8-tetrahydroquinoline (3n)



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 19.81, 27.30, 29.16, 38.60, 40.64, 121.00, 122.64, 124.64, 128.79, 129.65, 129.93, 130.09, 131.19, 132.42, 136.77, 139.89, 146.92, 159.32. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{18}H_{19}NBr$, 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® OD-3 column, 4.6 mm × 250 mm, Daicel

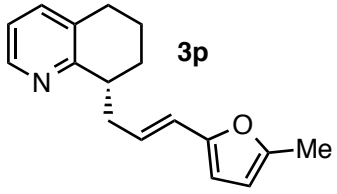
Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 11.77 min and 14.66 min for isomer.]

(*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** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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. **$[\alpha]_{24}^{D}$** = +93.34 (88% ee, c 1.0, $CHCl_3$). The ee value (88% 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 = 20.01 min and 24.83 min for isomer.]

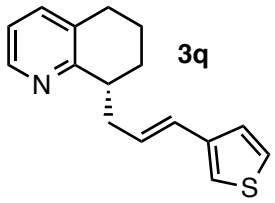
(*E*)-8-(3-(5-methylfuran-2-yl)allyl)-5,6,7,8-tetrahydroquinoline (3p)



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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** ($CDCl_3$) δ 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. **$[\alpha]_{25}^{D}$** = +26.07 (87% ee, c 0.30, $CHCl_3$). The ee value (87% ee) was determined by chiral HPLC analysis.

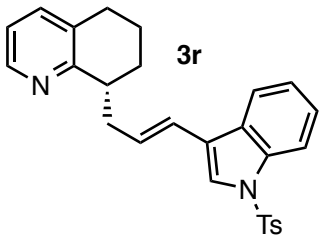
[CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 ºC, 220 nm UV detector, retension time = 17.71 min and 22.48 min for isomer.]

(*E*)-8-(3-(thiophen-3-yl)allyl)-5,6,7,8-tetrahydroquinoline (3q)



Isolated by silica gel chromatography (hexane/EtOAc 95:5). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 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). **^{13}C NMR** ($CDCl_3$) δ 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. **HRMS–EI** (*m/z*): [M] Calcd for $C_{16}H_{17}NS$, 255.10817; found, 255.10762. **$[\alpha]_{20}^{D}$** = +191.94 (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 = 16.49 min and 22.24 min for isomer.]

(*E*)-8-(3-(1-tosyl-1*H*-indol-3-yl)allyl)-5,6,7,8-tetrahydroquinoline (3r)



Isolated by silica gel chromatography (hexane/EtOAc 80:20). Colorless oil. **^{1}H NMR** ($CDCl_3$) δ 1.72-2.05 (m, 4H), 2.33 (s, 3H), 2.50-2.60 (m, 1H), 2.71-2.83 (m, 2H), 2.99-3.08 (m, 2H), 6.29-6.36 (m, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 7.05 (dd, *J* = 7.6, 5.2 Hz, 1H), 7.207.26 (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). **^{13}C NMR** ($CDCl_3$) δ 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. **HRMS–ESI** (*m/z*): $[M+H]^+$ Calcd for $C_{27}H_{27}N_2O_2S$,

443.17878; found, 443.17883. $[\alpha]_{25}^{D}$ = +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.]

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Publication List

1. Publications related to this thesis

1) Stereoselective C–H Borylations of Cyclopropanes and Cyclobutanes with Silica-Supported Monophosphane-Ir Catalysts.
Murakami, R.; Tsunoda, K.; Iwai, T,; Sawamura, M. *Chem. Eur. J*. **2014**, *20*, 13127-13131. (Chapter 1)

2) Site-selective and Stereoselective C(sp3)–H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Ir Catalyst.
Murakami, R.; Iwai, T,; Sawamura, M. *Synlett.* **2016**, *27*, 1187-1192. (Chapter 2)

2. Other publications (not related to this thesis)

1) Synthesis of Primary and Secondary Alkylboronates through Site-Selective C(sp3)–H Activation with Silica-Supported Monophosphine-Ir Catalysts. Kawamorita,S.; Murakami, R.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2013,** *135*, 2947-2950.

2) Silica-Supported Tripod Triarylphosphane: Application to Transition Metal Catalyzed C(sp3)–H Borylations. Iwai, T.; Murakami, R.; Harada, T.; Kawamorita, S.; Sawamura, M. *Adv. Synth. Catal*. **2014**, *356*, 1563-1570.

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