C(sp^3)-H Alkylation Assisted by Non-Covalent Interaction Between Substrates and Decatungstate Catalyst

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$C(sp^3)$−H Alkylation Assisted by Non-Covalent Interaction Between Substrates and Decatungstate Catalyst

JIANG HUI

Kuninobu Laboratory

Department of Interdisciplinary Engineering Sciences

Interdisciplinary Graduate School of Engineering Sciences

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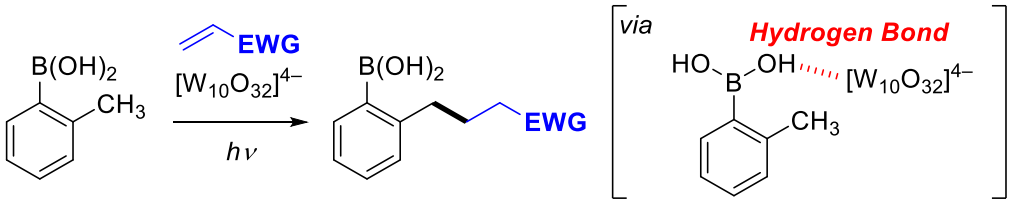
Contents

Abstract

In this thesis, decatungstate-catalyzed alkylation of benzylic carbon–hydrogen (C–H) bond assisted by non-covalent interaction is described.

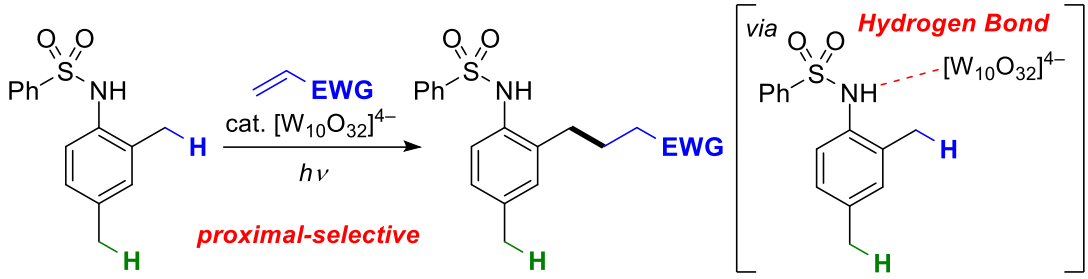
In **Chapter 1**, a general introduction to C–H transformations is provided. In C–H transformations, controlling the site-selectivity is highly important. The known strategies for controlling the site-selectivity in C–H transformations are based on the steric or electronic properties of the catalysts or substrates, directing groups of substrates, and non-covalent interactions between substrates and reagents or substrates and ligands (catalysts). Although significant progress has been made in achieving site-selective C–H transformations, challenges remain particularly for site-selective C(sp^3)–H transformations compared to C(sp^2)–H transformations. Our group is dedicated to developing "*non-covalent method"* for site-selective C(sp^3)–H transformations. During the research program in our group, the following chapters present my researches on non-covalent interaction-assisted C(sp^3)–H alkylation reactions.

Chapter 2: Boronic acid derivatives are indispensable molecules in synthetic organic chemistry because, despite the high stability of their carbon–boron bonds, they can be readily transformed into carbon–carbon and carbon–heteroatom bonds. Herein, I achieved the benzylic C(sp^3)–H alkylation of phenylboronic acids assisted by hydrogen bond between the boronyl group and decatungstate. This work offers a novel approach for the synthesis of aryl boronic acids.



Chapter 3: In the study of Chapter 2, while the C(sp^3)–H alkylation of 2-methylphenylboronic acids was successfully achieved, the site-selective reaction was not feasible. It was probably because the relatively weak hydrogen bond between the boronyl group of substrates and decatungstate. If anilide derivatives were used as a substrate, the stronger hydrogen bond between substrates and decatungstate was expected. Based on this strategy, I

have developed the proximal-selective C(sp³)–H alkylation of *N*-(*o*-tolyl)benzenesulfonanilide derivatives. Moreover, the reaction was applicable to *N*-(3,4-dicyano-2-phenylbutyl)benzenesulfonamide.



Chapter 4: (unpublished content)

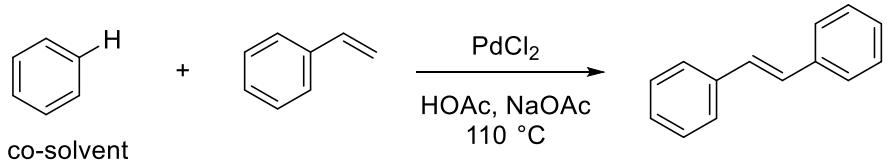
I explored the role of non-covalent interactions between substrates and catalysts. First, I achieved boronyl group-assisted decatungstate-catalyzed benzylic C(sp³)−H alkylation. Second, I developed a site-selective C(sp³)−H alkylation of sulfonanilides. Third, (unpublished content for Chapter 4). These studies provide new insights and methodologies for advancing C(sp³)–H transformations.

Chapter 1. General Introduction

1.1 General Introduction for C–H Transformations

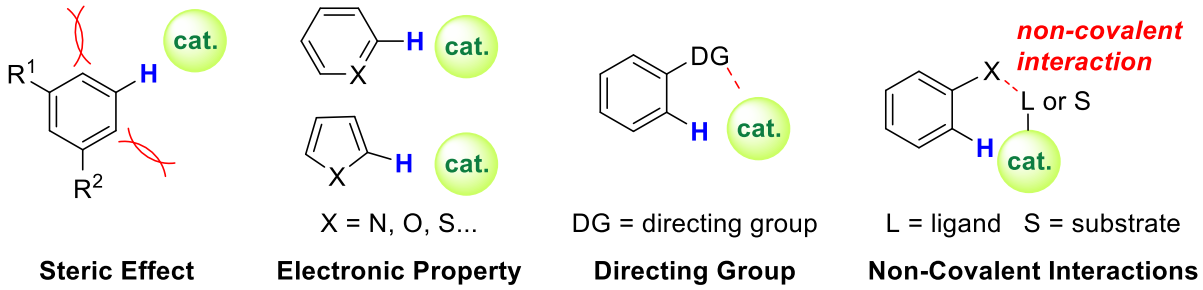
Carbon–hydrogen (C–H) bond is one of the most ubiquitous bonds in organic compounds, and C–H transformations can directly modify C–H bonds within organic molecules. Traditionally, C–H transformations have posed significant challenges due to the high bond dissociation energy of C–H bonds and their low reactivity compared to other chemical bonds. Over the past few decades, C–H activation has emerged as a cornerstone of modern organic synthesis. Although conventional organic reactions typically require pre-functionalized precursors, C–H bond activation bypasses the need for prior functional group introduction, resulting in more streamlined and efficient synthetic pathways. Given the high bond energy of C–H bonds (e.g., up to 414 kJ/mol in methane), these bonds exhibit considerable inertness in many chemical reactions, making C–H transformations so-called "holy grail" in organic chemistry.[1,2]

As early as 1967, Fujiwara and Moritani first reported a palladium-catalyzed C–H transformation for synthesizing stilbene from benzene and styrene (**Scheme 1-1**).[3] However, this reaction had significant drawbacks: 1) benzene was used in solvent quantities; and 2) when employing monosubstituted benzene, poor site-selectivity led to a mixture of products. Furthermore, for a long period, C–H activation was restricted to the transformations of C(sp^2)–H bonds of unsaturated hydrocarbons, as the high bond dissociation energy of C(sp^3)–H bonds hindered the development of C(sp^3)–H transformations for saturated hydrocarbons. It was not until 1982 that Bergman and Graham observed the activation of C–H bonds in saturated alkanes during reactions involving metal complexes and alkane molecules.[4] This discovery sparked a surge of interest among organometallic chemists in researching C–H activation.



Scheme 1-1

In earlier studies, non-directed catalyzed C–H transformations were extensively explored; however, these reactions often exhibited poor site-selectivity and low yields. For chemical reactions to have practical value, they must exhibit selectivity, including site-selectivity, chemoselectivity, and stereoselectivity. To achieve selective C–H transformations, the known strategies for controlling site-selectivity in C–H transformations include the steric or electronic properties of the catalyst or substrate, directing groups of substrates, and non-covalent interactions between the substrates or substrate and ligand (**Scheme 1-2**).



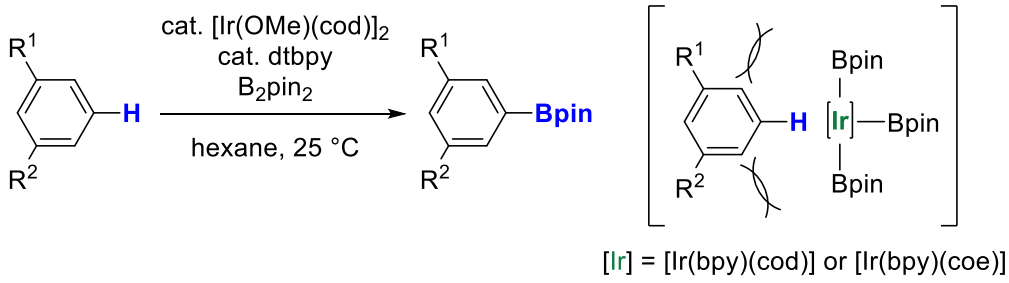
Scheme 1-2. Main methods for achieving site-selective C–H transformations

1.2 Selective C(sp^2)–H Transformation

1.2.1 Steric-Controlled Site-selective C(sp^2)–H Transformations

One of the simplest methods to achieve site-selective C(sp^2)–H transformations is to leverage the steric properties of the substrates. In this approach, the presence of large substituents or multiple substituents leads to steric repulsion between the substituents and the catalytically active species, thereby inhibiting the oxidative addition of C(sp^2)–H bonds near the substituents with the metal catalyst. Consequently, C(sp^2)–H transformations are selectively facilitated in sterically accessible positions.

For example, in iridium-catalyzed C(sp^2)–H borylation, the site-selectivity of the reaction is easily influenced by steric hindrance due to the bulky catalytic active species with three bulky pinacolboryl ligands. Consequently, in reactions of monosubstituted aromatic compounds, steric inhibition occurs at the *ortho*-position relative to the substituent, resulting in a mixture of products formed at the *meta*- and *para*-positions. In contrast, for 1,3-disubstituted aromatic compounds, the C–H borylation selectively occurs at sterically accessible positions (**Scheme 1-3**).[5]

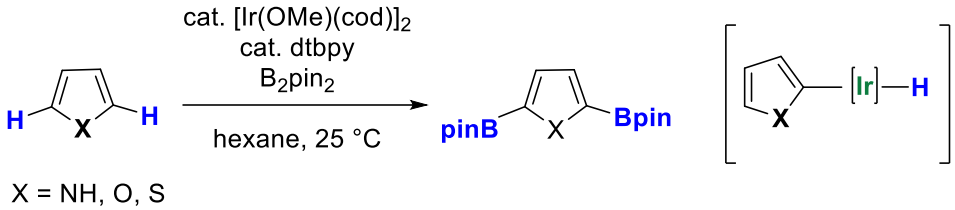


Scheme 1-3. Steric-controlled site-selective C–H borylation

1.2.2 Electronic-Controlled Site-selective C(sp^2)–H Transformations

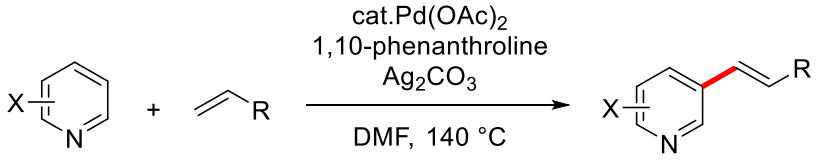
Since many substrates lack the potential to achieve site-selectivity by the steric hindrance, site-selectivity can be controlled by leveraging the electronic properties of the substrates. For instance, site-selective reactions proceed at the α-position of the five-membered heteroaromatic

compounds containing N, O or S atom. For example, the C(sp^2)–H borylation proceeds at the α-position of heteroatom-containing five-membered aromatic compounds (**Scheme 1-4**).[6]



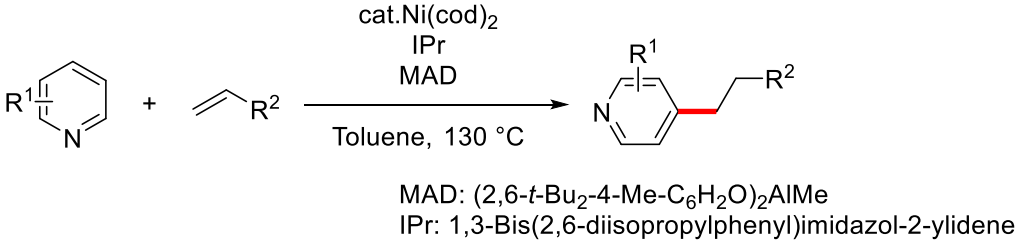
Scheme 1-4. Electronic-controlled *α*-position-selective C(sp^2)–H borylation

Based on the electronic properties of the substrates, the Yu group achieved C3-selective C(sp^2)–H alkenylation of pyridines by introducing an appropriate ligand (1,10-phenanthroline) (**Scheme 1-5**).[7]



Scheme 1-5. Electronic-controlled C3-selective C(sp^2)–H alkenylation

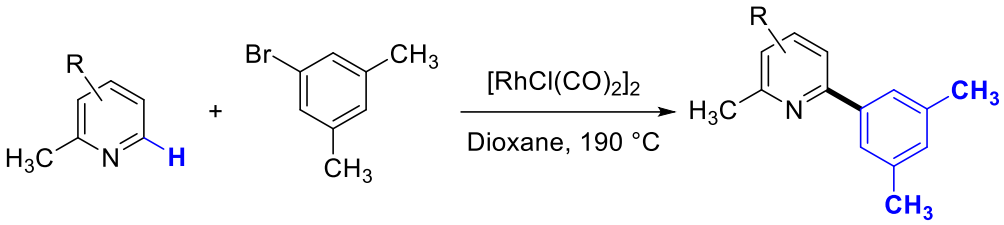
In addition, the Yu group achieved direct C4-selective alkylation of pyridines under Ni/Lewis acid cooperative catalysis with an *N*-heterocyclic carbene ligand (**Scheme 1-6**).[8]



Scheme 1-6. Electronic-controlled C4-selective C(sp^2)–H alkylation

1.2.3 Combined Steric- and Electronic-Controlled Site-selective C(sp^2)–H Transformations

Although site-selective C(sp^2)–H transformations can be achieved by the electronic effects of the substrates, the presence of two or more reaction sites affected by the same electronic influence may lead to the formation of a mixture of mono- and multi-functionalized products. For instance, it is sometimes difficult to produce only mono-borylated product as shown in **Scheme 1-4**. To obtain the selective products, both the steric and electronic properties have been used. For example, the Ellman group utilized the inherent electronic characteristics and steric factors of substrates, employing rhodium complex as a catalyst to achieve the direct C(sp^2)–H arylation of pyridine and quinoline derivatives (**Scheme 1-7**).[9]

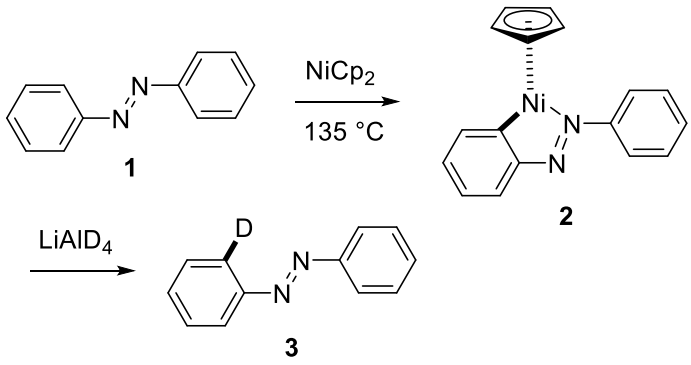


Scheme 1-7. Steric- and electronic-controlled site-selective C(sp^2)–H arylation

1.2.4 Directing Group-Controlled Site-selective C(sp^2)–H Transformations

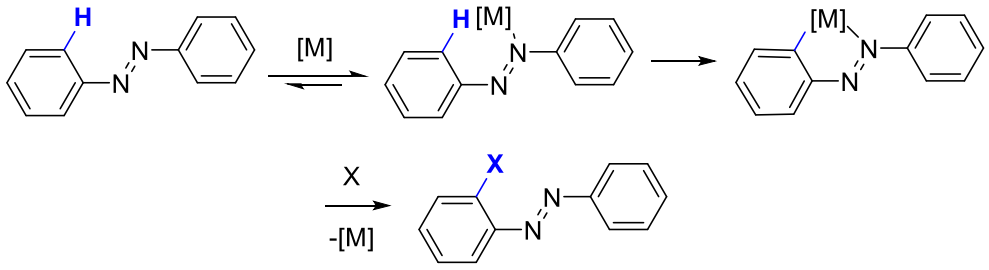
As early as 1955, Murahashi showed the potential of an amine as a directing groups in the reaction of synthesizing phthalimide using Schiff base and carbon monoxide by dicobalt octacarbonyl catalyst.[10] In 1963, Kleiman and Dudeck's group reported the instance of a nickel-mediated *ortho*-C(sp^2)–H deuteration (**Scheme 1-8**).[11] In this reaction, the azo group in azobenzene (**1**) serves as a directing group, coordinating to the nickel center and selectively activating the *ortho*-C(sp^2)–H bond, forming the corresponding nickel complex **2**. Upon treatment of complex **2** with $LiAlD_4$, the *ortho*-deuterated product **3** was exclusively obtained. This reaction demonstrated that it is possible to achieve site-selective C(sp^2)–H bond activation through the formation of a metalacyclic intermediate by introducing coordination functional

groups into substrates. This work laid the foundation for the development of directing group-controlled site-selective C(sp^2)–H transformations.



Scheme 1-8. Azo group-assisted *ortho*-C(sp^2)–H deuteration of azobenzene

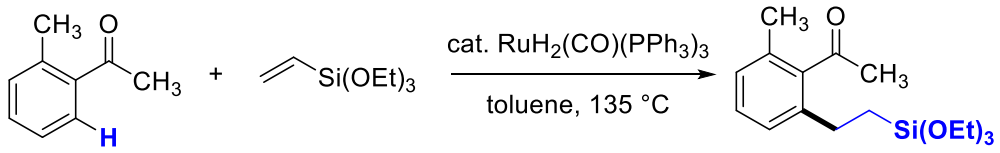
Directing groups can be categorized into weakly and strongly coordinating groups. In classically directing group-assisted C(sp^2)–H transformation reactions, the directing groups are typically strong coordinating groups containing elements such as N, S, or P. Examples include pyridines, oxazolines, sulfides, and phosphates, as these compounds are strong σ-donors and π-acceptors. Taking azobenzene mentioned in **Schemes 1-8** as an example, these substances generally coordinate with the metal to form a five- or six-membered metallacyclic transition state. The metallacyclic transition state then continues to react with the coupling reagent to yield the desired product (**Scheme 1-9**).



Scheme 1-9. Directing group-assisted *ortho*-C–H activation and sequential transformations

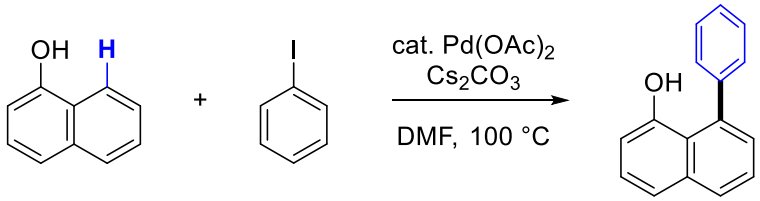
In 1993, Murai reported an efficient and highly *ortho*-selective C(sp^2)–H alkylation, in which aryl ketones and olefins were converted into the corresponding alkylated products under $RuH_2(CO)(PPh_3)_3$ catalysis.[12] In this reaction, the carbonyl group acts as a directing group,

forming a ruthenacyclic intermediate, thereby conferring excellent site-selectivity. Additionally, the reaction demonstrates good functional group compatibility, enabling the use of a variety of aryl ketones and olefins in this transformation (**Scheme 1-10**).



Scheme 1-10. Directing group-assisted ruthenium-catalyzed *ortho*-C–H alkylation of aromatic ketones

In 1997, the Miura group reported the first example of a palladium-catalyzed C(sp^2)–H transformation. They successfully achieved site-selective C(sp^2)–H arylation directed by the phenolic hydroxy group under basic conditions (**Scheme 1-11**).[13]



Scheme 1-11. Directing group-assisted palladium-catalyzed site-selective C–H alkylation of 1-naphthols

Based on the initial outstanding contributions by the Murai group, site-selective C(sp^2)–H transformations directed by various directing groups subsequently proliferated rapidly. In recent decades, researchers have developed directing group-controlled C(sp^2)–H transformations catalyzed by transition metal catalysts, such as Ru, Rh and Pd as well as more cost-effective metals like Fe, Co, Cu, and Ni, based on the aforementioned reaction mechanism (**Scheme 1-9**).[14]

1.2.5 Non-covalent Interaction-Controlled Site-selective C(sp^2)–H Transformations

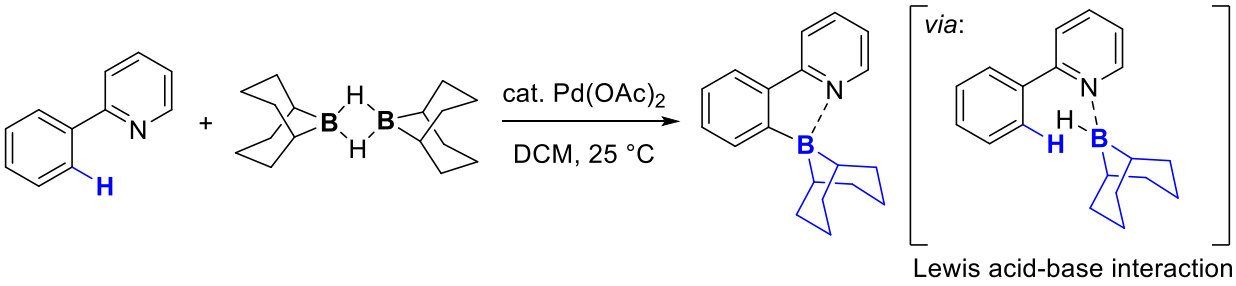
Non-covalent bonds do not rely on the sharing of electrons but rather on the attraction between opposite charges. Consequently, their strength is relatively weaker compared to

covalent bonds. In recent years, there has been a growing body of researches exploring site-selective C–H transformations using non-covalent interactions involving transition metal intermediates.[15-17] These studies aim to control the site-selectivity of reactions by leveraging non-covalent interactions between catalysts and substrates, as well as between substrates and reagents, including Lewis acid-base interactions, hydrogen bonding, and electrostatic interactions.

Lewis Acid-Base Interaction-Controlled *ortho*-selective C(sp^2)–H Transformations

The Lewis acid-base electronic theory defines that molecules, functional groups, and ions capable of accepting an electron pair is classified as an acid, while those capable of donating an electron pair are classified as bases. An electron pair acceptor (Lewis acid) and an electron pair donor (Lewis base) can form a coordination bond through their interaction.

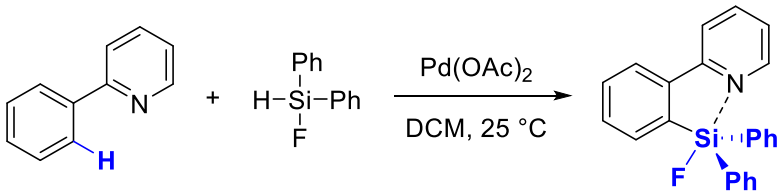
In 2013, Kuninobu achieved *ortho*-selective C(sp^2)–H borylation via Lewis acid-base interaction between the substrate and the borylation reagent. By selecting 9-borabicyclo[3.3.1]nonane (9-BBN), which has a higher Lewis acidity than pinacolborane (HBpin) and catecholborane (HBcat), as the borylation reagent, and using a catalytic amount of $Pd(OAc)_2$, the reaction with 2-phenylpyridine proceeded to give the *ortho*-C(sp^2)–H borylated product in high yield (**Scheme 1-12**).[18] They also accomplished a similar reaction using an Fe catalyst in 2017.[18]



Scheme 1-12. Lewis acid-base interaction-controlled *ortho*-selective C(sp^2)–H borylation

The reaction mechanism of *ortho*-selective C(sp^2)–H borylation controlled by Lewis acid-base interaction was subsequently applied to achieve *ortho*-selective C(sp^2)–H silylation. Electron-deficient silanes, which exhibit Lewis acidity, can form hypervalent pentacoordinate

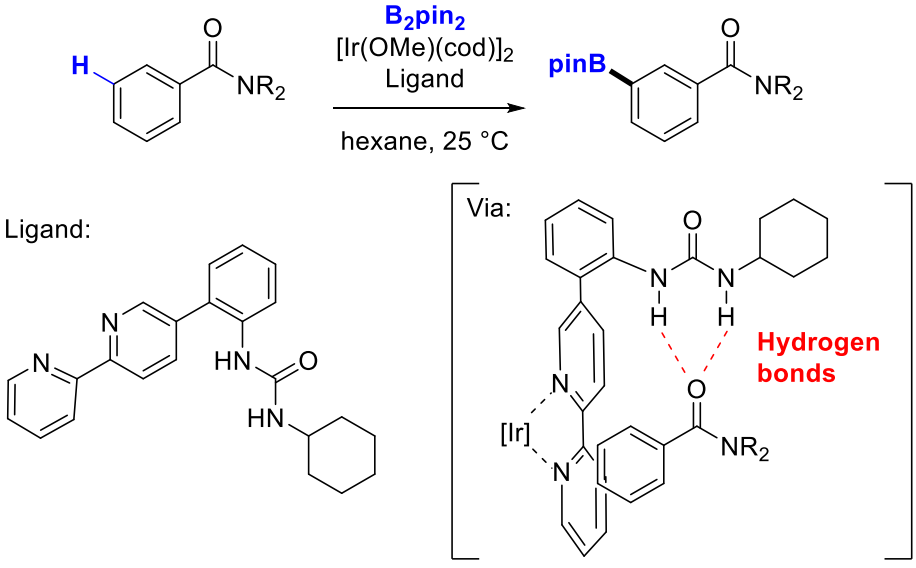
or hexacoordinate structures through Lewis acid-base interactions with Lewis bases. Treatment of 2-phenylpyridines with fluorohydrosilanes bearing Lewis acidity gave the corresponding *ortho*-C(sp²)–H silylated products in high yields (**Scheme 1-13**).[19, 20]



Scheme 1-13. Lewis acid-base interaction-controlled *ortho*-selective C(sp^2)–H silylation

Hydrogen Bond-Controlled Site-selective C(sp²)–H Transformations

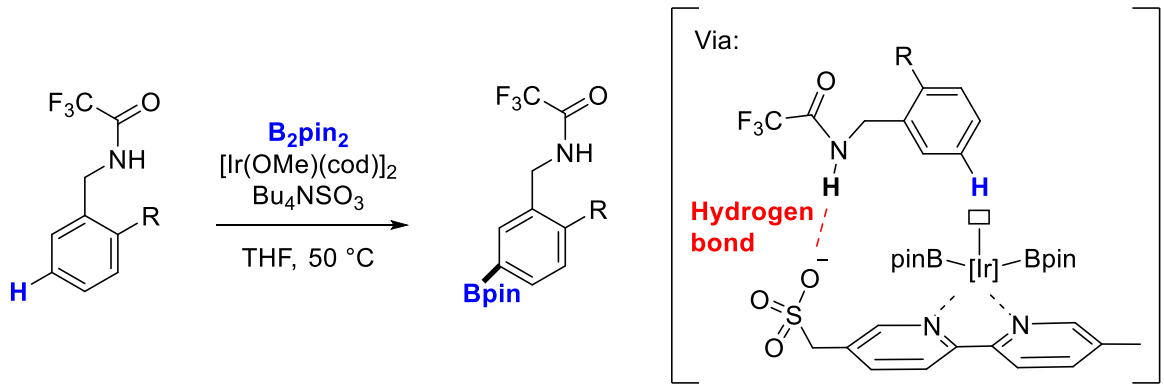
A hydrogen bond is an attractive interaction between a hydrogen atom (hydrogen bond donor) and a highly electronegative atom, such as oxygen and nitrogen atoms, andπ-electrons (hydrogen bond acceptor). The strength of hydrogen bond ranges from 10–40 kJ/mol, making them stronger than van der Waals forces but weaker than covalent bonds. In 2015, Kuninobu et al. designed a method to control the site-selectivity of C–H transformations using hydrogen-bond between a catalyst and substrate. By utilizing hydrogen bonds formed between a urea-containing bipyridine ligand and aromatic amide, they achieved *meta*-selective C(sp²)–H borylation under Ir catalysis (**Scheme 1-14**).[21]



Scheme 1-14. Hydrogen bond-controlled *meta*-selective C(sp^2)–H borylation

Subsequently, the Kuninobu group discovered that compared to bipyridine ligands without urea groups, the urea-containing bipyridine ligand shown in **Scheme 1-14** could accelerate the *meta*-selective C(sp²)–H borylation of aromatic compounds.[22] This enhancement is attributed to the ability of such ligands to recognize and capture aromatic substrates via hydrogen bond. Furthermore, modifying the electronic and steric properties of the ligand further enhanced this acceleration. Later, by modifying the structure of bipyridine-based ligands, they developed an Ir-catalyzed selective C(sp²)–H borylation reaction at the 2-position of indole derivatives.[23] The addition of a urea-derived catalyst significantly improved the reaction yield.

In 2017, the Phipps group reported a similar reaction, achieving *meta*-selective C(sp²)–H borylation of benzylamine, phenylethylamine, and phenylpropylamine-derived amides catalyzed by Ir.[24] The selectivity was accomplished through hydrogen bond between the anionic ligand and the NH group of the substrate (**Scheme 1-15**).



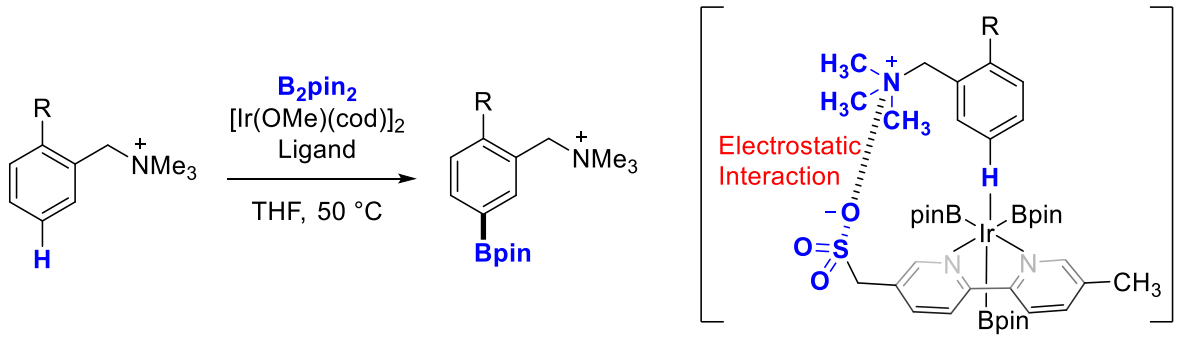
Scheme 1-15. Hydrogen bond-controlled *meta*-selective C(sp²)–H borylation

Electrostatic Interaction-Controlled Site-selective C–H Transformations

In a broad sense, electrostatic interactions refer to the interactions that occur when there is a deviation in charge distribution within a molecule. Most intermolecular forces are based on the attractive forces of electrostatic interactions. Electrostatic interactions used to control the site-selectivity of C–H transformations typically refer to the electrostatic attraction between cations and anions of opposite charges. Among non-covalent interactions, electrostatic interactions are relatively strong, with their strength potentially reaching up to ten times that of

hydrogen bonds.[25,26] In recent years, site-selective C–H transformationss mediated by electrostatic interactions have been explored.

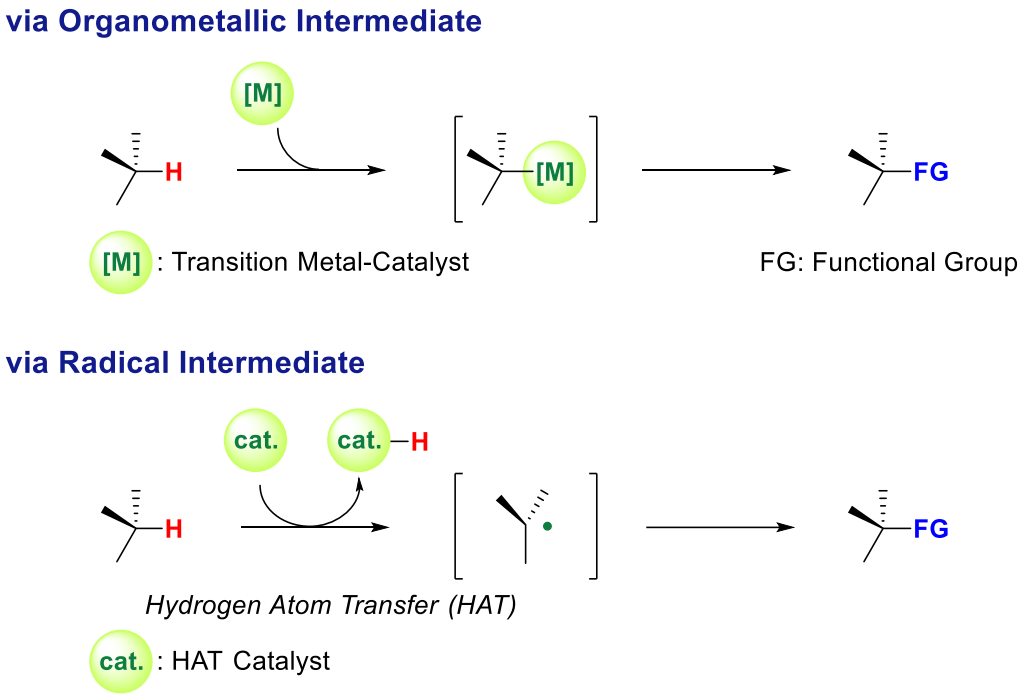
The Phipps group focuses on C(sp^2)–H borylation mediated by single-ion ligands. In addition to the aforementioned hydrogen bond (**Scheme 1-15**), they have made significant contributions to site-selective C(sp^2)–H transformations controlled by electrostatic interactions. For example, in 2016, Phipps et al. reported the introduction of an anionic sulfonate group into a bipyridine ligand to exploit electrostatic interactions with a cationic ammonium group, enabling the *meta*-selective C(sp^2)–H borylation of benzylammonium substrates (**Scheme 1-16**).[27]



Scheme 1-16. Electrostatic interaction-controlled *meta*-selective C(sp^2)–H borylation

1.3 Site-selective C(sp^3)–H Transformations

Site-selective C(sp^3)–H transformations can be broadly categorized into two main types: (1) metallation reactions through organometallic intermediates, and (2) radical reactions involving radical intermediates (**Scheme 1-17**).



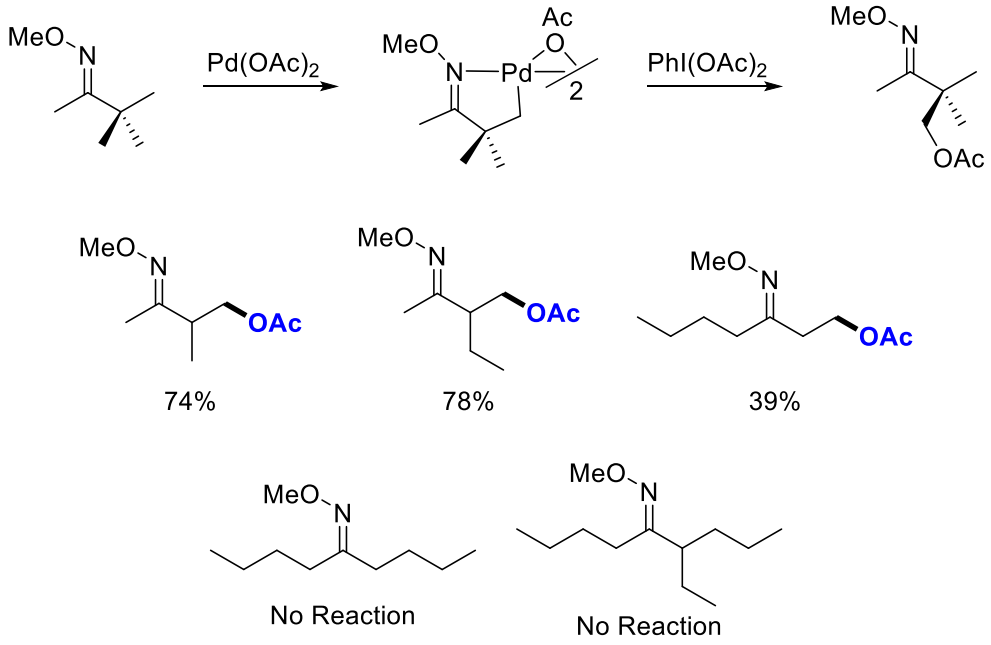
Scheme 1-17. Methods for catalytic C(sp^3)–H transformations

1.3.1 Site-Selective C(sp^3)−H Transformations via Organometallic Intermediates

To date, a significant number of site-selective C(sp^3)–H transformations through organometallic intermediates have been reported, which were primarily facilitated by transition metal catalysis with directing group assistance.[28-31]

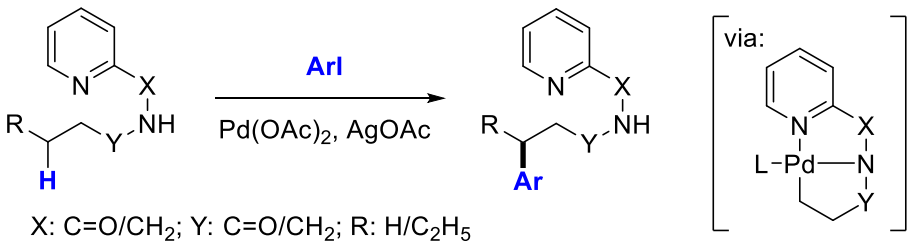
Compared to the significant progress in C(sp^2)−H transformations through organometallic intermediates, the catalytic C(sp^3)−H transformations remains a substantial challenge due to their lower acidity and the relatively weaker metal−alkyl bonds formation during the process.[30]

Moreover, methylene C(sp³)−H bonds are even more difficult to functionalize than primary C(sp³)−H bonds because of the increased steric hindrance encountered during the C−H metalation step. For example, in the earliest reported Pd-catalyzed acetoxylation of unactivated C(sp³)−H bonds, the reaction exhibited good site-selectivity when primary C(sp³)−H bonds exist at the *β*-position as reaction sites (**Scheme 1-18**).[33] However, when the substrate only contained methylene C(sp³)−H bonds as potential reactive sites, no reaction occurred.



Scheme 1-18. Palladium-catalyzed acetoxylation of unactivated C(sp^3)–H bonds

Subsequently, the Daugulis group achieved the arylation of methylene C(sp³)−H bonds by the strategy with a pyridine-based directing group.[34] In this approach, palladium acetate ($Pd(OAc)_2$) catalyzed the C(sp³)−H arylation through a Pd(II)/Pd(IV) catalytic cycle guided by the pyridine directing group (**Scheme 1-19**).

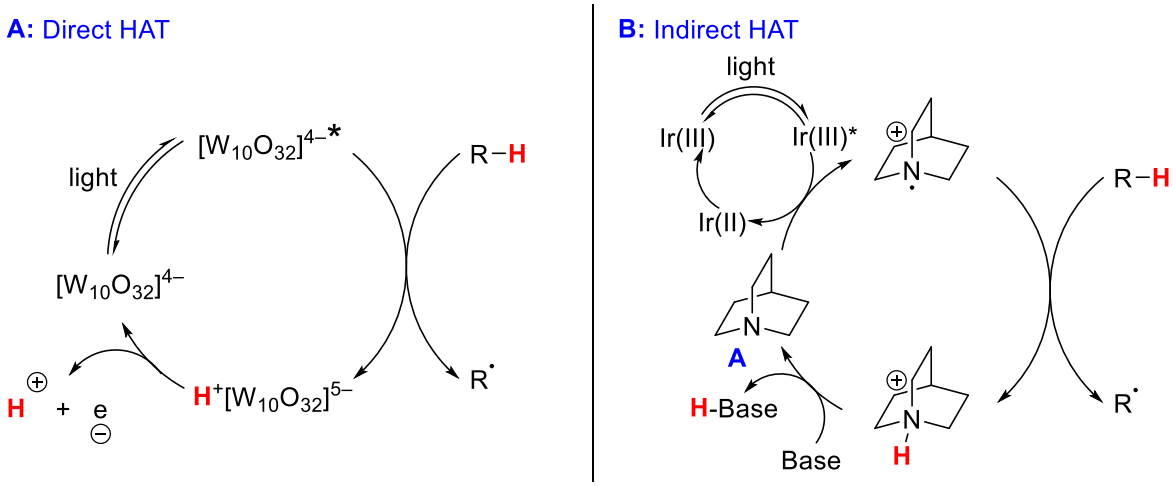


Scheme 1-19. Palladium-catalyzed arylation of unactivated C(sp^3)–H bonds

Directing group-assisted Pd-catalyzed C(sp^3)−H transformations have been extensively studied by many research groups including the Yu group being one of the prominent contributors in this field.[28, 29, 35] Interestingly, the first transition metal catalyst employed for directing group-based C(sp^3)−H transformations was platinum (Pt). In 2001, the Sames group reported the site-selective intramolecular C(sp^3)−H carboxylation of amino acids catalyzed by Pt.[36] To date, other transition metal catalysts include Fe, Co, Ni, Cu, Ru, Rh, and Ir capable of facilitating directing group-assisted C(sp^3)−H transformations.[28]

1.3.2 Site-selective C(sp^3)−H Transformations via Radical Intermediates

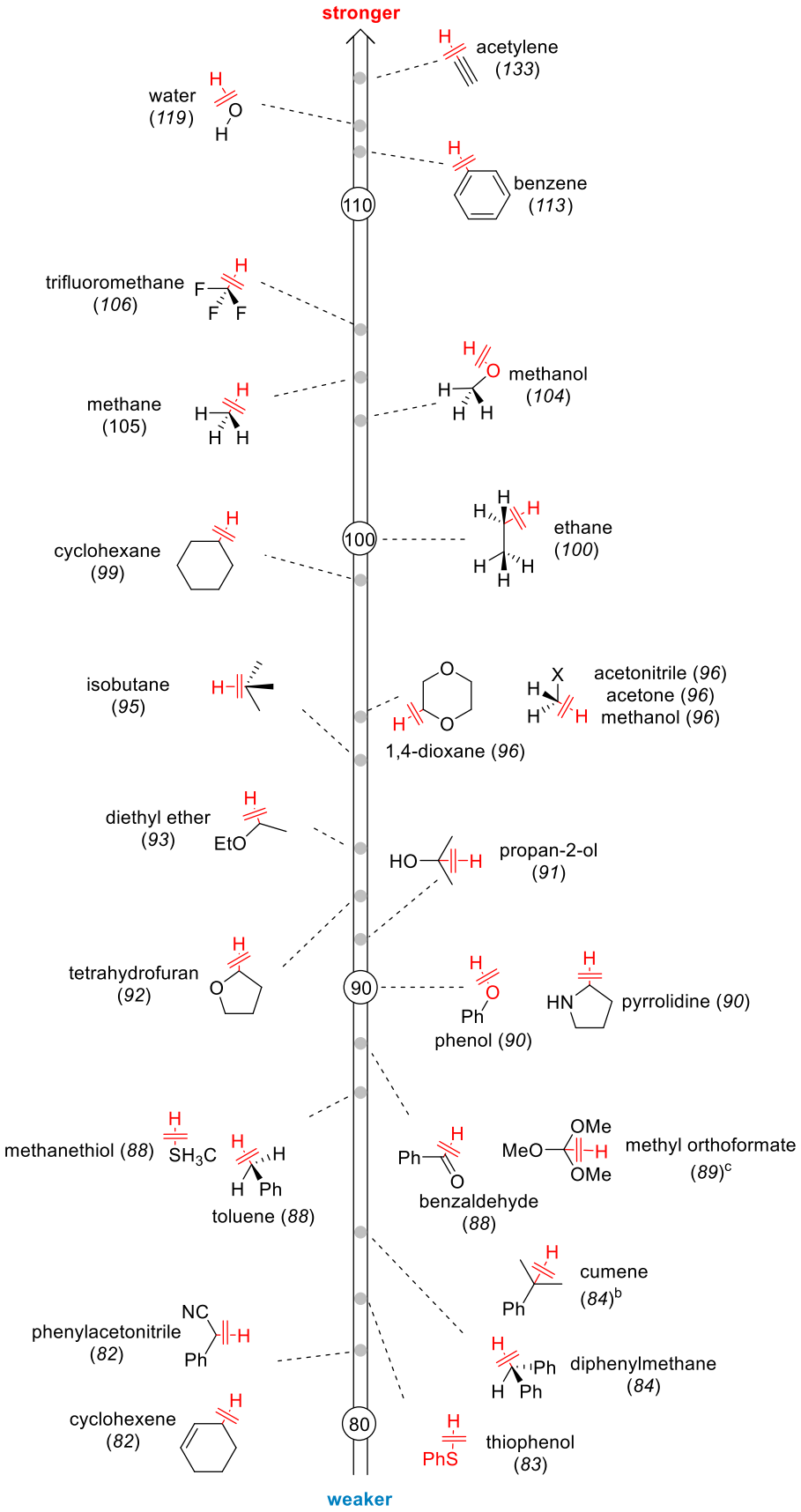
In recent years, C(sp^3)–H transformations via radical mechanisms have been one of the most important topics of extensive researches.[37] Hydrogen atom transfer (HAT) enables the direct transfer of a hydrogen atom (proton and electron) from one species to another in a single step. C(sp^3)–H transformations via HAT provide an efficient pathway for the functionalization of C(sp^3)–H bonds. Currently, photoinduced catalytic C(sp^3)–H transformations via HAT can be broadly classified into direct and indirect HAT processes (**Scheme 1-20**).[38-41] The direct HAT process means that the excited catalyst can directly abstract hydrogen atoms from the substrate. In recent years, the limited number of catalysts capable of directly abstracting hydrogen atom upon the excited state has paved the way for the development of indirect strategies.[42] In such strategies, quinuclidine **A** (reaction or co-catalyst, such as quinuclidine in **Scheme 1-20B**) are activated by the excited photocatalyst to generate thermally-driven hydrogen abstractors. Quinuclidine **A** act as a stoichiometric additive, or a catalyst, forming a dual-catalysis approach (**Scheme 1-20B**). In HAT C(sp^3)–H transformations process, catalysts preferentially catalyze the C(sp^3)–H bonds with lower bond dissociation energies (BDE). Consequently, when multiple reactive sites with similar BDEs are present in the substrate, it becomes challenging to obtain a single product. Therefore, to control site-selectivity of HAT C(sp^3)–H transformations, other methods based on the steric or directing groups of substrates, and non-covalent interactions between the substrates and catalyst.



Scheme 1-20. Reaction mechanisms of C(sp^3)–H transformations by HAT

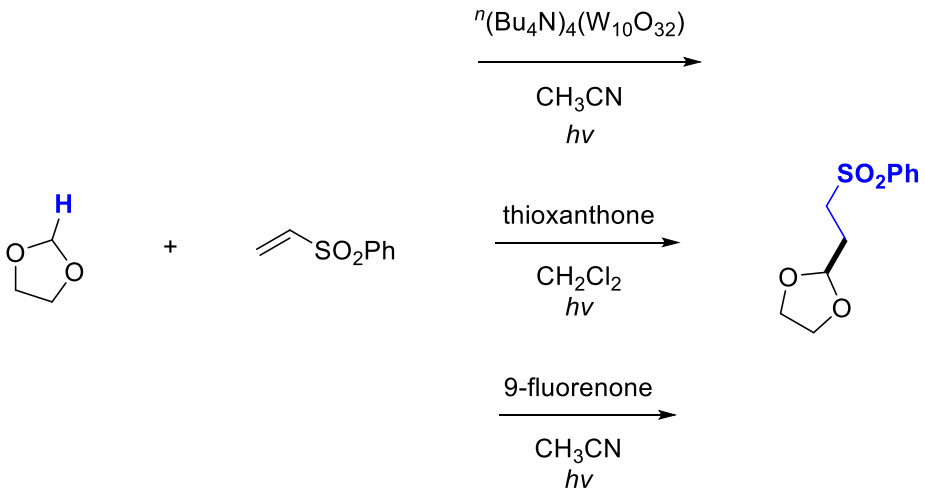
Bond Dissociation Energy-Controlled Site-selective C(sp^3)−H Transformations by HAT

The selectivity of C(sp^3)−H transformations by HAT is typically governed by bond dissociation energies (BDEs) of C(sp^3)−H bonds. As shown in **Scheme 1-21**, C(sp^3)−H bonds with weaker BDEs are preferentially cleaved to achieve C(sp^3)−H transformations. A substantial number of C(sp^3)−H transformations controlled by the BDEs have been reported.[39]



Scheme 1-21. BDEs (kcal/mol) of X−H bonds (in red)

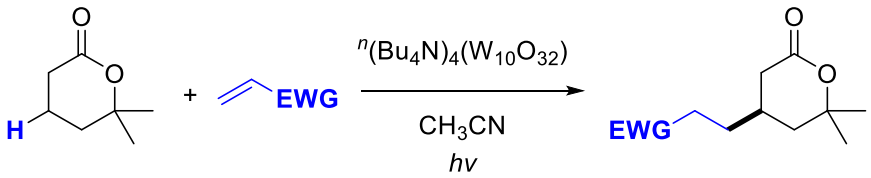
For example, Ravelli reported site-selective C(sp³)−H alkylation of aliphatic oxacycles catalyzed by different HAT catalysts. Taking 1,3-dioxolane as an example, the reaction selectively occurs at the C(sp³)−H bond located between the two oxygen atoms (**Scheme 1-22**).[43]



Scheme 1-22. BDE-controlled selective C(sp^3)–H alkylation

Steric-Controlled Site-selective C(sp³)−H Transformations by HAT

When multiple reactive C(sp³)−H bonds with similar BDEs exist in the substrates, the reaction selectively occurs at C(sp³)−H bond more accessible to the catalyst. In such cases, the site-selectivity is governed by the steric effect. For instance, the Ryu group reported a site-selective C(sp³)−H alkylation of 6,6-dimethyltetrahydro-2*H*-pyran-2-one controlled by the steric effect of substrates (**Scheme 1-23**).[44]

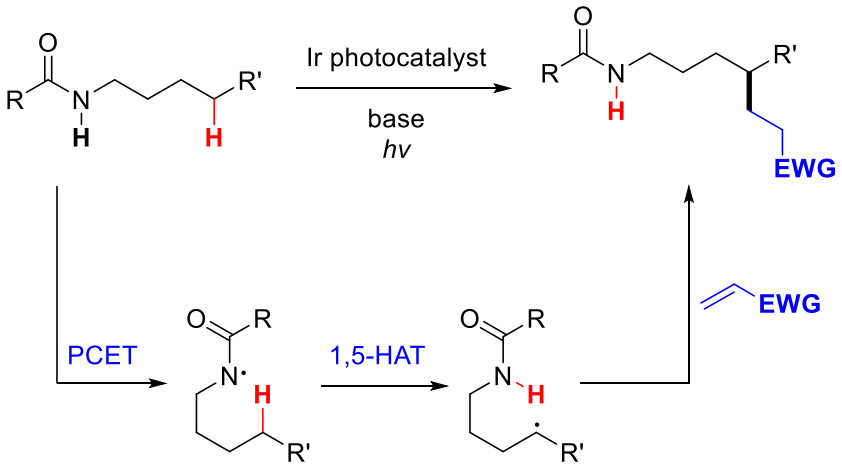


Scheme 1-23. Steric-controlled site-selective C(sp^3)–H alkylation

Site-selective C(sp³)–H Transformations by Intramolecular HAT

The intramolecular HAT strategy is a commonly used approach for site-selective C(sp³)–H transformations. The 1,5-hydrogen atom transfer (1,5-HAT) is the primary process for site-selective C(sp³)–H transformations. Key functional groups in HAT reactions are OH and NH groups with an electron-withdrawing substituent. Under photocatalytic conditions, these functional groups generate oxygen- or nitrogen-centered radicals, which subsequently undergo intramolecular HAT to form carbon-centered radicals. These intermediates then react with suitable reagents to produce functionalized products. In addition to thermodynamic and kinetic feasibility, C(sp³)–H transformations via 1,5-HAT are advantageous over other 1,n-HAT processes due to the favorable six-membered transition state.

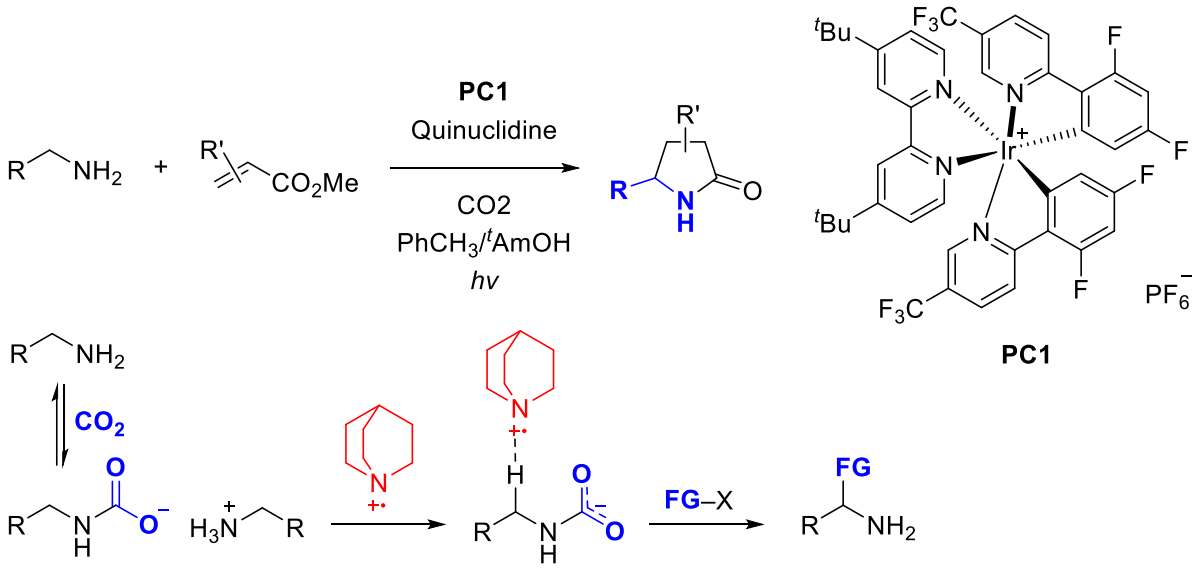
For example, Miller reported an amide group-assisted C(sp³)–H alkylation. Under the irradiation of UV light, through a concerted proton-coupled electron transfer (PCET), an excited-state iridium oxidant and a weak phosphate base act cooperatively to remove an electron from the amide substrate and a proton in a single elementary step, affording a reactive amide radical. Then 1,5-HAT occurs and carbon-centered radical is formed. This carbon radical reacts with an electron-deficient alkene, yielding δ-alkylated products (**Scheme 1-24**).[45] To date, numerous C(sp³)–H transformation reactions via the 1,5-HAT process have been reported.[46]



Scheme 1-24. C(sp³)–H alkylation by 1,5-HAT and its reaction mechanism

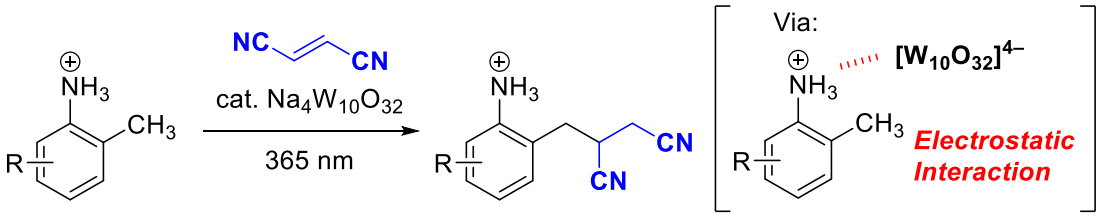
Non-covalent Interaction-Controlled C(sp³)–H Transformations

In 2018, Rovis group reported electrostatic interaction-controlled α-alkylation of primary aliphatic amines. In this reaction, carbon dioxide is used as an activator to directly convert aliphatic primary amines into *γ*-lactams under photoredox and hydrogen atom transfer catalysis (**Scheme 1-25**).[47]



Scheme 1-25. Electrostatic interaction-controlled *α*-alkylation of primary aliphatic amines

In recent years, Kuninobu-lab has focused on achieving site-selective C(sp³)–H transformations by employing the "non-covalent method".[16, 48, 49] In 2022, they reported proximal-selective C(sp³)–H alkylation controlled by the electrostatic interaction between a decatungstate photocatalyst and 2-methylanilinium salts (**Scheme 1-26**).[50] The site-selective C(sp³)–H alkylation of aniline salts enabled them to achieve selective C(sp³)–H alkylation of complex natural products like Val residues.[51]



Scheme 1-26. Electrostatic interaction-controlled proximal-selective C(sp³)–H alkylation

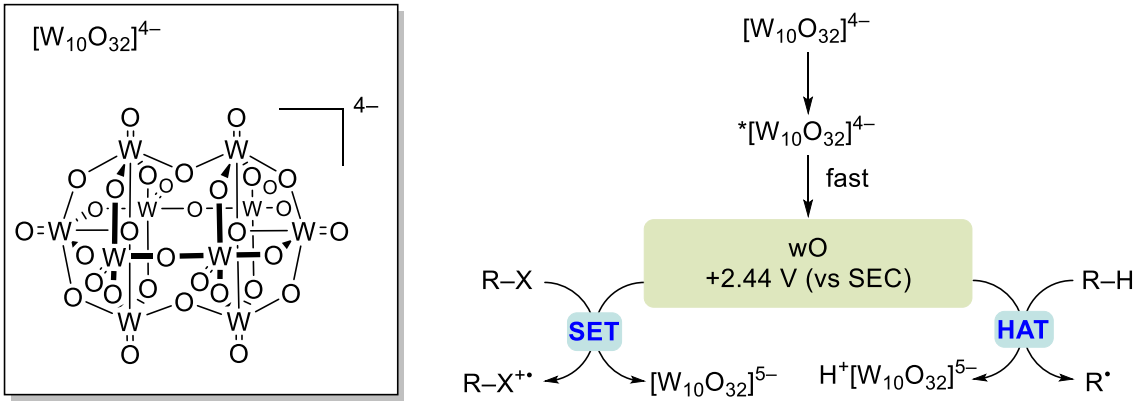
1.3.3 Decatungstates as Hydrogen Atom Transfer Catalysts Catalyst

Decatungstates, (^{n}Bu$_4$N)[W$_{10}$O$_{32}$] (TBADT) and Na$_{4[}$W$_{10}$O$_{32}$] (NaDT), are now well known as typical photocatalysts for hydrogen atom transfer in C–H transformations. Initially, the optical properties of 1:12- and 2:18-heteropoly tungstates were first reported by Varga in 1970.[52] Subsequently, in 1980, Politou observed that tungstates exhibit photochemical properties analogous to those of 18-molybdodiphosphate [P$_2$Mo$_{18}$O$_{62}$]$^{6-}$ when molybdenum is substituted with tungsten.[53] Four years later, Yamase provided the first report on the photocatalytic properties of decatungstate.[54] The mechanism of C–H bond cleavage via hydrogen atom transfer (HAT) by decatungstate photocatalyst was not fully understood until 1998.[55, 56]

The results of researches suggested that the highest occupied molecular orbital (HOMO) is primarily localized on the oxygen atoms in the case of polyoxotungstate compounds such as decatungstate ([W$_{10}$O$_{32}$]$^{4-}$), on the other hand, the lowest unoccupied molecular orbital (LUMO) is distributed on the tungsten atoms. Upon exposure to ultraviolet or violet light, electrons from the 2p orbitals of oxygen can transfer to the 5d orbitals of tungsten. This process, known as ligand-to-metal charge transfer (LMCT), facilitates intramolecular charge transfer and generates a highly reactive excited state. Furthermore, the structure of the decatungstate anion ([W$_{10}$O$_{32}$]$^{4-}$) features four nearly linear W–O–W bridges, which promote O→W electron transfer within the molecule. As a result, [W$_{10}$O$_{32}$]$^{4-}$ readily forms an active excited state through LMCT upon UV irradiation.[55]

Under ultraviolet or violet light irradiation, decatungstate is excited to generate the singlet excited state (*[W$_{10}$O$_{32}$]$^{4-}$), which rapidly (within 30 ps) transitions into the active species wO with a quantum yield of approximately 0.5–0.6. The wO species is a relaxed excited state, likely formed through reorganization of the orbitals occupied by unpaired electrons on the oxygen atoms, resulting in an electrophilic oxygen center. Its redox potential, E(wO/[W$_{10}$O$_{32}$]$^{5-}$)), is +2.44 V (vs. SCE). Consequently, if the oxidation potential of a substrate R–X is less than +2.44 V (vs. SCE), R–X undergoes single electron transfer (SET) with wO, forming the corresponding radical cation R–X$^{+\bullet}$. Conversely, when the oxidation potential of a substrate R–

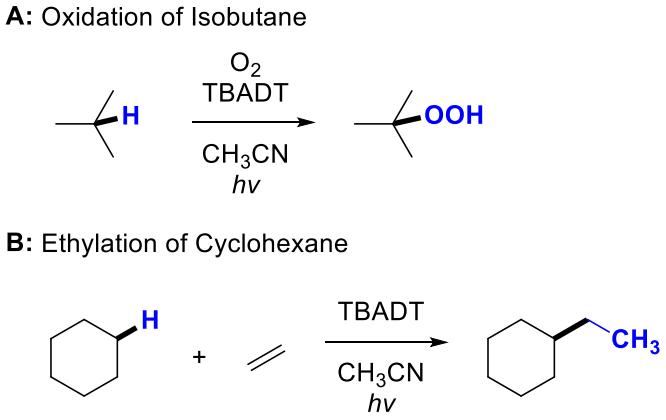
H exceeds +2.44 V (vs. SCE), hydrogen atom transfer (HAT) occurs, generating the corresponding radical R• (**Scheme 1-27**).[56]



Scheme 1-27. Mechanism of decatungstate in photocatalyzed reactions

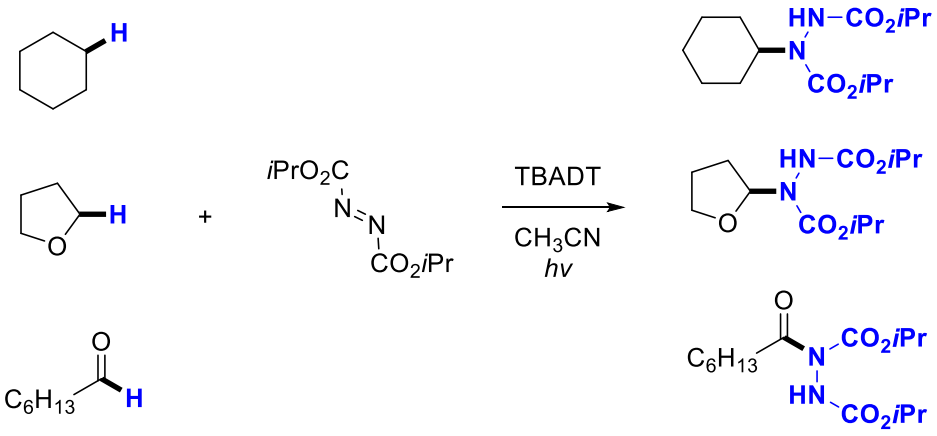
Decatungstates exhibit excellent photocatalytic properties. Under light irradiation, the excited $*[W_{10}O_{32}]^{4-}$ is capable of abstracting a hydrogen atom of C(sp^3)–H bonds, generating corresponding carbon-centered radicals and enabling C(sp^3)–H transformations under mild conditions. To date, decatungstate-based photocatalysts have been employed for C(sp^3)–H transformations to form C–C, C–N, C–O, C–F, C–S and C–Br bonds.[39,57-61]

In 1989, Hill et al. successfully achieved the site-selective oxidation of the methylene C(sp^3)–H bond in isobutane under t TBADT catalysis (**Scheme 1-28A**).[62] Subsequently, in 1993, they further demonstrated the C(sp^3)–H alkylation of saturated aliphatic compounds such as cyclohexane (**Scheme 1-28B**).[62] The Hill group made significant early contributions to the study of decatungstate-catalyzed C(sp^3)–H transformations, providing a strong basis for future advancements in this field.



Scheme 1-28. Decatungstate catalysed C(sp^3)–H functionalization

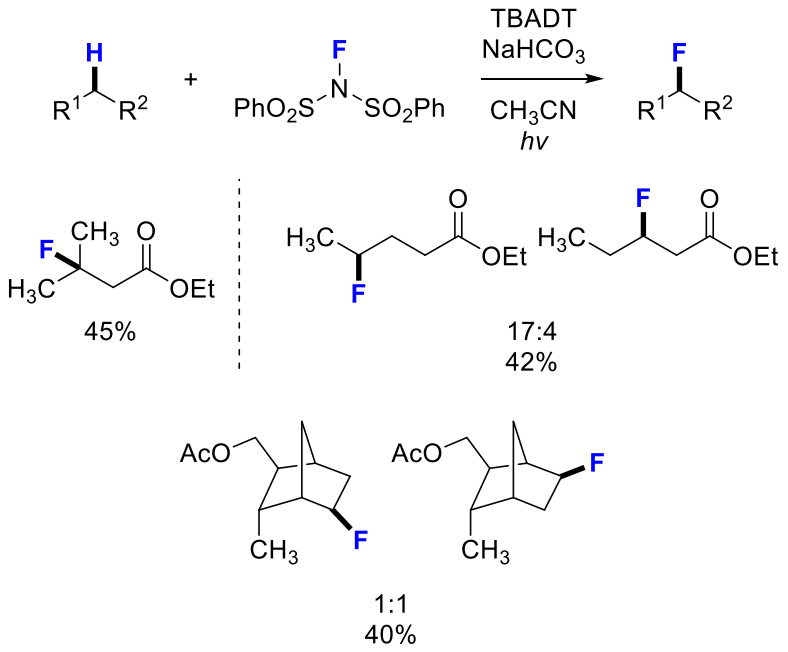
In 2013, Ryu successfully applied the TBADT photocatalytic strategy to construct C–N bonds. Under irradiation of light with a 500 W xenon lamp, the method enabled the addition of inert C–H bonds of saturated alkanes, cyclic ethers, and aldehydes to the N=N double bond of diisopropyl azodicarboxylate (**Scheme 1-29**).[58]



Scheme 1-29. Decatungstate-catalysed C–N bond formation

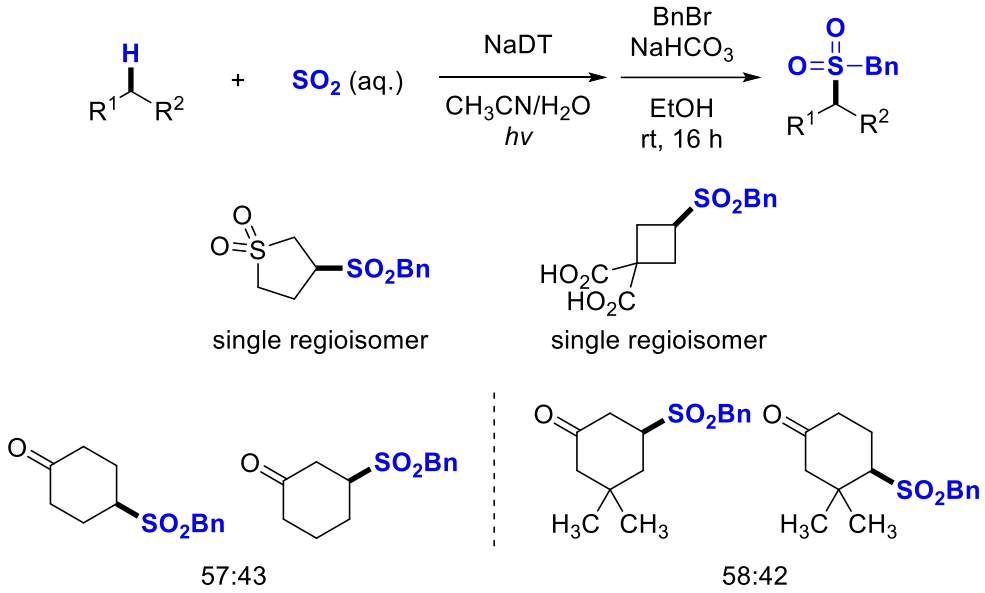
In 2014, the Britton group achieved fluorination of unactivated C(sp^3)–H bond of saturated alkanes using TBADT as a photocatalyst under UV (365 nm) irradiation (**Scheme 1-30**).[57] This method employed N-fluorobenzenesulfonimide ($(PhSO_2)_2NF$, NFSI) as the fluorinating agent and $NaHCO_3$ as an additive, enabling the fluorination of various organic molecules, including complex natural products, under mild conditions while preserving the stereochemical configuration of the substrates. However, the selectivity of this reaction is relatively poor. When

two similar reactive sites are present in the substrates, two reaction products are generated, as illustrated in **Scheme 1-30**.



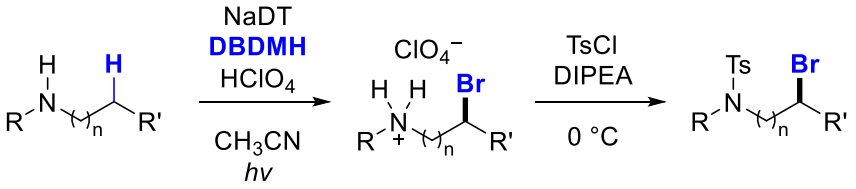
Scheme 1-30. Decatungstate-catalysed C–F bond formation

In 2021, the MacMillan group employed NaDT as a photocatalyst to directly transform robust aliphatic C(sp^3)−H bonds into the corresponding alkyl sulfinates under 390 nm light irradiation (**Scheme 1-31**).[59] This transformation could also be applied to a variety of C(sp^3)-rich scaffolds, including natural products and approved drugs, enabling the efficient synthesis of complex sulfur-containing compounds. Similarly, in this sulfuration reaction, the selectivity is primarily determined by the electronic properties or steric effects of the substrates. Positions that are electronically richer and more sterically accessible exhibit excellent selectivity.



Scheme 1-31. Decatungstate-catalysed C–S bond formation

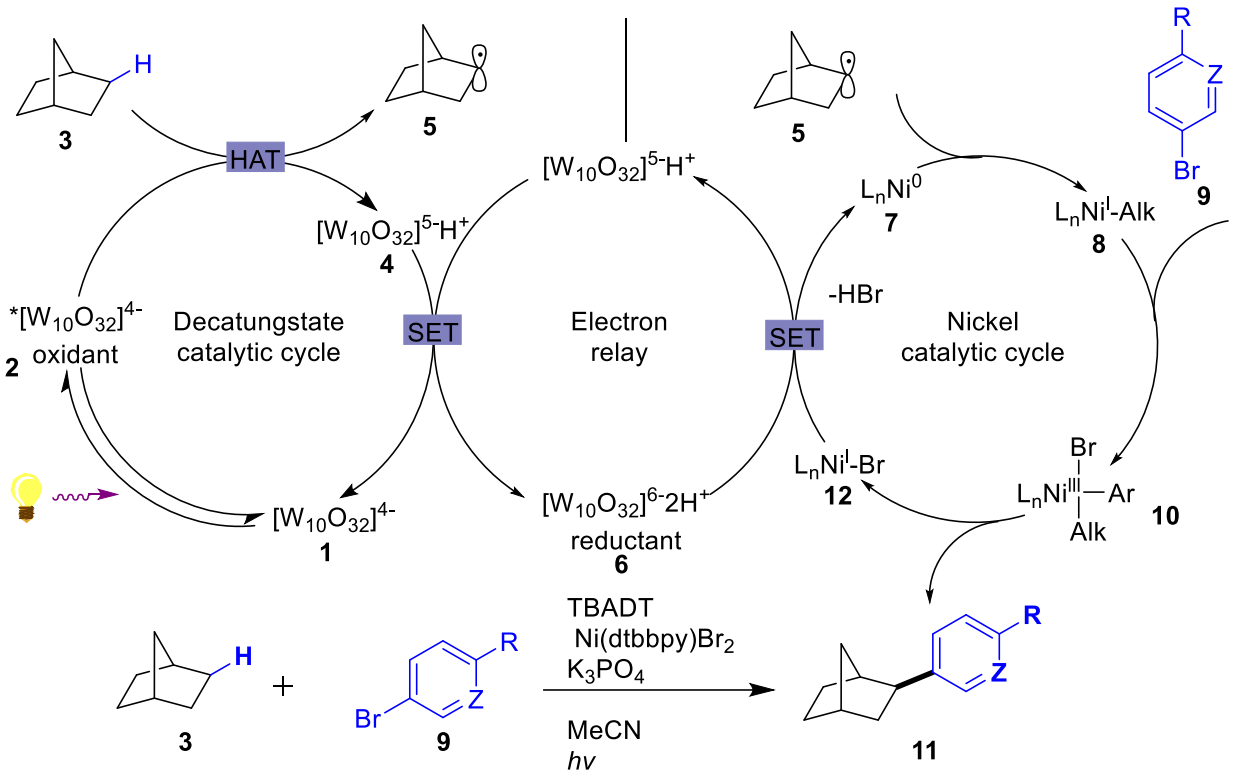
Recently, the Martin group developed a method for the distal-selective bromination of C(sp^3)–H bonds of aliphatic amines. Unlike the 1,5-HAT strategy, this study achieved site-selective C(sp^3)–H bromination of primary and secondary amines by modulating the electronic effect of the substrates (**Scheme 1-32**).[61]



Scheme 1-32. Decatungstate-catalysed C–Br bond formation

Decatungstate catalysts not only directly facilitate C(sp^3)–H transformations by HAT but also can be combined with other catalysts to achieve C(sp^3)–H transformations. For instance, in 2018, MacMillan reported a method combining decatungstate-promoted HAT with nickel catalysis for the direct C(sp^3)–H arylation of various aliphatic frameworks. For this strategy, the carbon-centered radical is generated under decatungstate catalysis, and the carbon radical reacts with aryl bromides in the presence of a nickel catalyst to generate C(sp^3)–C(sp^2) cross-coupling products (**Scheme 1-33**).[64] Subsequently, they also reported the use of decatungstate

catalyst in the combination with Cu (II) catalyst to achieve aliphatic C(sp³)–H trifluoromethylation.[65]



Scheme 1-33. C(sp^3)–H arylation by dual decatungstate and nickel catalysts

Decatungstate-catalyzed C(sp³)–H transformations have triggered significant attention because of not only their role as direct HAT catalysts in C–H transformations but also their ability to achieve complex reactions under relatively mild reaction conditions by combining with other catalysts. Moreover, the electron-deficient nature and oxygen-rich structure of decatungstates are important to achieve site-selective C(sp³)–H transformations.[64] Consequently, decatungstate-catalyzed C(sp³)–H transformations hold tremendous potential and continuous explorations are highly desirable.

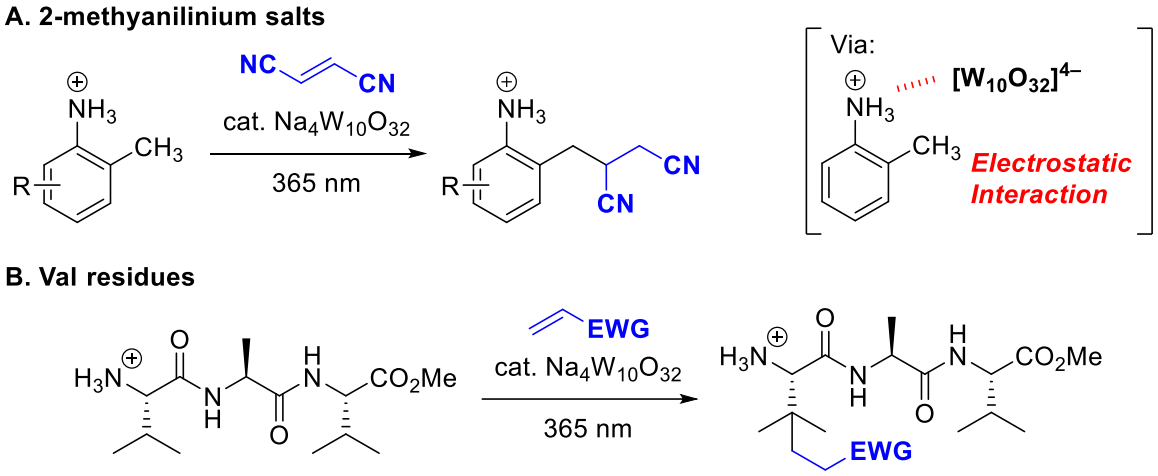
1.4 The Purpose of This Research

As described above, C–H transformations are significantly important in synthetic organic chemistry. Numerous site-selective C–H transformations have been reported, and some have even been applied in industrial productions. Compared with the C(sp^2)–H transformations of unsaturated hydrocarbons, challenges remain in the C(sp^3)–H transformations that need to be addressed.

First, while site-selective C(sp^3)−H transformations can be effectively achieved via the formation of organometallic intermediates, the site-selectivity in these reactions is generally governed by directing groups, which significantly limits the substrate scope. Second, although radical processes by hydrogen atom transfer (HAT) have been widely applied to C(sp^3)−H transformations, the site-selectivity decreased when substrates contain multiple reaction sites with similar reactivities. To address these challenges, in addition to controlling the site-selectivity by the bond dissociation energies (BDEs) of C(sp^3)−H bonds, researchers also achieved site-selectivity C(sp^3)−H transformations by the steric effect of substrate, directing groups, and non-covalent interactions between substrates and catalysts. However, to achieve high activity and site-selectivity controlled by BDEs or steric effect of substrates often requires excess amounts of substrates (sometimes even as solvent quantities), making this approach less atom-economical. Meanwhile, directing group-controlled C(sp^3)−H transformations remains constrained by a narrow substrate scope, and researches on non-covalent interaction-controlled C(sp^3)−H transformations are still limited.

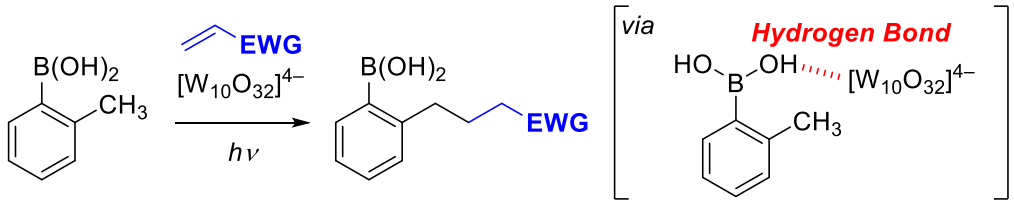
In recent years, our group has focused on achieving site-selective C–H transformations by employing the "non-covalent method".[16,47,48] To address the challenges associated with site-selective C(sp^3)−H transformations, our group has focused on the anionic nature of decatungstate and designed the substrate with cationic feature, achieving site-selective C(sp^3)−H alkylation. This kind of site-selective reactions were controlled by the electrostatic interaction between the anionic decatungstate photocatalyst and cationic 2-methylanilinium salts (**Scheme 1-34A**).[50] Later the site-selective C(sp^3)–H alkylation of anilinium salts enabled to achieve site-selective C(sp^3)–H alkylation of complex natural products like peptides (**Scheme 1-34B**).[51] I envisioned that the electron- and oxygen-rich decatungstates could also

interact with other functional groups by non-covalent interactions such as hydrogen bond to achieve site-selective C(sp³)–H transformations.



Scheme 1-34. Electrostatic interaction-controlled proximal-selective C(sp^3)–H alkylation

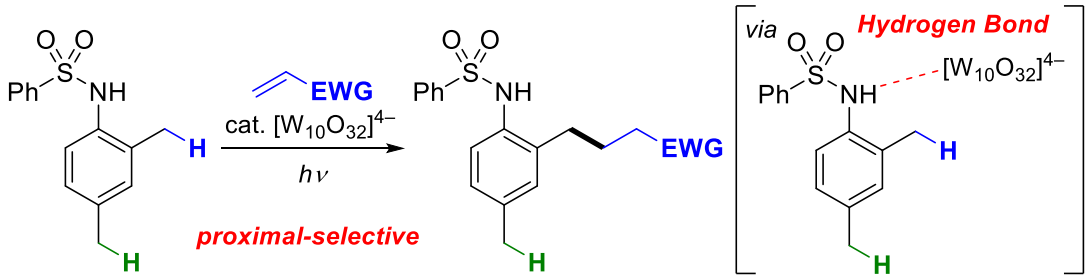
Boronic acid derivatives are indispensable molecules in synthetic organic chemistry. Despite the high stability of their carbon–boron bonds, these bonds can be readily transformed into carbon–carbon and carbon–heteroatom bonds.[65] Currently, boronic acids are typically synthesized through C–H borylation.[67] Herein, I exploit the structural characteristics of boronic acid and decatungstate, at the assistant of hydrogen bond between boronic acid and decatungstate, achieved the C(sp³)–H alkylation of 2-methylphenylboronic acids (**Scheme 1-35**).



Scheme 1-35. Hydrogen bond-assisted C(sp^3)–H alkylation

In the aforementioned reaction, although I successfully achieved the C(sp³)–H alkylation of 2-methylphenylboronic acids. However, the site-selectivity was relatively poor. I attribute this to the weak hydrogen bond between the boronyl group of substrates and decatungstate. To address this issue, I introduced an electron-withdrawing substituent on the NH_2 group of o-

toluidines to increase the hydrogen bond strength between the substrate and decatungstate. This strategy enabled the proximal-selective C(sp³)–H alkylation of sulfonanilides (**Scheme 1-36**).



Scheme 1-36. Hydrogen bond-controlled proximal-selective C(sp^3)–H alkylation

I have successfully achieved the proximal-selective C(sp³)–H alkylation of *N*-(*o*-tolyl)benzenesulfonanilides which was controlled by hydrogen bond between the substrate and decatungstate. However, remote-selective C(sp³)–H transformations controlled by non-covalent interactions have been poorly investigated.[31] unpublished content for Chapter 4

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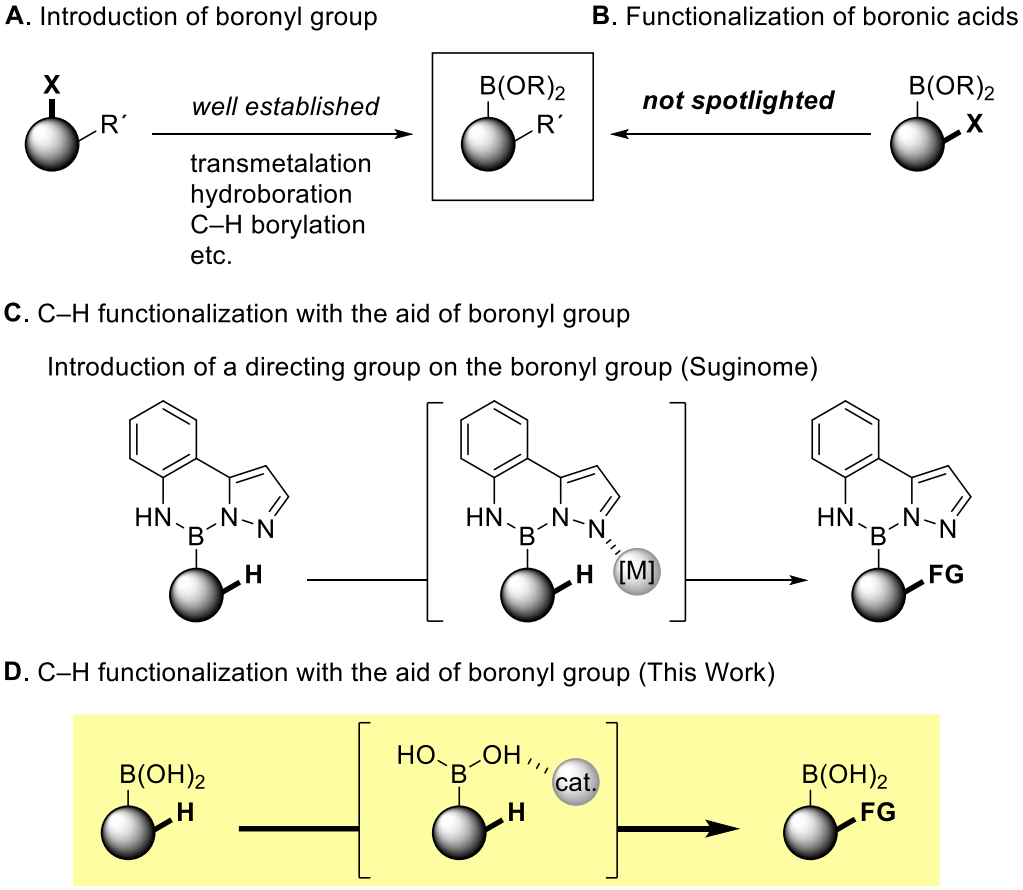
Chapter 2. Boronyl Group-Assisted Decatungstate-Catalyzed Benzylic C(sp^3)–H Alkylation

2.1 Introduction

Boronic acids remain a crucial position in synthetic organic chemistry. While their carbon−boron bonds exhibit high stability, they are readily transformed into carbon−carbon and carbon−heteroatom bonds.[1] Additionally, boronates can be prepared from simple synthetic intermediates, making significant contributions to modern pharmaceutical and materials sciences.[1–5] Particularly in the pharmaceutical field, boronic acids have important roles in Suzuki-Miyaura cross-coupling reaction,[6] diol protection,[7] Diels-Alder reaction,[8] asymmetric synthesis of amino acids,[9] selective reduction of aldehydes,[10] carboxylic acid activation,[11,12] and as templates in organic synthesis.[13] Moreover, as potential therapeutic agents, boronic acids have been utilized in the development of enzyme inhibitors,[14] boron neutron capture therapy (BNCT) agents,[15] feedback-controlled drug delivery polymers,[16] carbohydrate sensors,[17] and antibody mimetics for cell surface polysaccharides.[18] The therapeutic potential of boronic acids stems from their distinctive electronic and physicochemical properties. In the periodic table, boron resides in the same period as carbon but has one fewer electron. Therefore, it has many similarities with carbon in structural characteristics, which making it a significant role in carbon-based organic and medicinal chemistry.

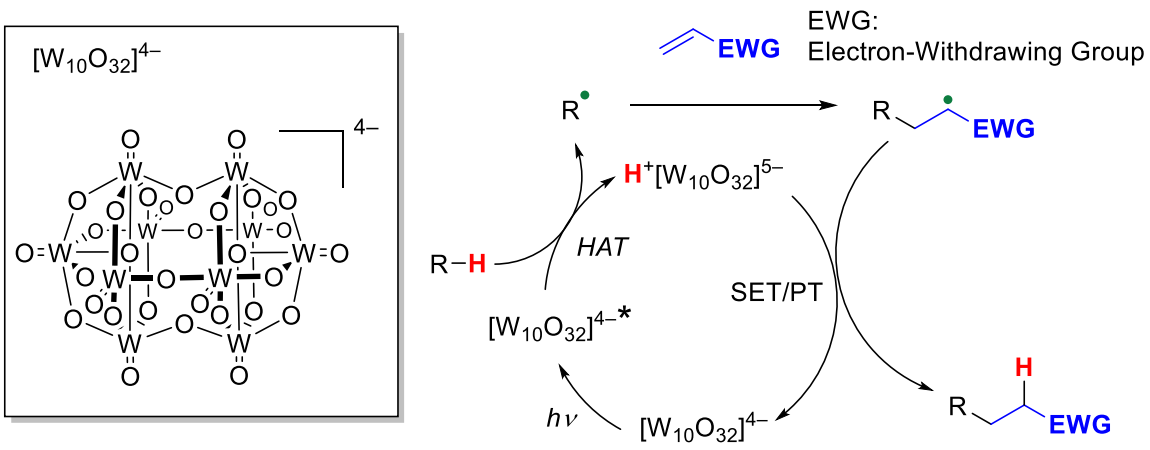
Given the significance of boronic acids in organic chemistry, numerous synthetic methods for boronic acids have been developed. The typical synthetic routes for boronic acids are transmetalation, hydroboration, catalytic borylation of carbon-halogen bonds, and C−H borylation (**Scheme 2-1A**).[1,19–26] In contrast, researches on the functionalization of boronic acids that preserves the boryl group have been limited (**Scheme 2-1B**). Although boronic acids have been frequently used as substrates in modern chemical reactions, studies on functionalized boronic acids with the aid of boryl group remains less explore. Suginome and colleagues achieved transition metal-catalyzed proximal C−H functionalization of boronic acids by introducing a directing group on the boron atom (**Scheme 2-1C**).[27–30] Despite the ingenuity of this approach, synthetic chemists often aim to avoid the preparation and introduction of

directing groups. Thus, the development of catalytic C−H functionalization methods to directly utilize the free boron group [−B(OH)$_2$] is highly desirable (**Scheme 2-1D**).



Scheme 2-1. Synthetic methods of boronic acids

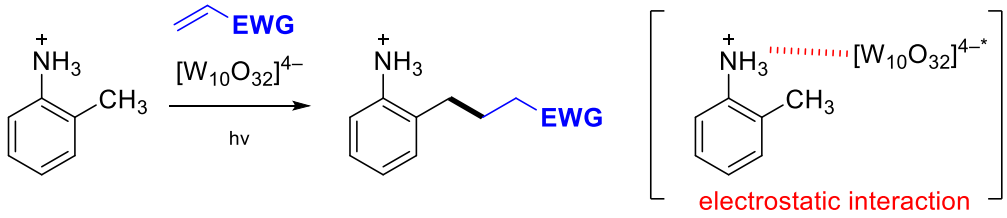
As mentioned in Chapter 1.3, decatungstate is used as a typical hydrogen atom transfer photocatalyst. Under UV irradiation, the excited decatungstate catalyst abstracts hydrogen atom of organic compounds to give carbon-centered radical, which react with alkenes to afford C–H alkylated products (**Scheme 2-2**). C(sp^3)–H transformations catalyzed by decatungstate have been extensively studied currently, but the selectivity of these reactions is controlled by steric and electronic properties of substrates. In addition, decatungstate catalyzed C(sp^3)–H transformation always require a large excess of substrates, sometimes even in solvent-equivalent amounts, which lead to inefficiency in many cases.[31]



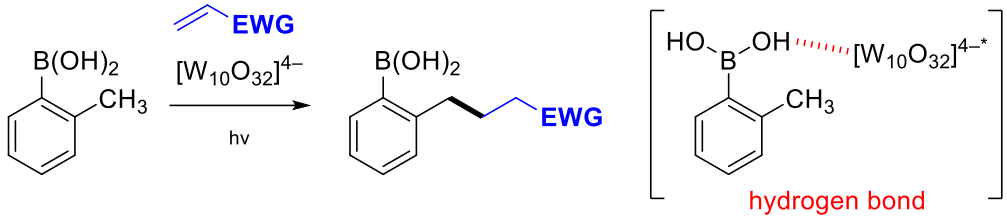
Scheme 2-2. Decatungstate catalyzed C–H alkylation

Our group reported an efficient proximal-selective C(sp^3)–H alkylation of 2-methylanilinium salts controlled by electrostatic interaction between the anionic $[W_{10}O_{32}]^{4-}$ and the cationic $^{+}NH_3$ group of the ammonium salts (**Scheme 2-3A**).[32] This strategy was also successfully applied to C(sp^3)–H alkylation of valine residues located at proximal to *N*-terminus.[33] In these reactions, electrostatic interactions between the cationic ammonium group ($-NH_3^+$) and anionic $[W_{10}O_{32}]^{4-}$ play a key role. I envisioned that electron-rich $[W_{10}O_{32}]^{4-}$ could function as a hydrogen bond acceptor and interact with a boronyl group, as a hydrogen bond donor. This conceptualization led me to hypothesize the catalytic functionalization of free boronic acids based on the interaction between decatungstate and their boronyl groups (**Scheme 2-3B**).

(A) Our previous work: Use of electrostatic interaction



(B) Working hypothesis: Use of hydrogen bond

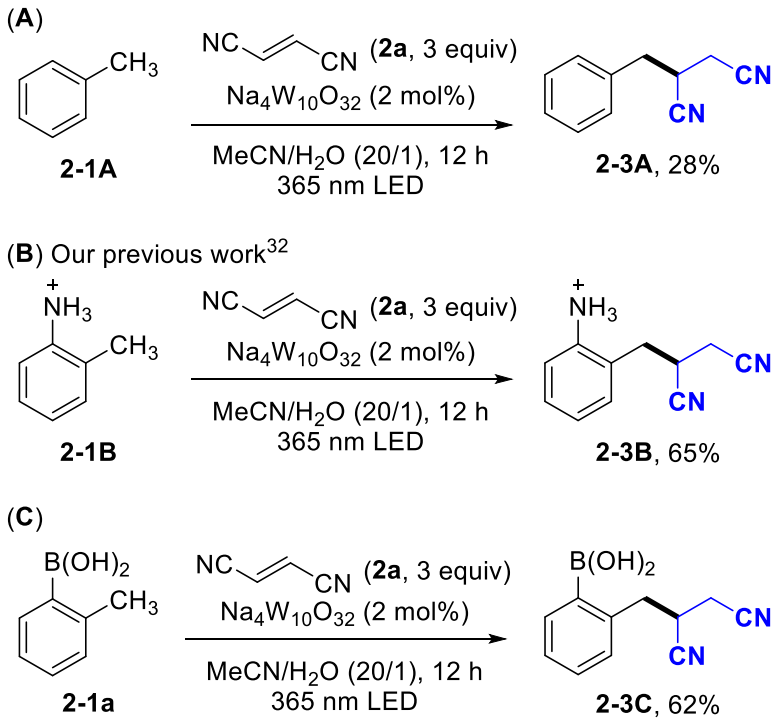


Scheme 2-3. Noncovalent interactions for decatungstate-catalyzed C(sp^3)−H alkylation

2.2 Results and Discussion

2.2.1 Effect of Boronyl Group

Based on our previous studies (**Scheme 3-2A**), I compared the reactivity of toluene (**2-1A**), 2-methylbenzenaminium (**2-1B**) and 2-methylphenylboronic acid (**2-1a**) under the same photoreaction conditions (**Scheme 2-4**). When **2-1A** without any functional group, reacted with fumaronitrile (**2-2a**), giving the alkylated product **2-3A** in 28% yield (**Scheme 2-4A**). In contrast, when using substrate (**2-1B**) with cationic ammonium group ($-NH_3^+$), which interacts with the anionic decatungstate ($[W_{10}O_{32}]^{4-}$) via electrostatic interactions, the product (**2-3B**) was obtained in 65% yield (**Scheme 2-4B**).[32] When **2-1a** was used as the substrate, the product (**2-3C**) was obtained in 62% yield (**Scheme 2-4C**). Based on these results, I believe that the boronyl group can assist C(sp³)–H alkylation like ammonium group in **Scheme 2-4B**.

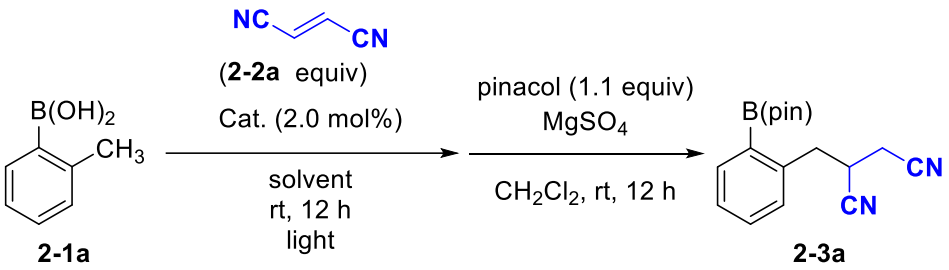


Scheme 2-4. Comparison of the reactivity of **2-A**, **2-B** and **2-1a**

2.2.2 Optimization of Reaction Conditions

The reaction conditions were optimized (**Table 2-1**). Based on reaction conditions in **Scheme 2-4**: to a Schlenk tube, 2-methyphenylboronic acid (**2-1a**, 68.0 mg, 0.500 mmol), fumaronitrile (**2-2a**, 117 mg, 1.50 mmol, 3.0 equiv), $Na_4W_{10}O_{32}$ (NaDT, 24.4 mg, 0.0100 mmol, 2.0 mol%), and MeCN/H_2O (20/1, 5.0 mL) were added, and the resulting mixture was stirred at room temperature for 12 h under irradiation of UV light (365 nm). After the reaction, the volatiles were removed under reduced pressure, and pinacol (65.0 mg, 0.550 mmol, 1.1 equiv), $MgSO_4$ (400 mg), and CH_2Cl_2 (1.0 mL) were added to the tube. After 12 h of the reaction, and dodecane was added to the filtrate as an internal standard. The yield of **2-3a** was 62% by gas chromatography (GC) (**Table 2-1**, entry 1). In this reaction system, the reactants and products did not decompose and no by-products including olefin polymerization were generated, and the pinacol ester **2-6** formed by **2-1a** after treated with pinacol was isolated in 35% yield. The amount of water affected the efficiency of this reaction (**Table 2-1**, entries 2–4). I found that water plays a role in dissolving the substrate and catalyst in the reaction mixture. When the water content is too little, the reactants in the reaction system cannot be completely dissolved and fully reacted (**Table 2-1**, entry 4). However, when the amount of water is too much, it will affect the hydrogen bond between the catalyst and the substrate, resulting in a decrease in yield (**Table 2-1**, entry 3). When the solvent was a mixture of acetonitrile and water (10:1), giving the alkylated product **2-3a** with better yield in 72%. When the amount of NaDT was increased to 3 mol%, the product yield slightly increased (**Table 2-1**, entry 5). But there was no significant change in the product yield when the amount of NaDT was further increased to 4 mol% (**Table 2-1**, entry 6). When prolonged the reaction time, the yield increased to 83% at most (**Table 2-1**, entries 7 and 8). I speculate that this may be because the boronic acid group of **2-3a** also forms hydrogen bonds with NaDT, inhibiting the alkylation of **2-1a**, probably due to that the boronyl group of the product **2-3a** can also form hydrogen bond with NaDT and inhibits the approach of the remaining reactant **2-1a** to the catalyst. Therefore, I prolonged the reaction time to 36 h, and the yield of **2-3a** slightly increased to 82% (**Table 2-1**, entry 9). When a larger amount of NaDT was added, the yield of **2-3a** reached to 83% (**Table 2-1**, entry 10). In the case of smaller scale (0.200 mmol), the yield of product **2-3a** was improved compared with the result

of **Table 2-1**, entry 2 (entry 11). In the 0.200 mmol scale, I found the yield gradually increases with the extension of reaction time. However, when the reaction time reaches 18 h (**Table 2-1**, entries 12), further prolonging the reaction time almost no change in the yield of product **2-3a**. When the amount of catalyst is gradually increased (**Table 2-1**, entries 14 and 15), the yield was slightly improved. Compared to the 0.500 mmol scale reactions, the yield under the same conditions with 0.200 mmol scale exhibits a slight increase, but the trend of yield variation with respect to reaction conditions remains similar. Three equivalents of **2-2a** are a suitable dosage, and the yield of product **2-3a** decreased to 62% when the amount of **2-2a** is reduced to 2 equivalents (**Table 2-1**, entry 16). When the amount of **2-2a** is increased to 4 equivalents, there is no significant change in the yield (**Table 2-1**, entry 17). NaDT was suitable catalyst and the corresponding tetrabutylammonium salt decreased the yield of **2-3a** (**Table 2-1**, entry 18). After the reaction was completed, **2-1a** was converted to the product **2-3a** with 23% yield, and the remaining substrate **2-1a** did not undergo alkylation and no other by-products are generated. 405 nm light source can be utilized, and **2-3a** was obtained in 60% yield (**Table 2-1**, entry 19). UV light was essential to promote the reaction as the reaction without light irradiation did not proceed at all (**Table 2-1**, entry 20).



2-1a **2-3a**

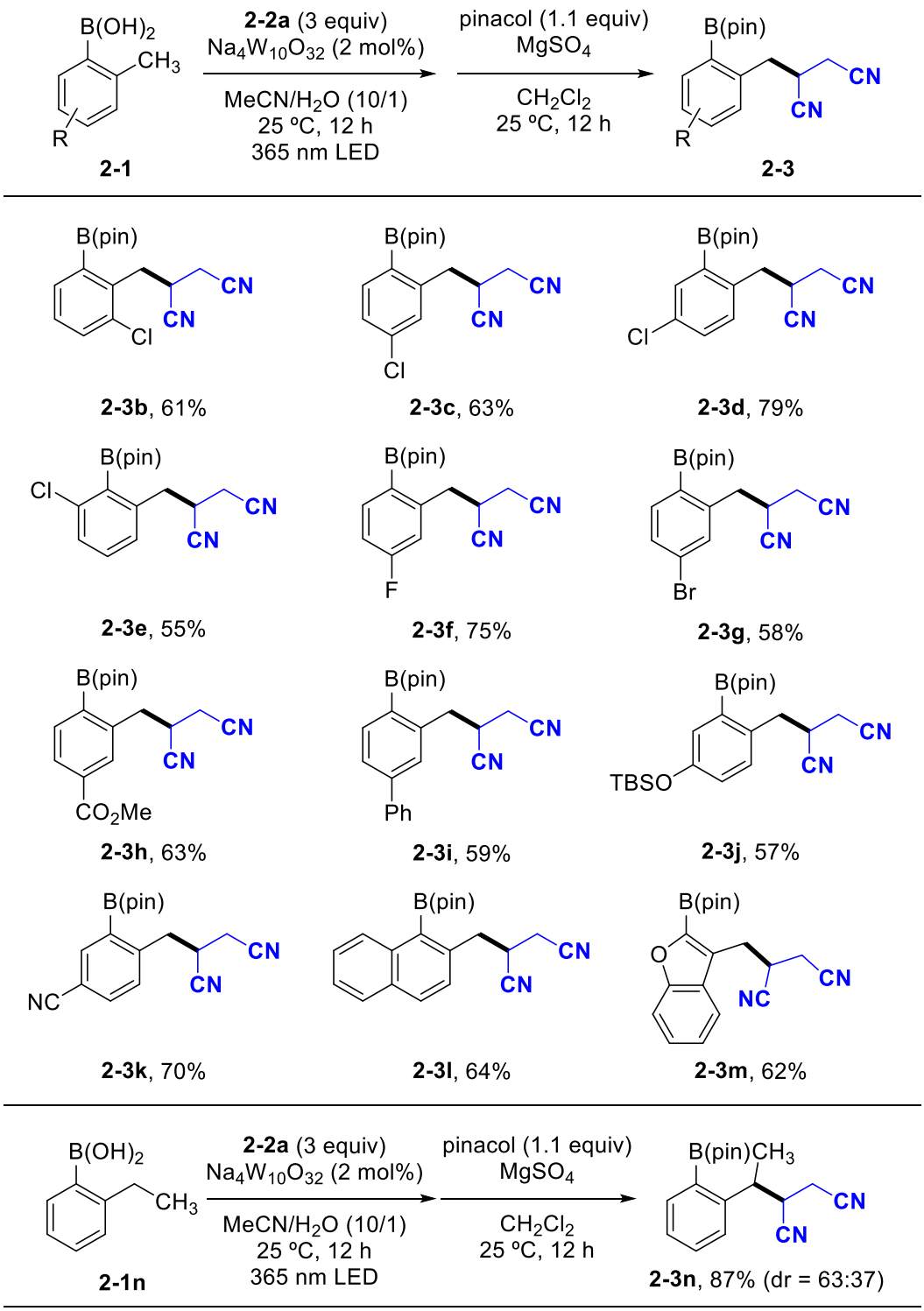
entry	solvent (5.0 mL)	NaDT (mol%)	**2-2a** (equiv)	light (nm)	Time (h)	yield (GC)
1	MeCN/H_2O = 20/1	2	3	365	12	62
2	**MeCN/H_2O = 10/1**	**2**	**3**	**365**	**12**	**72**
3	MeCN/H_2O = 5/1	2	3	365	12	54
4	MeCN	2	3	365	12	20
5	MeCN/H_2O = 10/1	3	3	365	12	74
6	MeCN/H_2O = 10/1	4	3	365	12	75
7	MeCN/H_2O = 10/1	3	3	365	18	78
8	MeCN/H_2O = 10/1	3	3	365	24	80
9	MeCN/H_2O = 10/1	3	3	365	36	82
10	MeCN/H_2O = 10/1	4	3	365	36	83
11[a]	MeCN/H_2O = 10/1	2	3	365	12	76
12[a]	MeCN/H_2O = 10/1	2	3	365	18	82
13[a]	MeCN/H_2O = 10/1	2	3	365	36	83
14[a]	MeCN/H_2O = 10/1	3	3	365	36	85
15[a]	MeCN/H_2O = 10/1	4	3	365	36	86
16	MeCN/H_2O = 10/1	2	2	365	12	62
17	MeCN/H_2O = 10/1	2	4	365	12	73
18[b]	MeCN/H_2O = 10/1	2	3	365	12	23
19	MeCN/H_2O = 10/1	2	3	405	12	60
20	MeCN/H_2O = 10/1	2	3	in dark	12	0

[a]0.200 mmol scale, 2.0 mL solvent; [b]TBADT instead of NaDT

Table 2-1. Optimizazion of reaction conditions

2.2.3 Scope of Boronic Acids and Alkenes

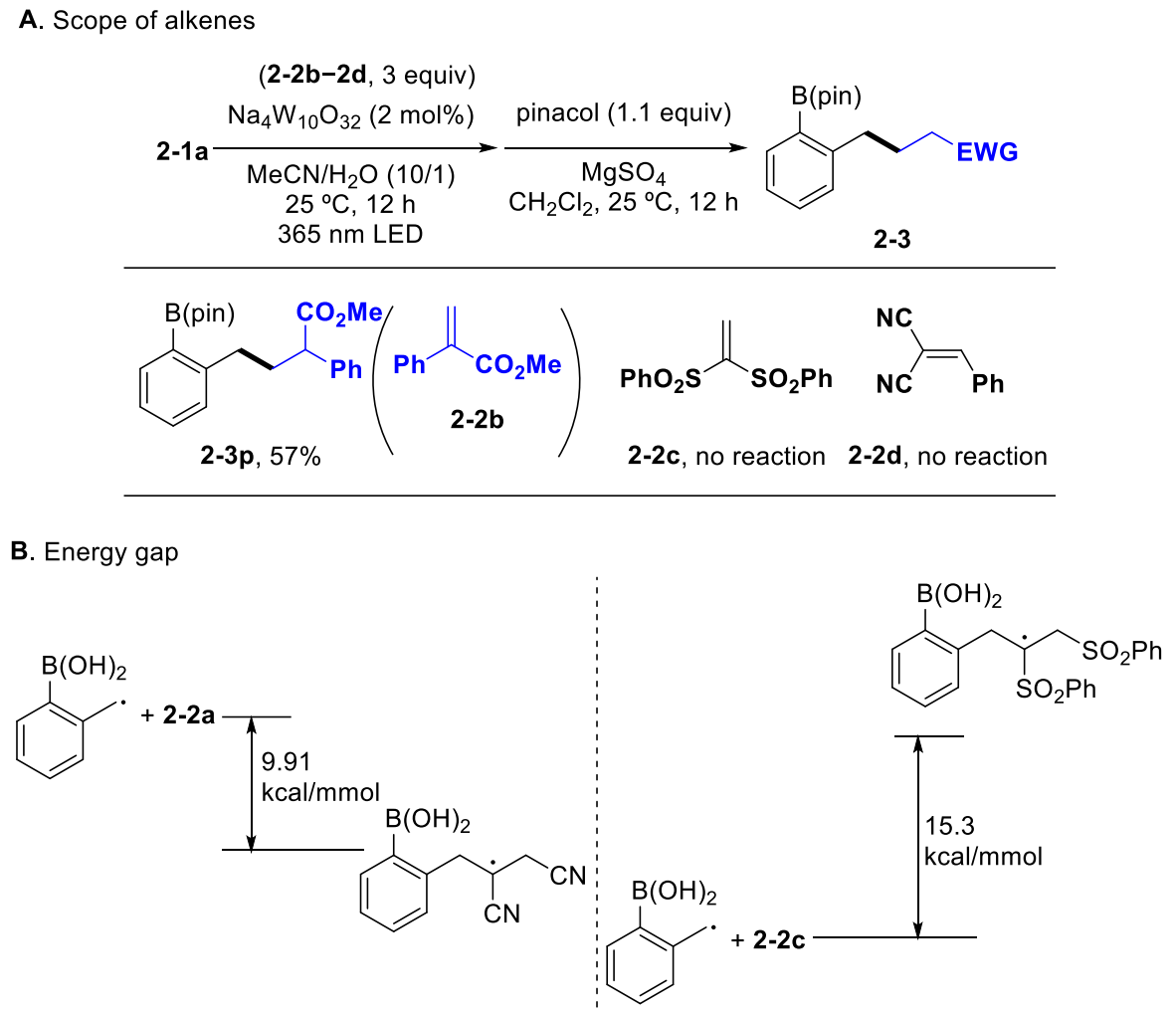
With the optimized reaction conditions: 2-methyphenylboronic acid (**2-1a**, 68.0 mg, 0.500 mmol), fumaronitrile (**2-2a**, 117 mg, 1.50 mmol, 3.0 equiv), $Na_4W_{10}O_{32}$ (NaDT, 24.4 mg, 0.0100 mmol, 2.0 mol%), and MeCN/H_2O (10/1, 5.0 mL) were added, and the resulting mixture was stirred at room temperature for 12 h under irradiation of UV light (365 nm). A variety of 2-methylphenylboronic acid derivatives **2-1** were reacted with **2-2a** to give alkylated products **2-3** (**Scheme 2-5**). Firstly, 2-methylphenylboronic acids which have a chlorine atom at four distinct positions were investigated. The investigation focused on elucidating the impact of the substitution positions on the phenyl ring. The substrates having a chlorine atom at 3- (**2-1b**), 4- (**2-1c**), 5- (**2-1d**), or 6- (**2-1e**) position were reacted with **2-2a**, and they gave alkylated products **2-3b-2-3e** in moderate to good yields. Notably, the steric effect of the chlorine atom at 3- and 6-positions did not affect the efficiency so much. When the chlorine atom exists at 5-position, the yield of alkylated product **2-3d** was the best (79%), which was higher than the yield of **2-3a**. And the boronic acid **1c** was also a suitable substrate, affording **2-3c** in 63% yield. Other halogen atoms (F and Br) were also tolerated and gave **2-3f** in good yield, but the yield of **2-3g** slightly decreased. A substrate bearing a phenyl group at the 4-position gave **2-3h** in 59% yield. Furthermore, functional groups, such as methoxycarbonyl, silyloxy and cyano groups successfully afforded alkylated products **2-3i**, **2-3j** and **2-3k** in 63%, 57% and 70% yield, respectively. 1-Naphthylboronic acid (**2-1l**) was also successfully converted to the alkylated product **2-3l** in 64% yield. Additionally, heteroaromatic substrate **2-1m** also provided the alkylated product **2-3m** in 62% yield. The methylene C(sp^3)–H alkylation of 2-ethylphenylboronic acid (**2-1n**) also proceeded well, and gave the corresponding alkylated product **2-3n** in 82% yield as a mixture of diastereomers (dr = 63:37). However, when (2-isopropylphenyl)boronic acid (**2-1o**) was reacted with **2-2a**, the yield of the alkylated product **2-3o** was less than 5%, although the bond dissociation energy (BDE) of the tertiary C(sp^3)–H bond of isopropylbenzene (84 kcal/mol) was lower than the C(sp^3)–H bond of toluene (88 kcal/mol), the steric effect of the isopropyl group of **2-3o** made the bulky catalyst NaDT hard to access the **2-3o**. Therefore, the alkylation of **2-3o** did not proceed well.



Scheme 2-5. Scope of (hetero)aryl boronic acids

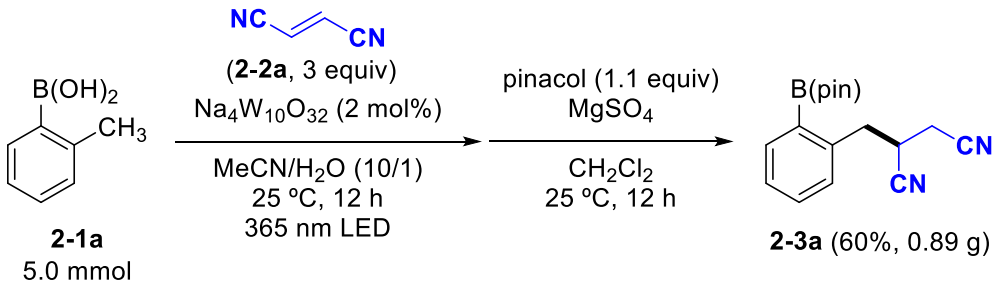
Although other alkenes, such as methyl 2-phenylacrylate (**2-2b**), (ethene-1,1-diyldisulfonyl)dibenzene (**2-2c**) and 2-benzylidenemalononitrile (**2-2d**), were treated with **2-1a** under the optimized conditions, only **2-2b** successfully gave the corresponding alkylated

product **2-3p** in 57% yield (**Scheme 2-6A**). The reaction with **2-2d** did not occur, probably due to the steric effect. In contrast, the steric effect in **2-2c** is relatively weaker than that in **2-2d**. To investigate the reason why **2-2c** did not undergo the reaction, I performed DFT (density functional theory) calculations and the energies of 2-boronic acid benzyl radical (radical of **2-1a**), **2-2a** and **2-2c** were calculated (B3LYP/6-31G(d) level of theory). The results are as follows: SOMO energy of radical species of **2-1a** is -4.63 eV; LUMO energy of **2-2a** is -3.06 eV; LUMO energy of **2-2c** is -1.70 eV. The energy gap between the SOMO of radical species of **2-1a** and LUMO of **2-2a** and the energy gap between the SOMO of radical of **2-1a** and LUMO of **2-2c** are 1.57 eV and 2.93 eV, respectively, and thus the latter energy gap is much larger than the former one. Therefore, it seems more difficult to promote the reaction of **2-2c** than that of **2-2a**, probably due to the energy gap. In addition, the process from benzyl radical to the formation of the adduct radical is non-equilibrium judging from the reported paper.[34] The DFT calculations (UB3LYP/6-31+G(d,p) level of theory) of reactants (benzylic radical and alkene) and corresponding radical products were performed. In the case of benzylic radical and **2-2a** as reactants, the energy of the corresponding radical adduct was 9.91 kcal/mmol lower than that of reactants. In contrast, the corresponding radical adduct of benzylic radical and **2-2c** was 15.3 kcal/mmol higher than that of reactants (**Scheme 2-6B**). According to these results, I consider the reaction of benzyl radical with **2-2c** is more difficult than that of benzylic radical with **2-2a**.



Scheme 2-6. Scope of alkenes

Under the optimized reaction conditions, 5 mmol-scale reaction of **2-1a** (0.680 g, 5.00 mmol) was performed, and product **2-3a** was obtained in 60% yield (0.890 g, **Scheme 2-7**). The yield of **2-3a** was not significantly decreased compared to the yield in 0.500 mmol -scale reaction (72%).



Scheme 2-7. 5 mmol-scale reaction

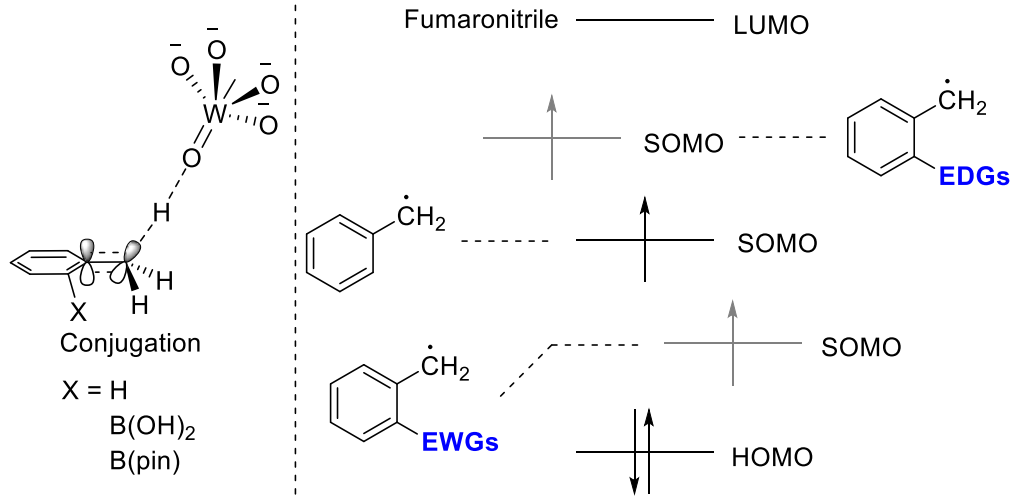
2.2.4 Mechanistic Studies

Due to the p-π conjugation effect, benzyl radicals have high stability. According to the frontier orbital theory, compared with benzyl radicals without any substituents, the energy level of SOMO orbital will be lower in benzyl radicals with electron-withdrawing groups (EWGs) on the benzene ring. On the other hand, the energy level of SOMO orbital will be higher in benzyl radicals with electron-donating groups (EDGs) on the benzene ring (**Scheme 2-8A**). The higher the energy level of SOMO orbital, the smaller the energy difference with the LUMO orbital of fumaronitrile (**Scheme 2-8A**). This is thought to improve reactivity. That is to say, the order of the reactivities of these radicals is as follows: benzyl radicals with EDGs > benzyl radical > benzyl radicals with EWGs (**Scheme 2-8A**).[35,36] Compared to benzyl radical, the *o*-boryl benzyl radicals have lower reactivity due to the electron-withdrawing ability of the boronyl group. Therefore, in the absence of other interactions, toluene demonstrates better reactivity than 2-methylphenylboronic acids (**Scheme 2-8A**).

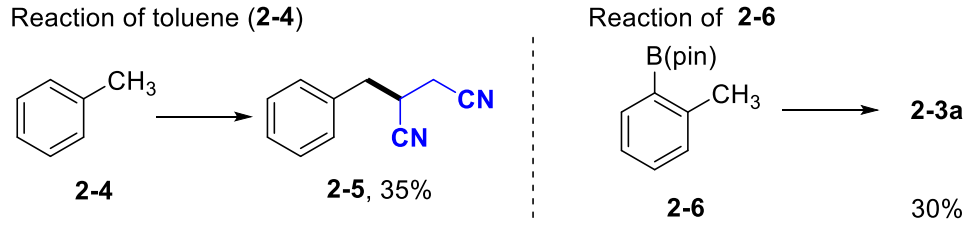
Then, under optimized conditions, the reactivity of toluene was compared with that of 2-methylphenylboronic acids. The reaction of **2-1a** gave **2-3a** in 72% yield. In contrast, alkylation of toluene (**2-4**) afforded the corresponding alkylated product **2-5** in only 35% yield, and the reaction of pinacol ester **2-6** afforded **2-3a** in 30% yield (**Scheme 2-8B**). I also compared the reaction rate of **2-4** and **2-1a**, comparing the change in products yields by changing the reaction time (5–25 min). As shown in **Figure 2-1**, the X- and Y-axes represent the reaction time and the concentration of the products, respectively. By increasing reaction time, the product concentration exhibits linear growth. However, the reaction rate of **2-1a** is 2.3 times faster than that of **2-4**. These results show the electron-withdrawing ability of the boronyl group is not the controlling factor and the free hydroxy group(s) of a boronyl group is important. In addition, the influence of the electronic properties of boronyl group was examined using *para*-tolylboronic acid (**2-7a**) and its pinacol ester (**2-7b**) (**Scheme 2-8C**). The yields of the corresponding alkylated product **2-3q** were similar to those of reaction **2-4**, indicating a negligible electronic effect of the boronyl group in the reactions of **2-1a** and **2-6**. To evaluate the interaction strength between the boronyl group and $[W_{10}O_{32}]^{4-}$, the reaction of 2,4-dimethylphenylboronic acid with **2-2a** was conducted (**Scheme 2-8D**). To limit the formation

of dialkylated products, the reaction was performed using 3 equiv of substrate **2-8** relative to **2-2a** over 4 h. Boronic acid **2-8a** yielded the proximal alkylated product **2-3r** and the distal alkylated product **2-3r** in 14% and 9% yields, respectively. In contrast, the pinacol ester **2-8b** gave **2-3r** and **2-3r'** in 5% and 13% yields, respectively. These results suggest that there is an interaction between boronyl group and the decatungstate catalyst, even though the interaction is relatively weak.

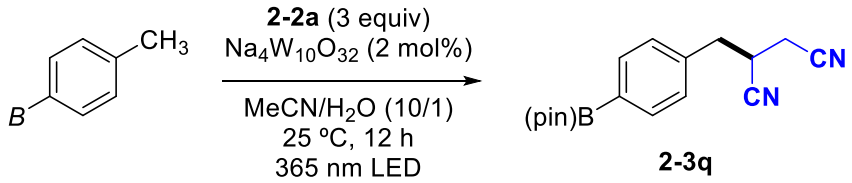
A. Reactivity of benzyl radicals



B. Decatungstate-catalyzed benzylic C(sp^3)–H addition to fumaronitrile (**2-2a**)



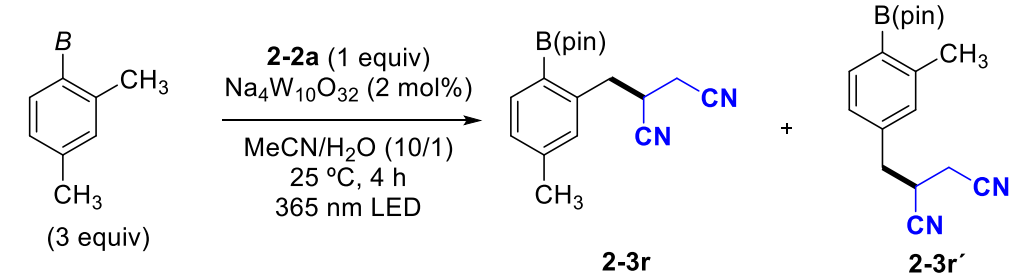
C. Electronic effect of boronyl groups



B = $B(OH)_2$ (**2-7a**) from **2-7a**[a] 36%
B(pin) (**2-7b**) from **2-7b** 33%

[a]After treatment with pinacol/$MgSO_4$

D. Selectivity in the reaction of 2,4-dimethylphenylboronic acid derivatives **2-8a** and **2-8b**



B = $B(OH)_2$ (**2-8a**) from **2-8a**[a] 14% 9%
B(pin) (**2-8b**) from **2-8b** 5% 13%

[a]After treatment with pinacol/$MgSO_4$

Scheme 2-8. Decatungstate-catalyzed benzylic C(sp^3)−H alkylation

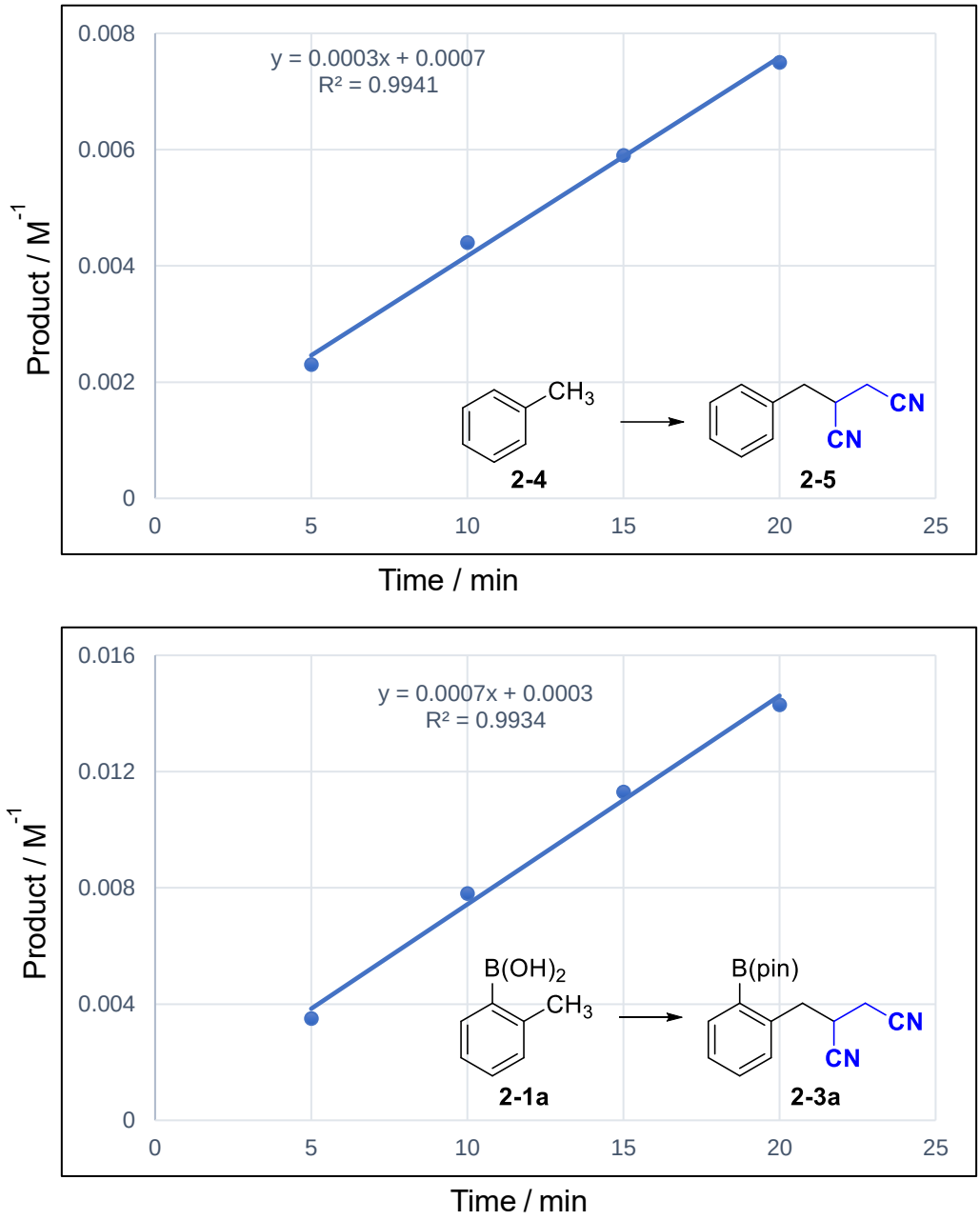
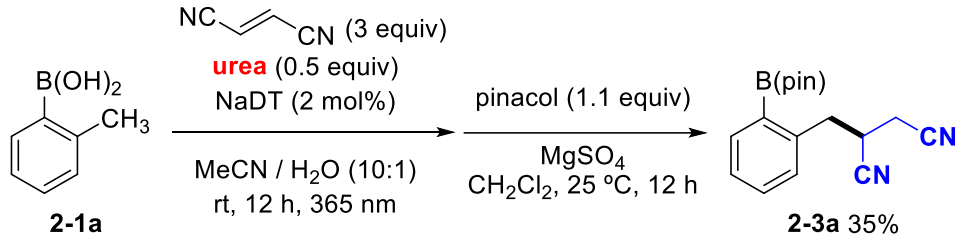


Figure 2-1. The yield trend curves for the C(sp³)–H alkylation reactions of **2-4** and **2-1a** at different photoreaction times.

Since the proton signals of hydroxy groups in the boronyl group were not detected by ^{1}H NMR, I cannot confirm the presence of hydrogen bond by the ^{1}H NMR spectrum of **2-1a** with or without addition of NaDT. On the other hand, when the ratio of water in the mixed solvent increased (changing the ratio of MeCN/H_2O from 10:1 to 5:1), the yield of the alkylated product significantly decreased from 72% to 54% (see **Table 2-1**). This result indicates that an excess

amount of water weakens the hydrogen bond between decatungstate and **2-1a**, whereas an appropriate amount of water facilitates the reaction. To further verify the hydrogen bond, I added urea, a hydrogen bond inhibitor, into the reaction. As a result, the yield of the alkylation product **2-3a** was dramatically decreased to 35% (**Scheme 2-9**). This result suggests the presence of hydrogen bonding between **2-1a** and decatungstate.



Scheme. 2-9. Inhibition of C(sp^3)-H alkylation by urea

Lewis acid-base interaction between the boronyl group of substrates and NaDT is another possible interaction. Therefore, I also investigated ^{11}B NMR experiments to deny the existence of Lewis acid-base interaction between the boronyl group of **2-1a** and NaDT.

1) **2-1a** (4.08 mg, 0.0300 mmol) was dissolved in MeCN/H_2O (10/1, 1.0 mL), and the solution was analyzed by ^{11}B NMR (δ 30.7).
2) **2-1a** (4.08 mg, 0.0300 mmol, 1.0 equiv) and $Na_4W_{10}O_{32}$ (73.3 mg, 0.0300 mmol, 1.0 equiv) were dissolved in MeCN/H_2O (10/1, 1.0 mL), and the solution was analyzed by ^{11}B NMR (δ 30.7).

The reported chemical shift values of 2-methyphenylboronic acid and 4-hexylphenylboronate in ^{11}B NMR (128 MHz, DMSO-d_6+D_2O or 96 MHz, D_2O) spectra are 29.6 ppm[37] and 5.89 ppm,[38] respectively. Therefore, the ^{11}B NMR spectrum of **2-1a** (30.7 ppm) dissolved in a mixed solvent of acetonitrile and water is that of 2-methyphenylboronic acid rather than of the 2-methyphenyl trihydroxyborate. The change of chemical shift was not observed compared to the solution of **2-1a** (**Figure 2-2**), indicating there are no Lewis acid-base interactions between **2-1a** and $Na_4W_{10}O_{32}$.

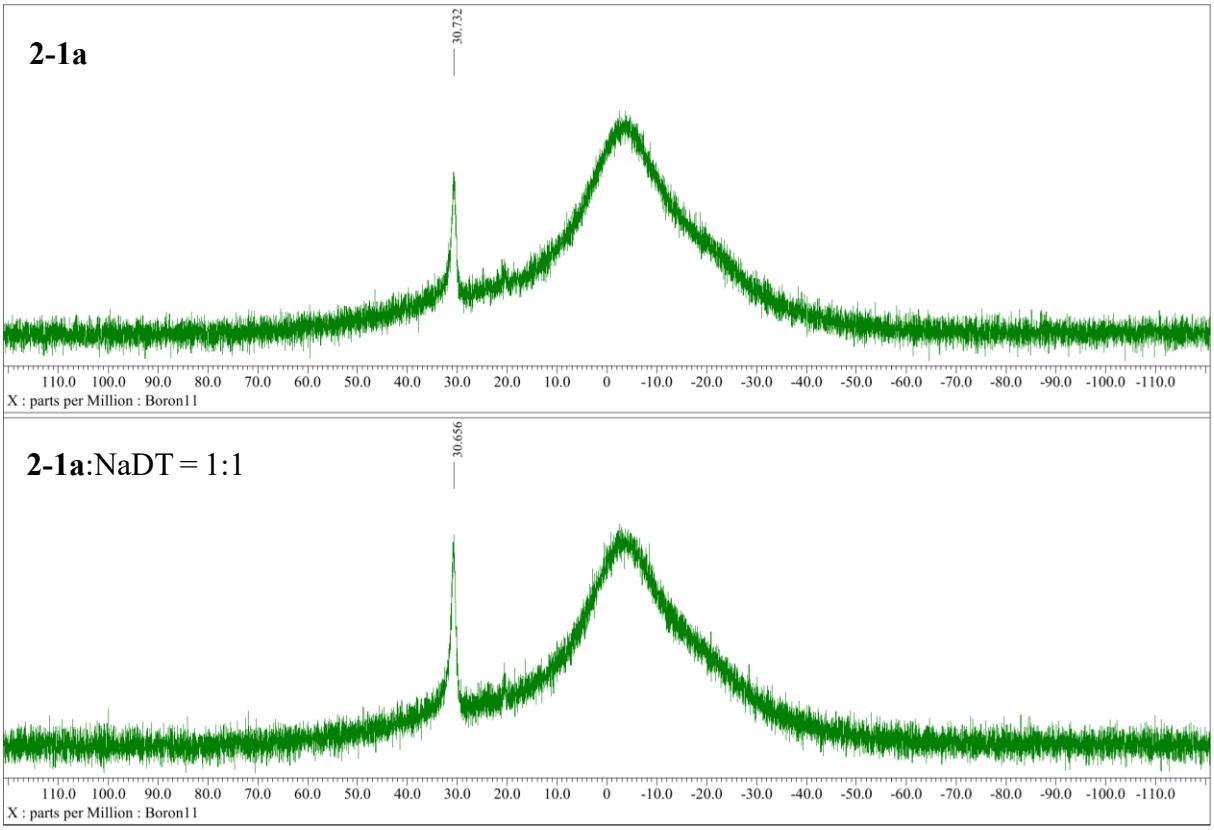
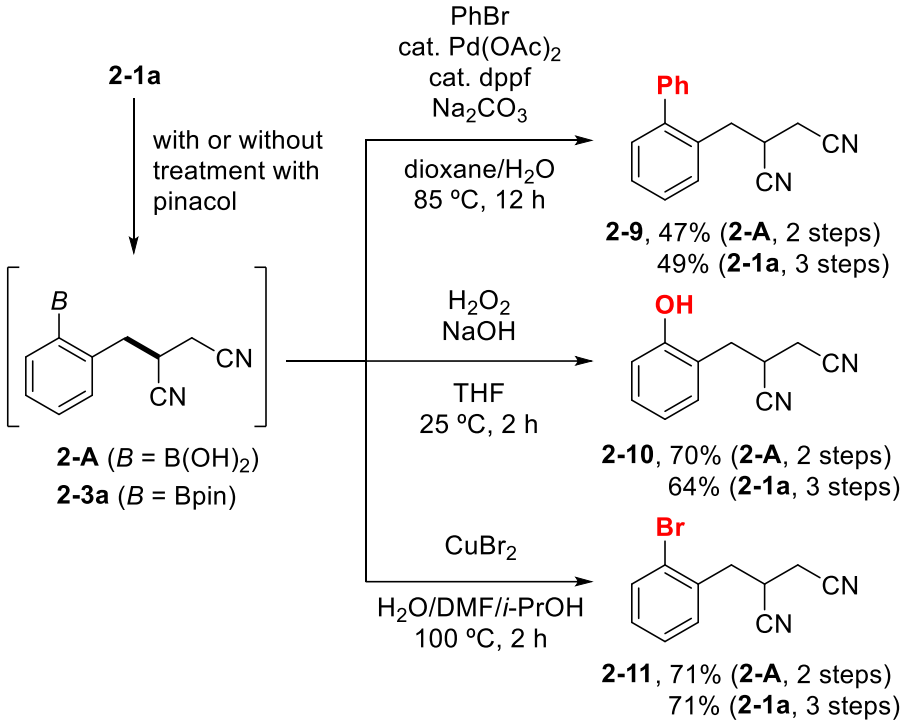


Figure 2-2. ^{11}B NMR spectra of **2-1a** and a mixture of **2-1a** and NaDT (1:1)

2.2.5 Transformations of Boronyl Group in Alkylated Products

I investigated the transformations of the boronyl group of the alkylated products (**Scheme 2-10**). After the alkylation of **2-1a**, the resulting mixtures were directly utilized in subsequent transformations without purification after solvent removal under vacuum. Upon conducting Suzuki-Miyaura cross-coupling reactions of either **2-A** or **2-3a** with bromobenzene, the biaryl product **2-9** was obtained in 47% and 49% yields, respectively. Oxidation of **2-A** or **2-3a** with H_2O_2/NaOH yielded the corresponding phenol derivative **2-10** in 70% and 64% yields, respectively. Additionally, bromination of **2-A** or **2-3a** with $CuBr_2$ successfully produced aryl bromide **2-11** in 71% yield.



Scheme 2-10. Transformations of boronyl and pinacolboryl groups of alkylated products

2.3 Conclusion

In conclusion, I have developed a benzylic C(sp^3)−H alkylation method facilitated by a free-boronyl group, utilizing electron-deficient alkenes as coupling partners. The decatungstate-catalyzed C(sp^3)−H alkylation of *ortho*-tolylboronic acid demonstrated higher efficiency compared to toluene or pinacol ester, suggesting the presence of noncovalent interactions between the free boronyl group and the electron-rich $[W_{10}O_{32}]^{4-}$ anion. In addition, the results of several experiments suggest the existence of hydrogen bond to promote the reaction efficiently. This approach allowed for the successful alkylation of various *ortho*-tolylboronic acid derivatives, including the methylene C(sp^3)−H alkylation of (2-ethylphenyl)boronic acid. Additionally, the boronyl group in the alkylated products was readily transformed into other functional groups, such as phenyl, hydroxyl, and bromo groups, without purification of the intermediates.

On the other hand, the low hydrogen bond ability of the boronyl group was also highlighted. Therefore, I decided to investigate the need to utilize stronger hydrogen bond between the substrate and catalyst to control the site-selectivity of the reaction as well as to improve the reaction efficiency in Chapter 3.

2.4 Experimental Section

2.4.1. General

All reactions were carried out under nitrogen atmosphere unless otherwise noted. ^{1}H (400 MHz), ^{13}C (101 MHz) and ^{11}B (128 MHz) NMR spectra were recorded using a JEOL ECZ400 spectrometer, and ^{1}H (600 MHz) spectra were recorded using a JEOL JNM-ECA600 spectrometer. Proton chemical shifts are reported relative to residual solvent peak ($CDCl_3$ at δ 7.26 ppm, CD_3OD at δ 3.31 ppm and $(CD_3)_2CO$ at δ 2.05 ppm). Carbon chemical shifts are reported relative to $CDCl_3$ at δ 77.0 ppm, CD_3OD at δ 49.0 ppm and $(CD_3)_2CO$ at δ 29.8 ppm). Boron chemical shifts are reported relative to $BF_3 \cdot OEt_2$ at δ 0.0 ppm. High resolution mass spectra (HRMS) were recorded on JEOL JMS-700 (EI) and JEOL JMS-700 (FAB) spectrometer. Double-focusing mass spectrometer (DFMS) was used for the HRMS measurements. Infrared (IR) spectra were recorded on Fourier transform infrared spectrophotometer (JASCO FT/IR-4200). Controller 8332A (CCS) and LED light heads AC8361 (λ = 365 nm, CCS) were used as light sources and set to 100% power as the emission spectrum and controller 8332C (CCS) and LED light heads AC8375-405 (λ = 405 nm, CCS) were used as light sources and set to 80% power as the emission spectrum (the distance from light source to the irradiation vessel: <5 mm, Figure S1). The emission spectra of AC8361 and AC8375 are provided by CCS. Borosilicate Schlenk flasks (50 mL, outer diameter: 2.5 cm) were used as photoreaction vessel.

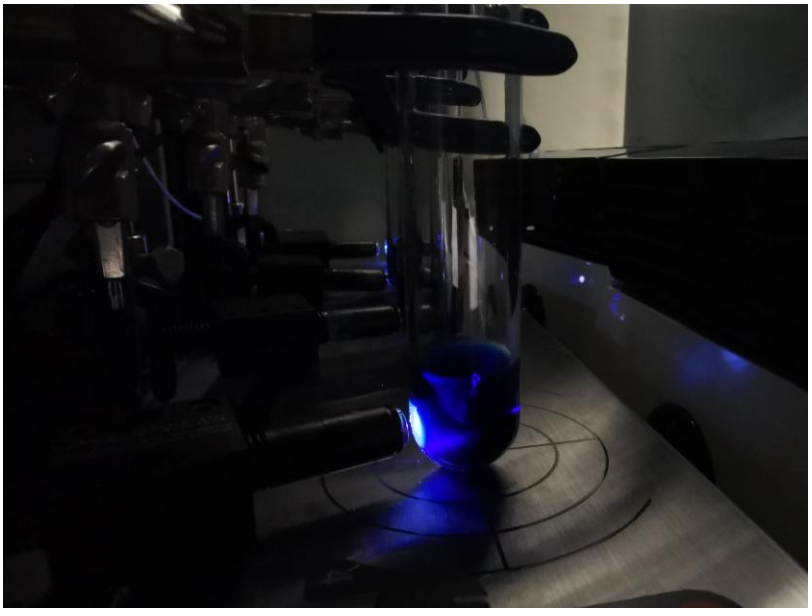


Figure 2-2. Reaction setup

2.4.2. Materials

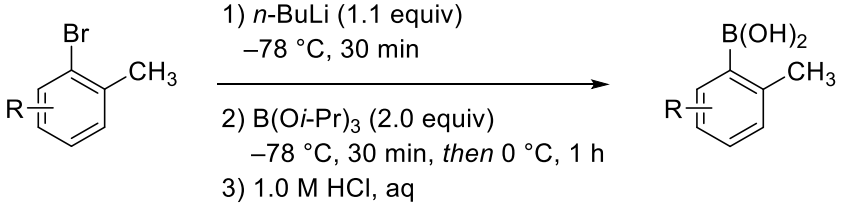
***Solvents, catalysts, and reagents*:** Acetonitrile was distilled over calcium hydride and degassed prior to use. Distilled water was degassed prior to use. Decatungstate photocatalysts $Na_4W_{10}O_{32}$ and ($^nBu_4N_4$)$W_{10}O_{32}$ were prepared according to the reported procedure.[39] The other reagents were purchased from commercial sources and used without further purification.

***Arylboronic acids*:** Boronic acids **2-1a**, **2-1b**–**1d** and **2-1f**–**1h** were purchased from commercial sources and used without further purification.

Synthesis of decatungstate photocatalyst $Na_4W_{10}O_{32}$

To a 3 L beaker containing a boiling solution (95 °C) of $Na_2WO_4{\cdot}2H_2O$ (33.0 g, 100 mmol) in deionized water (200 mL), a boiling aqueous solution (95 °C) of HCl (1.0 M, 200 mL) was added. The resulting solution was allowed to boil for 30 s, then rapidly cooled to 30 °C in a dry ice/methanol bath with stirring. Sodium chloride was added to near saturation, then the mixture was cooled to 0 °C. The precipitates were filtered, washed with cooled brine, and dried in vacuum overnight. The precipitate was suspended in hot acetonitrile (80 mL), then filtered, and the filtrate was placed in a freezer (–20 ºC) overnight. The crystal was filtered and dried in vacuum to afford $Na_4W_{10}O_{32}$ (12.2 g, 5.00 mmol, 50%) as a colorless block crystal.

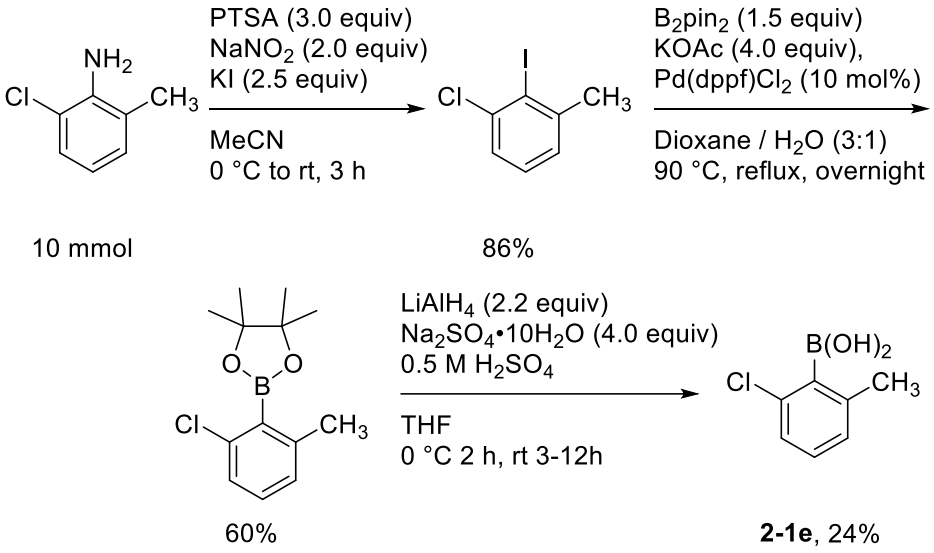
***Synthesis of arylboronic acids 2-1e, 2-1i–1o, 2-7a and 2-8a*[40]**



General Procedure I: An aryl bromide (5.00 mmol, 1.0 equiv) was dissolved in THF (20 mL) and cooled to –78 °C. *n*-BuLi (1.6 M in *n*-hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) was added dropwise and the mixture was stirred for 30 min. B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) was added dropwise and the mixture was stirred for 30 min. The reaction mixture was then

allowed to warm to 0 °C and was stirred at the same temperature for 1 h. The reaction mixture was then quenched with 1.0 M HCl (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting mixture was purified by column chromatography on silica gel and recrystallization in hexanes/EtOAc.

Synthesis of (2-chloro-6-methylphenyl)boronic acid (2-1e)

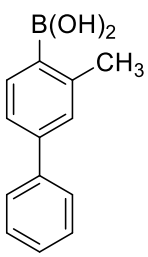


To a Schlenk tube containing 2-chloro-6-methylaniline (1.42g, 10.0 mmol, 1.0 equiv) and MeCN (30 mL), *p*-toluenesulfonic acid monohydrate (PTSA·H_2O, 5.73 g, 30.0 mmol, 3.0 equiv) was added and the mixture was stirred at room temperature for 10 min. After cooling to 0 °C, $NaNO_2$ (1.38 g, 20.0 mmol, 2.0 equiv) in H_2O (15 mL) and KI (4.15 g, 25.0 mmol, 2.5 equiv) in H_2O (20 mL) were added dropwise. The mixture was stirred at 0 for 10 min, then warm to 25 °C and stirred for 3 h. H_2O (50 mL) was added to the mixture and the pH was adjusted to around 10 by the addition of aq. $NaHCO_3$ (1.0 M). $Na_2S_2O_3$ (2.0 M, 60 mL) was added to the mixture and the organic materials were extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane) to afford 1-chloro-2-iodo-3-methylbenzene (1.22 g, 86%) as a light-yellow oil.[32]

To a solution of 1-chloro-2-iodo-3-methylbenzene (2.17 g, 8.60 mmol, 1.0 equiv) and bis(pinacolato)diboron (3.28 g, 12.9 mmol, 1.5 equiv) in dioxane/H_2O (3:1, 140 mL) were added $PdCl_2$(dppf) (629 mg, 0.860 mmol, 10 mol%) and KOAc (3.38 g, 34.4 mmol, 4.0 equiv). The resulting mixture was degassed and refilled with N_2 for three times and stirred at 90 °C in an oil bath for 12 h under N_2 atmosphere. Then the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (hexane/EtOAc = 8/1) to afford 2-(2-chloro-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.30 g, 60%).

To a suspension of $LiAlH_4$ (431 mg, 11.4 mmol, 2.2 equiv) in anhydrous THF (28 mL) was added dropwise a solution of 2-(2-chloro-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.30 g, 5.16 mmol, 1.0 equiv) in anhydrous THF (13 mL) at 0 ºC. The mixture was stirred at 0 °C for 2 h and then at room temperature for 1 h. $Na_2SO_4 \cdot 10H_2O$ (6.65 g, 20.6 mmol, 4.0 equiv) was added to the reaction mixture. The aluminum salts were dissolved by the addition of aq. H_2SO_4 (0.5 M). The obtained aqueous solution was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure.[41] Purification by column chromatography on silica gel (hexane/EtOAc = 5/1) afforded pure **2-1e** (211 mg, 1.24 mmol, 24%) as a white solid.[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.14 (m, 2H), 7.06 (d, *J* = 6.8 Hz, 1H), 4.96 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 136.2, 130.2, 127.6, 125.7, 22.1. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.8. HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_7H_8O_2BCl$: 170.0306, Found: 170.0308.

(3-Methyl-[1,1´-biphenyl]-4-yl)boronic acid (2-1i)

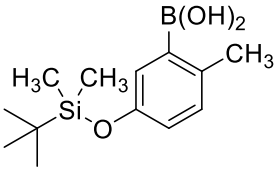


2-1i

2-Bromo-5-iodotoluene (1.78 g, 6.00 mmol, 1.0 equiv), phenylboronic acid (732 mg, 6.00 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (210 mg, 0.300 mmol, 5.0 mol%), aq. Na_2CO_3 (2.0 M, 6.0 mL), and toluene (18 mL) were added to two neck flask and the mixture was stirred under reflux (115 °C) for 30 min, and then the reaction mixture was cooled to room temperature and an organic layer was washed with distilled water. After drying with $MgSO_4$ and filtration, 4-bromo-3-methyl-1,1´-

biphenyl (1.33g, 90%) was obtained by column chromatography on silica gel (hexane). According to the *General Procedure I*, 4-bromo-3-methyl-1,1′-biphenyl (1.33 g, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-1i** (742 mg, 3.50 mmol, 70%) as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 4/1).[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.6 Hz, 1H), 7.70-7.66 (m, 2H), 7.62-7.38 (m, 5H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 144.7, 140.7, 137.9, 129.3, 128.8, 127.7, 127.2, 123.9, 23.3. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{13}O_2B$: 212.1009, Found: 212.1010.

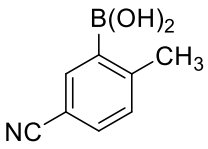
[5-((*tert*-Butyldimethylsilyl)oxy)-2-methylphenyl]boronic acid (2-1j)



2-1j

According to the *General Procedure I*, (3-bromo-4-methylphenoxy)(*tert*-butyl)dimethylsilane (1.50 g, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-1j** (905 mg, 3.40 mmol, 68%) as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 6/1).[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz 1H), 6.93 (dd, *J* = 8.0, 2.8 Hz, 1H), 2.75 (s, 3H), 1.01 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 139.0, 131.7, 128.3, 124.1, 25.7, 22.3, 18.2, –4.5. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 28.2; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{23}O_3BSi$: 266.1510, Found: 266.1508.

(5-Cyano-2-methylphenyl)boronic acid (2-1k)

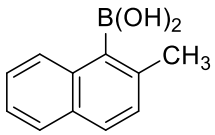


2-1k

According to the *General Procedure I*, 3-bromo-4-methylbenzonitrile (975 mg, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-1k** (491 mg, 3.05 mmol, 61%) as a white solid after

purification by column chromatography on silica gel (hexane/EtOAc = 4/1).[45] ^{1}H NMR (400 MHz, CD_3OD) δ 7.63-7.59 (m, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 4.90 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 147.3, 136.0, 133.3, 131.1, 120.1, 110.0, 22.4. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, CD_3OD) δ 30.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_8H_8NO_2B$: 161.0648, Found: 161.0649.

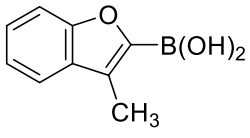
(2-Methylnaphthalen-1-yl)boronic acid (2-1l)



2-1l

$B(OMe)_3$ was used instead of B(O*i*-Pr)$_3$. According to the *General Procedure I*, 1-bromo-2-methylnaphthalene (1.10 g, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and $B(OMe)_3$ (1.04 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-1l** (512 mg, 2.75 mmol, 55%) as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 4/1).[46] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.76 (m, 3H), 7.49-7.40 (m, 2H), 7.33 (d, *J* = 8.8 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 135.0, 131.2, 128.9, 128.3, 128.2, 127.3, 126.3, 124.9, 22.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{11}H_{11}O_2B$: 186.0852, Found: 186.0852.

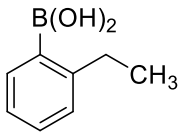
(3-Methylbenzofuran-2-yl)boronic acid (2-1m)



2-1m

The aryl lithium intermediate was generated by deprotonation of 3-methylbenzofuran. According to the *General Procedure I*, 3-methylbenzofuran (660 mg, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-1m** (510 g, 2.90 mmol, 58%) as a white solid after recrystallization.[47] ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.62 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35-7.31 (m, 1H), 7.23 (td, *J* = 7.8, 0.8 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 157.4, 130.8, 128.5, 126.2, 122.9, 121.0, 111.9, 9.0. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $(CD_3)_2CO$) δ 27.1; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_9H_9O_3B$: 176.0645, Found: 176.0644.

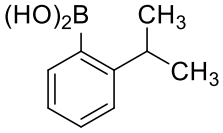
(2-Ethylphenyl)boronic acid (2-1n)



2-1n

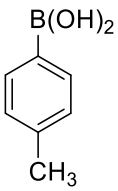
According to the *General Procedure I*, 1-bromo-2-ethylbenzene (920 mg, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-1n** (457 mg, 3.05 mmol, 61%) as a white solid after recrystallization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.50 (td, *J* = 7.6, 1.6 Hz, 1H), 7.34-7.30 (m, 2H), 3.23 (q, *J* = 7.6 Hz, 2H), 1.35 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 137.4, 132.4, 129.2, 125.3, 28.9, 17.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.7.

(2-Isopropylphenyl)boronic acid (2-1o)



According to the *General Procedure I*, 1-bromo-2-isopropylbenzene (995 mg, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-1o** (459 mg, 2.80 mmol, 56%) as a white solid after recrystallization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.54 (td, *J* = 7.4, 1.4 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.31 (td, *J* = 7.4, 1.4 Hz, 1H),4.16-4.09 (m, 1H), 1.36 (d, *J* = 7.2, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 137.4, 132.7, 125.3 (2C), 31.7, 24.5. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9.

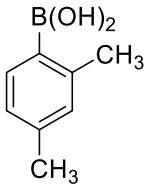
(4-Methylphenyl)boronic acid (2-7a)



2-7a

According to the *General Procedure I*, 1-bromo-4-methylbenzene (950 mg, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-7a** (619 mg, 4.55 mmol, 91%) as a white solid after recrystallization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 133.7, 128.8, 21.9. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.1.

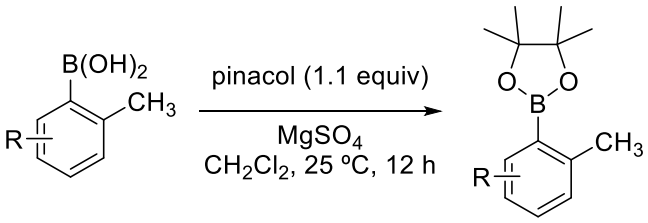
(2,4-Dimethylphenyl)boronic acid (2-8a)



2-8a

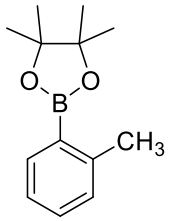
According to the *General Procedure I*, 1-bromo-2,4-dimethylbenzene (920 mg, 5.00 mmol, 1.0 equiv), *n*-BuLi (1.6 M in hexane, 3.4 mL, 5.50 mmol, 1.1 equiv) and B(O*i*-Pr)$_3$ (1.88 g, 10.0 mmol, 2.0 equiv) were used to obtain product **2-8a** (563 mg, 3.75 mmol, 75%) as a white solid after recrystallization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 1H), 7.13-7.10 (m, 2H), 2.78 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 142.4, 137.4, 131.5, 126.0, 23.0, 21.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.2.

Synthesis of arylboronic acid pinacol esters



General Procedure II: Arylboronic acid (5.00 mmol, 1.0 equiv), pinacol (5.50 mmol, 1.1 equiv) and $MgSO_4$ (36.3 mmol, 6.6 equiv) were added in a reaction flask, then dichloromethane (10 mL) was added. The mixture was stirred at 25 °C for 12 h. After filtration, the solvent was removed under reduced pressure. The resulting crude material was purified by column chromatography on silica gel to afford arylboronic acid pinacol esters.

(2-Methylphenyl)boronic acid pinacol ester (2-6)

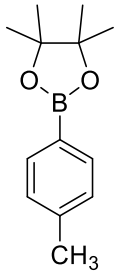


2-6

According to the *General Procedure II*, product **2-6** (982 mg, 4.50 mmol, 90%) was obtained as a colorless liquid after purification by column chromatography on silica gel (hexane/Et_2O = 15/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6, 1H), 7.35 (td, *J* = 7.6, 1.6 Hz, 1H), 7.22-7.17 (m, 2H), 2.59 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 135.8,

130.8, 129.7, 124.7, 83.3, 24.8, 22.2. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.2.

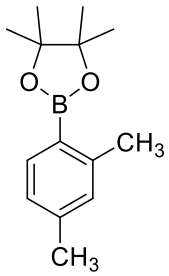
(4-Methylphenyl)boronic acid pinacol ester (2-7b)



2-7b

According to the *General Procedure II*, product **2-7b** (982 mg, 4.50 mmol, 90%) was obtained as a colorless liquid after purified by column chromatography on silica gel (hexane/Et_2O = 15/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8, Hz, 2H), 2.37 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 134.8, 128.5, 83.6, 24.8, 21.7. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.8.

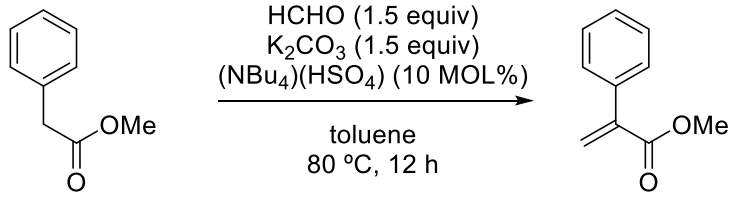
(2,4-Dimethylphenyl)boronic acid pinacol ester (2-8b)



2-8b

According to the *General Procedure II*, product **2-8b** (1.07 g, 4.60 mmol, 92%) was obtained as a colorless liquid after purified by column chromatography on silica gel (hexane/EtOAc = 50/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 6.8 Hz, 1H), 7.06 (s, 1H) 7.05 (d, *J* = 6.8 Hz, 1H), 2.58 (s, 3H), 2.38 (s, 3H), 1.39 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 140.8, 136.1, 130.7, 125.5, 83.1, 24.8, 22.1, 21.4. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.1.

Synthesis of methyl 2-phenylacrylate (2-2b)[32]



2-2b

To a 300 mL two-necked flask with a reflux condenser, methyl 2-phenylacetate (4.51 g, 30.0 mmol, 1.0 equiv), paraformaldehyde (1.35 g, 45.0 mmol, 1.5 equiv), K_2CO_3 (6.22 g, 45.0

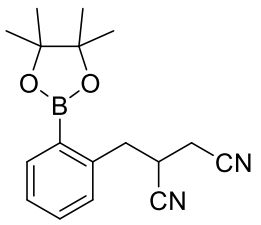
mmol, 1.5 equiv), and tetrabutylammonium hydrogen sulfate (1.02 g, 3.00 mmol, 10 mol%) were added. This mixture was dissolved in toluene and the solution was stirred at 80 °C for 12 h. After cooling to room temperature, water (200 mL) was added and the organic materials were extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane) to afford alkene **2-2b** (3.41 g, 21.0 mmol, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 6.37 (d, J = 1.2 Hz, 1H), 5.90 (d, J = 1.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 141.2, 136.7, 128.3 (2C), 128.2, 128.1 (2C), 127.0, 52.2.

2.4.3. Scope of Substrates and Alkenes (Scheme 2-5–7)

Reaction of ortho-tolylboronic acid (2-1a)

General Procedure III: To a Schlenk tube, 2-methyphenylboronic acid (**2-1a**, 68.0 mg, 0.500 mmol), fumaronitrile (**2-2a**, 117 mg, 1.50 mmol, 3.0 equiv), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%), and MeCN/H_2O (10/1, 5.0 mL) were added, and the resulting mixture was stirred at room temperature for 12 h under irradiation of UV (365 nm). After the reaction, the volatiles were removed under reduced pressure, and pinacol (65.0 mg, 0.550 mmol, 1.1 equiv), $MgSO_4$ (400 mg), and CH_2Cl_2 (1.0 mL) were added to the tube. After 12 h, the resulting mixture was purified by column chromatography on silica gel (hexane/EtOAc = 8/1) to afford **2-3a** (107 mg, 0.360 mmol, 72%).

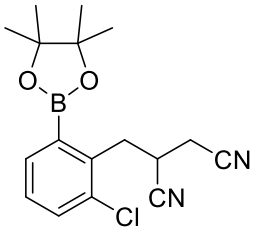
2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3a)



2-3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.2, 1.6 Hz, 1H), 7.45 (td, J = 7.2, 1.6 Hz, 1H), 7.33 (td, J = 7.2, 1.2 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 3.33-3.26 (m, 3H), 2.75-2.64 (m, 2H), 1.37 (s, 6H), 1.36 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 137.3, 131.8, 130.4, 127.3, 119.0, 115.8, 84.1, 37.8, 31.0, 24.93, 24.86, 20.4. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.7; HRMS (EI-DFMS) m/z: $[M]^+$ Calcd for $C_{17}H_{21}N_2O_2B$: 296.1696, Found: 296.1695.

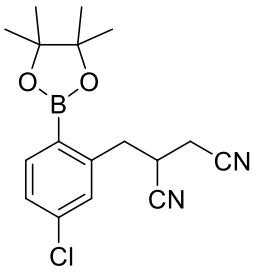
2-[2-Chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3b)



2-3b

According to the *General Procedure III*, the reaction was carried out using **2-1b** (85.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3b** (101 mg, 0.305 mmol, 61%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 3.83-3.76 (m, 1H), 3.42-3.33 (m, 2H), 2.82 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.72 (dd, *J* = 16.8, 5.6 Hz, 1H), 1.39 (s, 6H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 135.8, 135.0, 132.7, 128.6, 118.5, 115.7, 84.6, 33.3, 29.4, 24.9, 24.8, 20.7. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.5; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{17}H_{21}ClN_2O_2B$: 331.1385, Found: 331.1385.

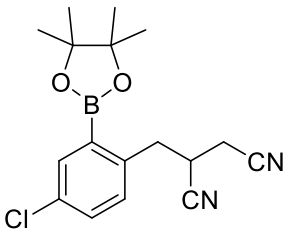
2-[5-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3c)



2-3c

According to the *General Procedure III*, the reaction was carried out using **2-1c** (85.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3c** (104 mg, 0.315 mmol, 63%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 3.33-3.23 (m, 3H), 2.73-2.72 (m, 2H), 1.363 (s, 6H), 1.359 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 138.7, 137.9, 130.3, 127.6, 118.6, 115.5, 84.4, 37.3, 30.9, 24.9, 24.8, 20.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.6; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{17}H_{21}ClN_2O_2B$: 331.1385, Found: 331.1381.

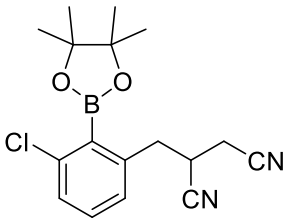
2-[4-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3d)



2-3d

According to the *General Procedure III*, the reaction was carried out using **2-1d** (85.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3d** (130 mg, 0.395 mmol, 79%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/CH_2Cl_2 = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 3.35-3.17 (m, 3H), 2.76-2.66 (m, 2H), 1.37 (s, 6H), 1.36 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 136.9, 133.7, 131.9, 131.6, 118.7, 115.5, 84.6, 37.1, 30.9, 24.9, 24.8, 20.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.2; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{17}H_{21}ClN_2O_2B$: 331.1385, Found: 331.1383.

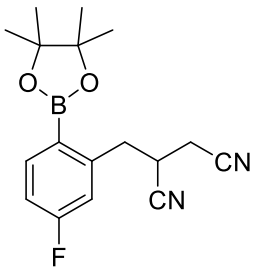
2-[3-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3e)



2-3e

According to the *General Procedure III*, the reaction was carried out using **2-1e** (85.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3e** (90.8 mg, 0.275 mmol, 55%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 4.4 Hz, 1H), 7.30 (d, *J* = 4.0 Hz, 1H), 7.18-7.13 (m, 1H), 3.41-3.34 (m, 1H), 3.14 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.98 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.68 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.57 (dd, *J* = 17.2, 6.8 Hz, 1H), 1.42 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 139.1, 131.2, 128.6, 127.9, 118.5, 115.5, 85.0, 37.9, 30.1, 25.1, 24.8, 19.8. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.8; HRMS (ET-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{17}H_{20}ClN_2O_2B$: 330.1306, Found: 330.1301.

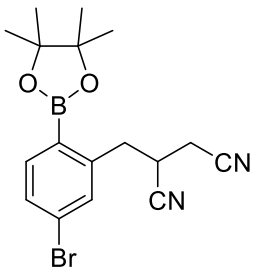
2-[5-Fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3f)



2-3f

According to the *General Procedure III*, the reaction was carried out using **2-1f** (77.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3f** (118 mg, 0.375 mmol, 75%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.0, 6.6 Hz, 1H), 7.04-6.98 (m, 2H), 3.37-3.27 (m, 3H), 2.78-2.67 (m, 2H), 1.362 (s, 6H), 1.357 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (d, *J* = 255 Hz), 148.8 (d, *J* = 7.8 Hz), 139.7 (d, *J* = 8.8 Hz), 118.6, 117.5 (d, *J* = 21.3 Hz), 115.5, 114.4 (d, *J* = 19.3 Hz) 84.3, 37.5, 30.9, 24.9, 24.8, 20.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.5; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{17}H_{21}FN_2O_2B$: 315.1680, Found: 315.1681.

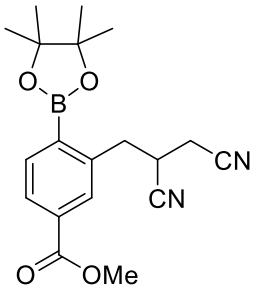
2-[5-Bromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3g)



2-3g

According to the *General Procedure III*, the reaction was carried out using **2-1g** (107 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3g** (109 mg, 0.280 mmol, 58%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 3.30-3.22 (m, 3H), 2.74-2.69 (m, 2H), 1.362 (s, 6H), 1.351 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 138.8, 133.2, 130.6, 126.5, 118.5, 115.5, 84.4, 37.3, 30.9, 24.9, 24.8, 20.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.5; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{17}H_{21}BrN_2O_2B$: 375.0879, Found: 375.0878.

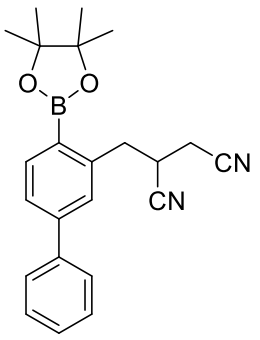
Methyl 3-(2,3-dicyanopropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2-3h)



2-3h

According to the *General Procedure III*, the reaction was carried out using **2-1h** (97.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3h** (112 mg, 0.315 mmol, 63%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 0.8 Hz, 2H), 7.91 (s, 1H), 3.93 (s, 3H), 3.36-3.25 (m, 3H), 2.73 (d, *J* = 6.0 Hz, 2H), 1.383 (s, 6H), 1.376 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 142.1, 137.4, 132.8, 130.8, 128.1, 118.6, 115.5, 84.6, 52.3, 37.5, 31.0, 24.92, 24.86, 20.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.6; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{19}H_{24}N_2O_4B$: 355.1833, Found: 355.1828.

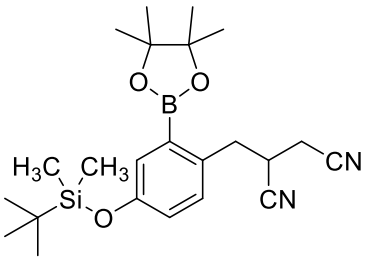
2-[(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-(1,1'-biphenyl)-3-yl)methyl]succinonitrile (2-3i)



2-3i

According to the *General Procedure III*, the reaction was carried out using **2-1i** (106 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3i** (110 mg, 0.295 mmol, 59%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.63-7.60 (m, 2H), 7.56 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.48-7.44 (m, 2H), 7.40-7.36 (m, 1H), 3.41-3.29 (m, 3H), 2.79-2.68 (m, 2H), 1.384 (s, 6H), 1.379 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 142.4, 140.1, 137.9, 129.1, 128.9, 128.0, 127.2, 125.9, 119.0, 115.7, 84.2, 37.9, 31.1, 24.94, 24.87, 20.5. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{25}N_2O_2B$: 372.2009, Found: 372.2009.

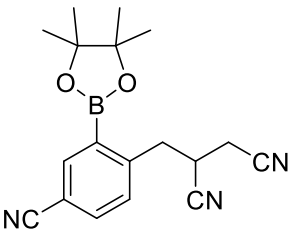
2-[4-((*tert*-Butyldimethylsilyl)oxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3j)



2-3j

According to the *General Procedure III*, the reaction was carried out using **2-1j** (133 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3j** (122 mg, 0.285 mmol, 57%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.8 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.89 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.25-3.22 (m, 3H), 2.68-2.65 (m, 2H), 1.36 (s, 6H), 1.35 (s, 6H), 0.99 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 134.3, 131.7, 128.5, 122.8, 119.1, 115.8, 84.1, 37.0, 31.1, 25.7, 24.91, 24.85, 20.3, 18.1, –4.4. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.6; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{36}N_2O_3SiB$: 427.2588, Found: 427.2592.

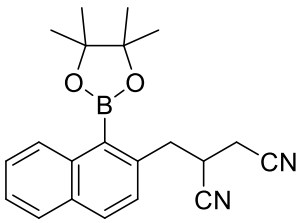
2-[4-Cyano-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3k)



2-3k

According to the *General Procedure III*, the reaction was carried out using **2-1k** (80.5 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3k** (112 mg, 0.350 mmol, 70%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 1.8 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 3.50-3.41 (m, 3H), 2.82-2.72 (m, 2H), 1.38 (s, 6H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 140.8, 134.7, 131.1,118.3, 118.2, 115.3, 111.7, 84.9, 37.6, 30.7, 24.9, 24.8, 20.8. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.1; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{20}N_3O_2B$: 321.1649, Found: 321.1647.

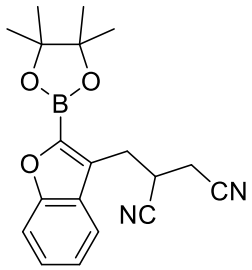
2-[(1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)methyl]succinonitrile (2-3l)



2-3l

According to the *General Procedure III*, the reaction was carried out using **2-1l** (93.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3l** (111 mg, 0.320 mmol, 64%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.55-7.47 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 3.50-3.41 (m, 2H), 3.32-3.26 (m, 1H), 2.73-2.62 (m, 2H), 1.502 (s, 6H), 1.497 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 137.0, 132.4, 131.2, 128.4, 128.1, 127.7, 126.9, 126.0, 119.0, 115.8, 84.6, 38.6, 30.9, 25.2, 25.0, 20.0. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.9; HRMS (FAB-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{23}N_2O_2B$: 346.1856, Found: 346.1852.

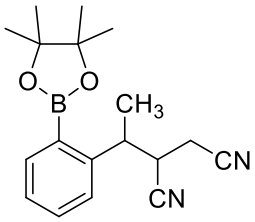
2-[(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-yl)methyl]succinonitrile (2-3m)



2-3m

According to the *General Procedure III*, the reaction was carried out using **2-1m** (88.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). Product **2-3m** (104 mg, 0.310 mmol, 62%) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.43-7.38 (m, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 3.52-3.40 (m, 2H), 3.37-3.30 (m, 1H), 2.73 (dd, *J* = 6.6, 1.8 Hz, 2H), 1.41 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 128.0, 127.1, 126.8, 123.2, 119.6, 118.6, 115.6, 112.5, 85.1, 29.4, 26.2, 24.9, 24.8, 20.4. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 27.9; HRMS (FAB-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{21}N_2O_3B$: 336.1649, Found: 336.1649.

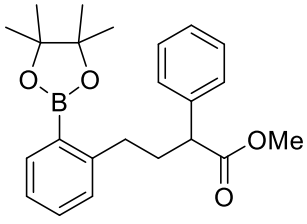
2-[1-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]succinonitrile (2-3n)



2-3n

According to the *General Procedure III*, the reaction was carried out using **2-1n** (75.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) for 12 h under the irradiation of UV light (365 nm). A mixture of diastereomers of **2-3n** (127 mg, 0.41 mmol, 87%, dr = 67:37) was obtained as a white solid after purification by column chromatography on silica gel (hexane/EtOAc = 6/1). The diastereomers could be partially separated by column chromatography on silica gel (hexane/EtOAc = 6/1). *Major diastereomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.49 (td, *J* = 7.6, 1.2 Hz, 1H), 7.34-7.29 (m, 2H), 3.93-3.86 (m, 1H), 3.32-3.26 (m, 1H), 2.70 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.58 (dd, *J* = 16.8, 6.0 Hz, 1H), 1.51 (d, *J* = 7.6 Hz, 3H), 1.37 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 137.0, 131.9, 127.0, 125.6, 118.3, 115.9, 84.2, 38.4, 36.6, 24.9, 24.8, 19.8, 17.3. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{23}N_2O_2B$: 310.1853, Found: 310.1850. *Minor diastereomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.51-7.44 (m, 2H), 7.32 (td, *J* = 7.2, 1.6 Hz, 1H), 4.18-4.11 (m, 1H), 3.29-3.24 (m, 1H), 2.61 (dd, *J* = 16.8, 5.0 Hz, 1H), 2.45 (dd, *J* = 16.8, 9.6 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.37 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 137.1, 131.7, 127.1, 125.9, 118.6, 116.3, 84.1, 37.2, 35.8, 24.9, 24.8, 17.9, 17.6. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{23}N_2O_2B$: 310.1853, Found: 310.1852.

Methyl 2-phenyl-4-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butanoate (2-3p)



2-3p

According to the *General Procedure III*, the reaction was carried out using **2-1a** (68.0 mg, 0.500 mmol), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%) and **2-2b** (243 mg, 1.50 mmol, 3.0 equiv) for 12 h under irradiation of UV (365 nm). product **2-3p** (108 mg, 0.285 mmol, 57%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.36-7.32 (m, 5H), 7.28-7.23 (m, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 3.66-3.63 (m, 4H), 2.88-2.80 (m, 2H), 2.39-2.29 (m, 1H), 2.12-2.03 (m, 1H), 1.32 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 148.5, 139.2, 136.2, 130.9, 129.2, 128.6, 128.0, 127.1, 125.2, 83.4, 51.9, 51.6, 36.5, 33.8, 24.83, 24.80. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.1. HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{29}O_4B$: 380.2159, Found: 380.2159.

5 mmol scale reaction

200 mL two-necked flask was used as a reaction vessel, and three LED light heads were used for irradiation of UV (365 nm). According to the *General Procedure III*, the reaction was carried out using **2-1a** (0.68 g, 5.0 mmol), $Na_4W_{10}O_{32}$ (244 mg, 0.1 mmol, 2 mol%) and **2-2a** (1.71 g, 15 mmol, 3 equiv). Product **2-3a** (0.89 g, 3.0 mmol, 60%) was obtained after purification by column chromatography on silica gel (hexane/EtOAc = 8/1).

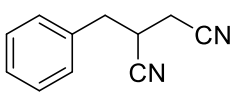
2.4.4 Mechanism Study (Scheme 2-8)

Reaction of toluene (2-4)

General Procedure IV: To a Schlenk tube, toluene (**2-4**, 46.0 mg, 0.500 mmol), fumaronitrile (**2-2a**, 117 mg, 1.50 mmol, 3.0 equiv), $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%), and MeCN/H_2O (10/1, 5.0 mL) were added, and the resulting mixture was stirred at room temperature for 12 h under irradiation of UV (365 nm). After the reaction, dodecane (11.9 mg, 0.070 mmol) was added as an internal standard, and the resulting mixture was analyzed by GC to determine the yield of **2-5** (35%). Pure **2-5** (28.1 mg, 0.165 mmol, 33%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 5/1).

2-Benzylsuccinonitrile (2-5)[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 3H), 7.28-7.26 (m, 2H), 3.20-3.03 (m, 3H), 2.64-2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 129.1, 129.0, 128.0, 118.5, 115.6, 36.9, 30.0, 20.0.



2-5

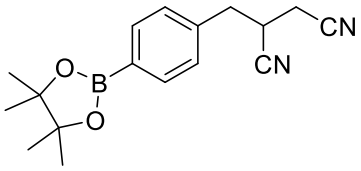
Reaction of pinacol ester 2-6

According to the *General Procedure IV*, the reaction was carried out using **2-6** (109 mg, 0.500 mmol). After the reaction, dodecane (10.9 mg, 0.064 mmol) was added as an internal standard, and the resulting mixture was analyzed by GC to determine the yield of **2-3a** (30%).

Reaction of 2-7a

According to the *General Procedure III*, the reaction was carried out using **2-7a** (68.0 mg, 0.500 mmol). After the reaction, dodecane (11.0 mg, 0.064 mmol) was added as an internal standard, and the resulting mixture was analyzed by GC to determine the yield of **2-3q** (36%). Pure **2-3q** (53.3 mg, 0.180 mmol, 36%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 8/1).

2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3q)



2-3q

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 3.18-3.02 (m, 3H), 2.67-2.56 (m, 2H), 1.34 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 135.5, 128.4, 118.4, 115.4, 83.9, 37.0, 29.8, 24.8, 19.9. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{17}H_{21}N_2O_2B$: 296.1699, Found: 296.1698.

Reaction of 2-7b

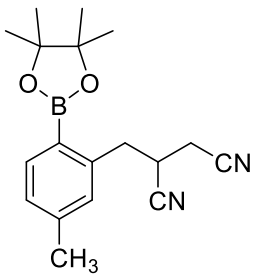
According to the *General Procedure IV*, the reaction was carried out using **2-7b** (109 mg, 0.500 mmol). After the reaction, dodecane (11.6 mg, 0.068 mmol) was added as an internal standard, and the resulting mixture was analyzed by GC to determine the yield of **2-3q** (33%).

Selectivity in the reaction of 2,4-dimethylphenylboronic acid derivatives 2-8a and 2-8b (Scheme 2-8C)

Reaction of 2-8a

According to the *General Procedure III*, the reaction was carried out using **2-2a** (39.0 mg, 0.500 mmol) and 3 equivalents of **2-8a** (225 mg, 1.50 mmol) for 4 h. After the reaction, dodecane (11.7 mg, 0.069 mmol) was added as an internal standard, and the resulting mixture was analyzed by GC to determine the yield of **2-3r** (14%) and **2-3r'** (9%). Pure **2-3r** and **2-3r'** were obtained as colorless oils after purification by column chromatography on silica gel (hexane/EtOAc = 8/1 for **2-3r** and hexane/EtOAc = 6/1 for **2-3r'**). The structures of **2-3r** and **2-3r'** were determined by NOE and the data were as followed.

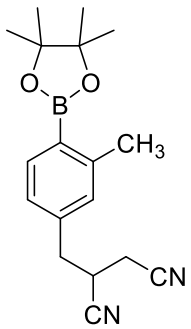
2-[5-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3r)



2-3r

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 3.31-3.24 (m, 3H), 2.75-2.64 (m, 2H), 2.37 (s, 3H), 1.36 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 141.9, 137.3, 131.2, 128.0, 119.0, 115.8, 83.9, 37.6, 31.0, 24.9, 24.8, 21.5, 20.4. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{18}H_{23}N_2O_2B$: 310.1853, Found: 310.1851.

2-[3-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]succinonitrile (2-3r')



2-3r'

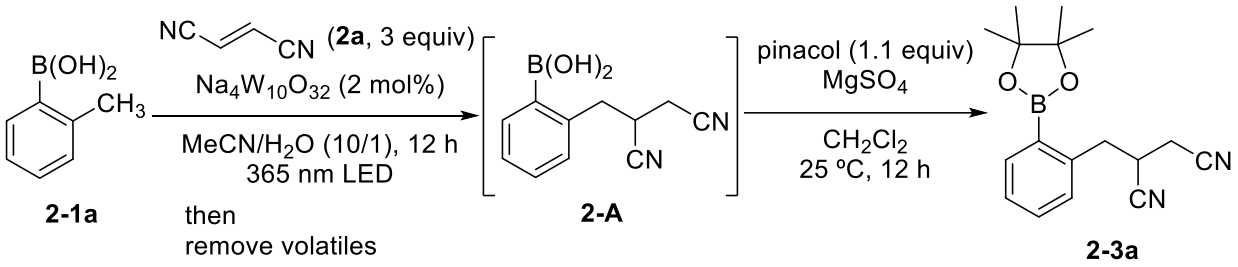
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 6.4 Hz, 1H), 7.05 (s, 1H) 3.17-3.08 (m, 2H), 3.05-2.99 (m, 1H), 2.61 (dd, *J* = 7.0, 2.4 Hz, 2H), 2.54 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 136.8, 136.7, 130.4, 125.3, 118.4, 115.5, 83.6, 36.9, 29.8, 24.8, 22.2, 19.9. The boron-bound carbon was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.2; HRMS (FAB-DFMS) *m*/*z*: $[M+H]^+$ Calcd for $C_{18}H_{23}N_2O_2B$: 310.1853, Found: 310.1850.

Reaction of 3-8b

According to the *General Procedure IV*, the reaction was carried out using **2-2a** (39.0 mg, 0.500 mmol) and 3 equivalents of **2-8b** (348 mg, 1.50 mmol) for 4 h. After the reaction, dodecane (11.7 mg, 0.069 mmol) was added as an internal standard, and the resulting mixture was analyzed by GC to determine the yield of **2-3r** (5%) and **2-3r´** (13%).

2.4.5. Synthetic Conversion of Alkylated Products (Scheme 2-9)

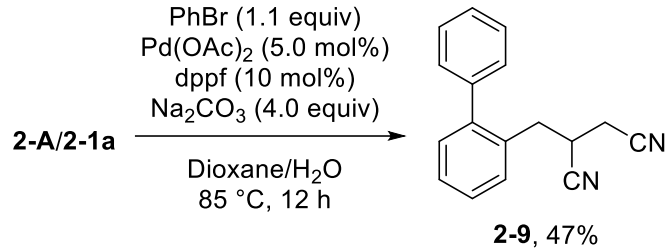
Synthesis of 2-A and 2-1a



Synthesis of **2-A**: 2-Methyphenylboronic acid (**2-1a**, 68.0 mg, 0.500 mmol) was reacted with **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) in MeCN/H_2O (10/1, 5.0 mL) under UV irradiation (365 nm) at room temperature for 12 h in the presence of $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%).

Synthesis of **2-1a**: 2-Methyphenylboronic acid (**2-1a**, 68.0 mg, 0.500 mmol) was reacted with **2-2a** (117 mg, 1.50 mmol, 3.0 equiv) in MeCN/H_2O (10/1, 5.0 mL) under UV irradiation (365 nm) at room temperature for 12 h in the presence of $Na_4W_{10}O_{32}$ (24.4 mg, 0.0100 mmol, 2.0 mol%). After the reaction, the volatiles were removed under reduced pressure, and pinacol (65.0 mg, 0.550 mmol, 1.1 equiv), $MgSO_4$ (400 mg), and CH_2Cl_2 (1.0 mL) were added to the tube. The mixture was stirred at room temperature for 12 h.

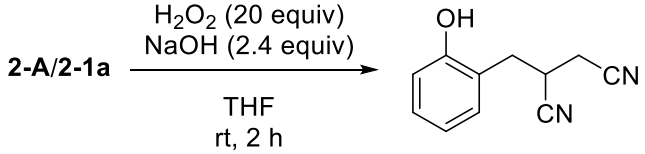
2-([1,1′-Biphenyl]-2-ylmethyl)succinonitrile (2-9)



2-9, 47%

After the photoreactions of **2-A**/**2-1a**, the volatiles were removed under reduced pressure, and bromobenzene (85.8 mg, 0.550 mmol, 1.1 equiv), $Pd(OAc)_2$ (5.61 mg, 0.0250 mmol, 5.0 mol%), dppf (27.7 mg, 0.0500 mmol, 10 mol%), Na_2CO_3 (212 mg, 2.00 mmol, 4.0 equiv), 1,4-dioxane (2.5 mL) and H_2O (1.0 mL) were added to the tube. The resulting mixture was stirred at 85 ºC in an oil bath for 12 h. After cooling to room temperature, aq. NaOH (1.5 M, 5.0 mL) and dichloromethane (3.0 mL) were added, and the organic materials were extracted with dichloromethane (3 x 3.0 mL). The combined organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to afford product **2-9** (from **2-A**: 57.8 mg, 0.235 mmol, 47%; from **2-1a**: 60.3 mg, 0.245 mmol, 49%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.37 (m, 6H), 7.31-7.27 (m, 3H), 3.19-3.07 (m, 2H), 2.77-2.70 (m, 1H), 2.46 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.39 (dd, *J* = 17.2, 6.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 140.2, 132.1, 130.8 130.2, 128.84, 128.79, 128.2, 127.8, 118.4, 115.2, 35.0, 29.0, 20.3; IR (ATR, cm^{-1}) 3060, 3023, 2972, 2934, 2249, 1717, 1599, 1480, 1447, 1382, 1349, 1276, 1143, 1073, 1010, 913, 864, 752, 704; HRMS (EI- DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{17}H_{14}N_2$: 246.1157, Found: 246.1160.

2-(2-Hydroxybenzyl)succinonitrile (2-10)

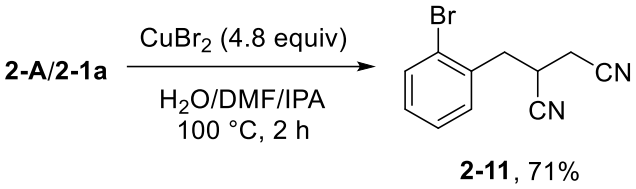


2-10, 70%

After the photoreactions of **2-A**/**2-1a**, the volatiles were removed under reduced pressure and 30% H_2O_2 (1.0 mL, 20 equiv), aq. NaOH (1.0 M, 3.0 mL, 2,4 equiv) and THF (20 mL) were added to the tube. The mixture was stirred at room temperature for 2 h. Then the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over

$MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to afford product **2-10** (from **2-A**: 65.1 mg, 0.350 mmol, 70%; from **2-1a**: 59.5 mg, 0.320 mmol, 64%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.18 (m, 2H), 6.93 (td, *J* = 7.6, 1.2 Hz, 1H), 6.77 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.40 (s, 1H), 3.45-3.38 (m, 1H), 3.15 (dd, *J* = 13.6, 7.2 Hz, 1H), 3.06 (dd, *J* = 13.6, 7.8 Hz, 1H), 2.72 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.64 (dd, *J* = 16.8, 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 131.5, 129.5, 121.2, 119.0, 115.9, 115.5 (2C), 32.6, 28.1, 20.3; IR (ATR, cm^{-1}) 3388, 2930, 2258, 1596, 1505, 1458, 1419, 1350, 1239, 1179, 1102, 1044, 863, 846, 756; HRMS (EI- DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{11}H_{10}N_2O$: 186.0793, Found: 186.0795.

2-(2-Bromobenzyl)succinonitrile (2-11)



2-11, 71%

After the photoreactions of **2-A**/**2-1a**, the volatiles were removed under reduced pressure, and $CuBr_2$ (536 mg, 2.40 mmol, 4.8 equiv), H_2O (6.0 mL), DMF (4.5 mL) and *i*-PrOH (3.0 mL) were added to the tube. The mixture was refluxed at 100 ºC in an oil bath for 2 h under nitrogen atmosphere. After cooling to room temperature, the solvent was removed in vacuo at 60 ºC in a water bath. Then the mixture was dissolved in water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 6/1) to afford product **2-11** (from **2-A**: 87.5 mg, 0.355 mmol, 71%; from **2-1a**: 87.5 mg, 0.355 mmol, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.38-7.32 (m, 2H), 7.24-7.19 (m, 1H), 3.40-3.33 (m, 1H), 3.25-3.15 (m, 2H), 2.79 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.70 (dd, *J* = 17.2, 6.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1, 133.3, 131.7, 129.9, 128.2, 124.2, 118.2, 115.3, 37.7, 28.3, 20.5; IR (ATR, cm^{-1}) 3060, 2934, 2249, 1723, 1568, 1471, 1442, 1362, 1279, 1164, 1119, 1027, 912, 867, 750; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{11}H_9N_2Br$: 247.9949, Found: 247.9949.

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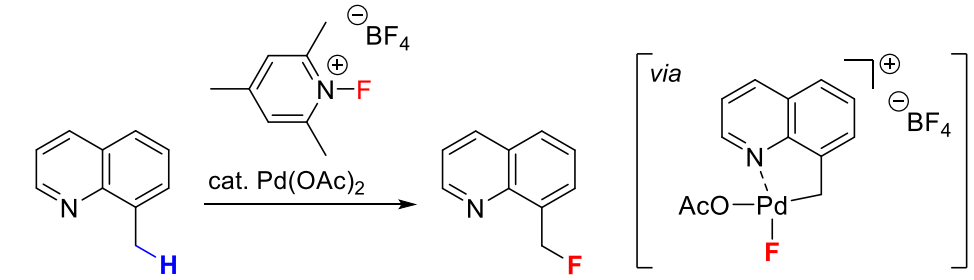
Chapter 3. Hydrogen Bond-Controlled Site-Selective C(sp^3)−H Alkylation of Sulfonanilides

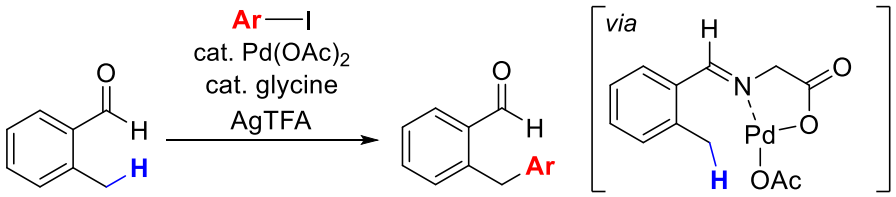
3.1 Introduction

The control of selectivity in C–H transformations is key to achieve efficient, precise, and sustainable C–H transformations and represents a significant challenge in advancing modern synthetic organic chemistry and catalytic science. Existing strategies for controlling site-selectivity typically rely on steric[1] and electronic effects[2–5] or the use of directing groups.[6–8] In site-selective C(sp³)–H transformations, the use of directing groups to control site-selectivity has attracted considerable attention due to its atom economy. For example, Sanford and co-workers reported a palladium-catalyzed C(sp³)–H fluorination at the benzylic position of 8-methylquinoline (**Scheme 3-1A**);[9] however, the substrate scope of this method is limited. The Yu group achieved palladium-catalyzed benzylic C(sp³)–H arylation by introducing glycine as a transient directing group. The introduced glycine needs to be removed from the product (**Scheme 3-1B**).[10] Olivo, Stefano, and Costas et al. reported the introduction of a crown ether into a manganese catalyst, enabling remote C(sp³)–H oxidation of aliphatic ammonium salts by hydrogen bond between the crown ether and the substrate (**Scheme 3-1C**).[11] Nonetheless, the distal products of this method exhibit moderate selectivity, and the applicable substrate scope remains highly restricted.

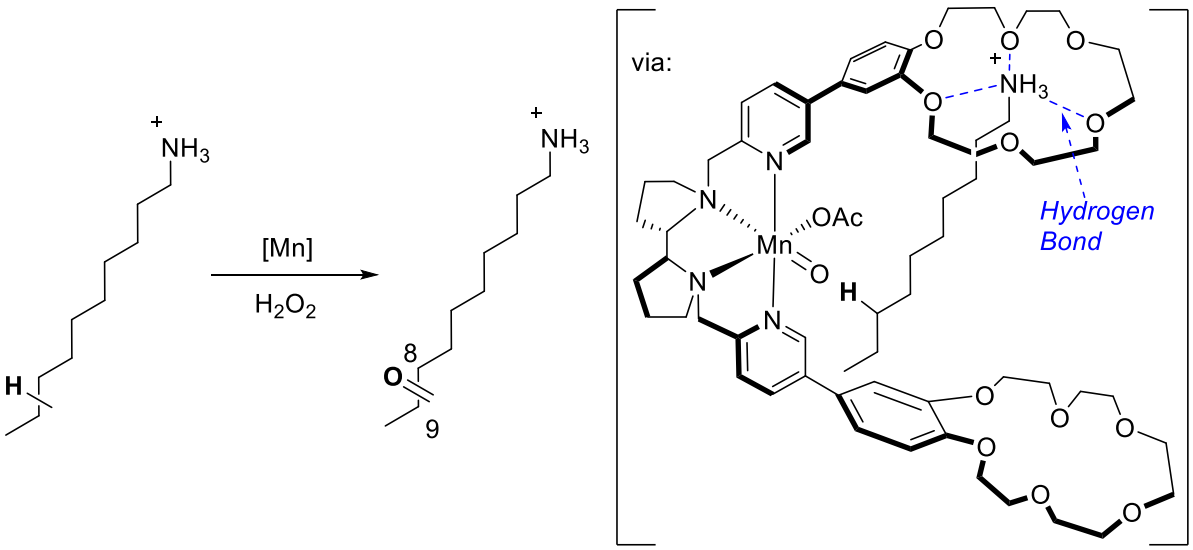
A. Assisted by directing group (Sanford 2006)[9]



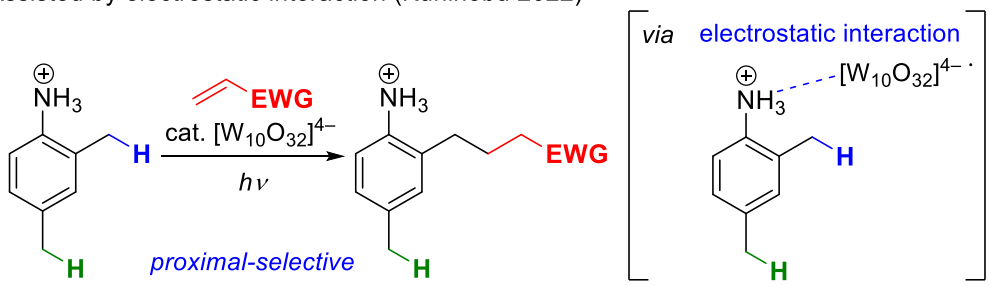
B. Assisted by transient directing group (Yu 2016)[10]



C. Assisted by supramolecular (Olivo, Stefano, Costas 2017)[11]

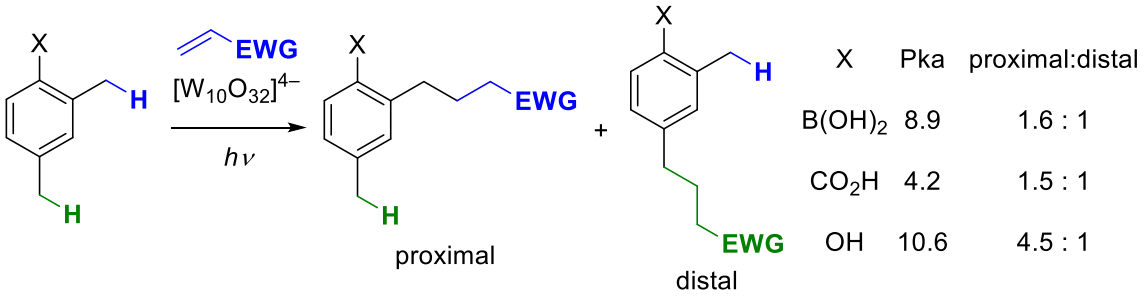


D. Assisted by electrostatic interaction (Kuninobu 2022)[19]



Scheme3-1. Selective-C(sp³)−H transformations

Our group has developed a "non-covalent method"[12–14] to control the site-selectivity of C–H transformations by harnessing non-covalent interactions between the catalyst and substrate. This approach enabled us to achieve *meta*- and *ortho*-selective C(sp²)–H borylation of aromatic compounds.[15,16] Based on the anionic properties of decatungstate photocatalysts,[17,18] our group have achieved proximal-selective C(sp³)–H alkylation of 2-methylanilinium salts (**Scheme 3-1D**)[19]. And I have established a free-boronyl group-assisted benzylic C(sp³)–H alkylation using electron-deficient alkenes as the alkylation reagents (**Chapter 2**). However, when substrates having two reaction sites with similar reactivity, such as 2,4-dimethylphenylboronic acid, were employed, the site-selectivity was low: the ratio of proximal to distal products was only 1.6:1 (**Scheme 3-2**). It is probably because the insufficient hydrogen-bond donating ability of the boronyl group toward the decatungstate catalyst. I considered that strengthening the hydrogen bond between the substrate and catalyst enables high site-selectivity in C(sp³)–H alkylation.

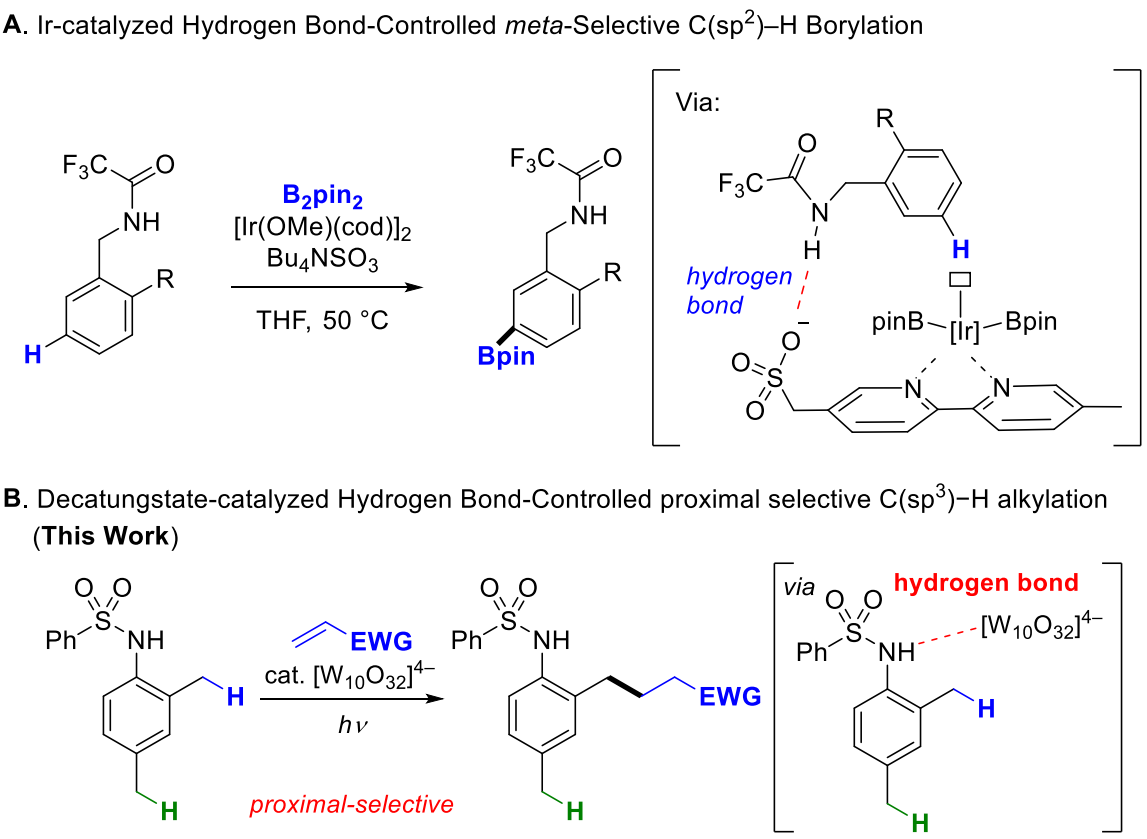


X	Pka	proximal:distal
$B(OH)_2$	8.9	1.6 : 1
CO_2H	4.2	1.5 : 1
OH	10.6	4.5 : 1

Scheme3-2. Effect of acidity on hydrogen bonding

Preliminary investigation of several functional groups in substrates, such as carboxyl and hydroxy groups, as a hydrogen bond donor revealed that the ratio of proximal to distal products was 1.6:1 for 2,4-dimethylphenylboronic acid, 1.5:1 for 2,4-dimethylbenzoic acid, and 4.5:1 for 2,4-dimethylphenol (**Scheme 3-2**). These results indicate that the site-selectivity is not correlated with the acidity of functional groups. Thus, I reconsidered what was a suitable functional group for site-selective C(sp³)–H alkylation. Phipps group recently achieved *meta*-selective C(sp²)–H borylation of aromatic compounds under Ir catalysis through hydrogen bond between electron-rich sulfonate group of the ligand and the amide group of the substrate

(**Scheme 3-3A**).[20] Based on the report and my preliminary experimental results, I considered that an amide group can strengthen the hydrogen bond between decatungstate and the substrate. In this chapter, the development of proximal-selective C(sp³)–H alkylation of *N*-(*o*-tolyl) sulfonamide derivatives are described (**Scheme 3-3B**).



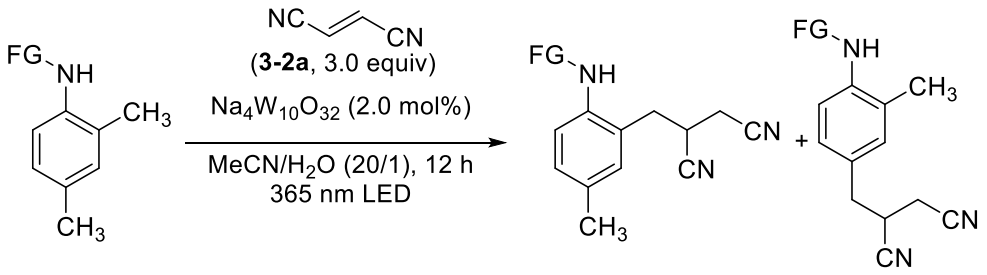
Scheme3-3. Non-covalent interaction controlled selective-C−H transformations

3.2 Results and Discussion

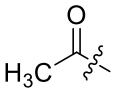
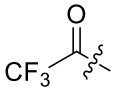
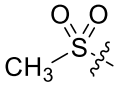
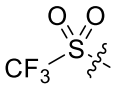
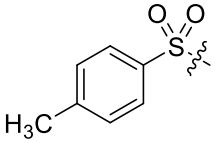
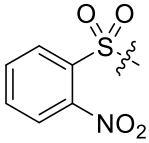
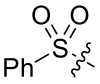
3.2.1 Screening of Functional Groups on the Amino Group of Aniline

To investigate the effect of the amide group to exhibit the site-selectivity, reactions of various anilides **3-1** prepared from 2,4-dimethylaniline were conducted under the the following reaction conditions: **3-1** (0.200 mmol, 1.0 equiv) and fumaronitrile (**3-2a**; 0.600 mmol, 3.0 equiv) were reacted in the presence of $Na_4W_{10}O_{32}$ (NaDT, 2.0 mol%) in MeCN/H_2O (20:1, 2.0 mL) under UV light (365 nm LED) irradiation for 12 h (**Table 3-1**). When an acetyl group was

introduced, the reaction of anilide **3-1A** gave alkylated product **3-3A** in 19% yield along with the generation of **3-3A'** (**3-3A**:**3-3A'** = 91:9) (entry 1). In the case of anilide **3-1B**, bearing a trifluoroacetyl group with stronger electron-withdrawing ability than the acetyl group, the reaction also underwent to produce **3-3B** in 27% yield, although the site-selectivity decreased to 72:28 (entry 2). Subsequently, sulfonyl groups with stronger electron-withdrawing abilities than acyl groups were evaluated (entries 3-7). Methylsulfonanilide **3-1C** gave alkylated product **3-3C** in 39% yield (**3-3C**:**3-3C'** = 82:18) (entry 3). When trifluoromethylsulfonyl group which has stronger electron-withdrawing ability than the methylsulfonyl group was used, the alkylated product **3-3D** was formed in 29% yield, and the selectivity also decreased to 84:16 (**3-3D**:**3-3D'**) (entry 4). The anilide **3-1E** with a tosyl group was also investigated, and gave proximal-selective product **3-3E** in 11% yield (**3-3E**:**3-3E'** = 89:11) (entry 5). But when the 4-methylbenzene was changed to 2-nitrobenzene, the 2-nitrobenzenesulfonanilide **3-1F** did not promote the reaction (entry 6). Although the yield of **3-3a** (28%) was low under the reaction conditions, benzenesulfonanilide **3-1a** provided the best selectivity (**3-3a**:**3-3a'** = 92:8) (entry 7). Therefore, I proceeded to investigate the site-selectivity of benzenesulfonanilide derivatives.



3-1 **3-3** **3-3'**

entry	FG	yield of **3-3** (%)[a]	**3-3:3-3'**[b]
1	 **3-1A**	19(**3-3A**)	91:9
2	 **3-1B**	27(**3-3B**)	72:28
3	 **3-1C**	39(**3-3C**)	82:18
4	 **3-1D**	29(**3-3D**)	84:16
5	 **3-1E**	11 (**3-3E**)	89:11
6	 **3-1F**	<1 (**3-3F**)	—
7	 **3-1a**	28 (**3-3a**)	92:8

[a] Determined by ^{1}H NMR yield; [b] Determined by GC.

Table. 3-1 Screening of functional groups

3.2.2 Optimization of Reaction Conditions

The reaction conditions were optimized to improve the site-selectivity and the product yield. Considering the effect of water on hydrogen bond and the poor solubility of NaDT in pure acetonitrile solvent but high solubility of NaDT in water, I first examined the effect of

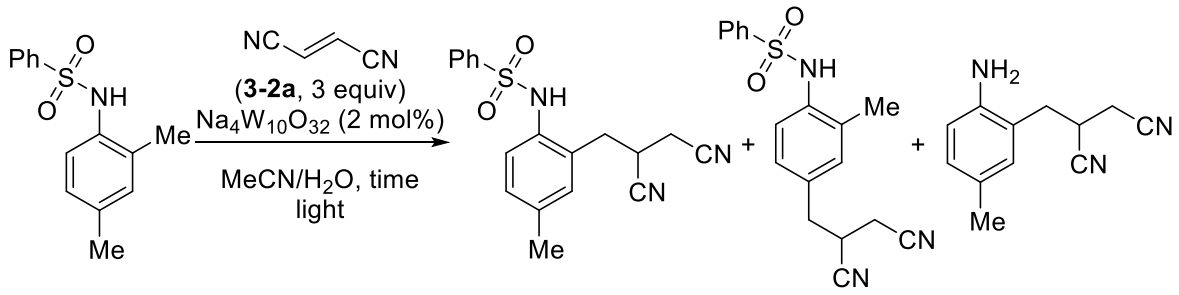
water content in the reaction solvent (**Table 3-2**, entries 1–5). The optimal yield and selectivity (30% yield, **3-3a**:**3-3a'** = 95:5, **Table 3-2**, entry 4) were achieved with a MeCN/H_2O ratio of 80:1. Increasing the amount of water resulted in reducing the yield and selectivity (**Table 3-2**, entry 3), while decreasing the amount of water led to a slight improvement in the selectivity but a significant decrease of yield (**Table 3-2**, entry 5). To improve the yield, I analyzed the reaction. During longer reaction time, an overreaction such as dialkylation at both proximal and distal positions is possible. After 16 h, 91% of substrate **3-1a** was converted (**Table 3-2**, entry 4). Although the formation of dialkylated products were not observed, 2-(2-amino-5-methylbenzyl)succinonitrile (**3-4**), which was produced by the decomposition of product **3-3a**, was detected. However, in addition to **3-4**, there are large number of other byproducts formed. It was yellow liquid and the molecular ion peak cannot be detected by GC-MS. I also tried to isolate it but failed. And it was hard to analyze the ^{1}H NMR spectrum of byproducts. Based on the observation, the shorter reaction times were examined (**Table 3-2**, entries 6–8). In the case of 12 h, the yield of alkylation product **3-3a** increased to 40% with only a small amount of 2-(2-amino-5-methylbenzyl)succinonitrile **3-4** (**Table 3-2**, entry 6). Further reducing the reaction time did not improve the yield nor the selectivity significantly though the decomposition of **3-3a** was not detected (**Table 3-2**, entries 7 and 8).

In order to know what factors lead to the decomposition of product **3-3a**, I investigated the following reactions:

1) **3-3a**（33.9 mg, 0.100 mmol, 1.0 equiv) and fumaronitrile (**3-2a**; 23.4 mg, 0.300 mmol, 3.0 equiv) in the presence of NaDT (4.89 mg, 2 mol%) in MeCN/H_2O (80:1, 1.0 mL), irradiated at 365 nm for 6 h. As a result, 67% of **3-3a** was decomposed.
2) **3-3a**（33.9 mg, 0.100 mmol, 1.0 equiv) in MeCN/H_2O (80:1, 1.0 mL), irradiated at 365 nm for 6 h. 52% of **3-3a** was decomposed.
3) **3-3a**（33.9 mg, 0.100 mmol, 1.0 equiv) in MeCN/H_2O (80:1, 1.0 mL), without irradiation of 365 nm light. Decomposition of **3-3a** was not observed.

These results suggest that **3-3a** is decomposed to **3-4** by the irradiation of UV light (365 nm). It is hypothesized that altering the irradiation light source in the reaction may offer a potential solution to the decomposition of product **3-3a**. Therefore, I investigated the effect of light wavelengths (390, 405 and 456 nm) (**Table 3-2**, entries 9–11). Light irradiation at 405 nm increased the yield of **3-3a** to 73% (**3-3a**:**3-3a'** = 90:10, **Table 3-2**, entry 10) and no **3-4** was detected. Under irradiation at 405 nm, extending the reaction time led to the generation of a small amount of **3-4** (**Table 3-2**, entry 13). Three equivalents of **3-2a** are a suitable amount, and the yield of product **3-3a** decreased to 57% (**3-3a**:**3-3a'** = 84:16) when the amount of **2-2a** was reduced to 2 equivalents (**Table 3-3**, entry 14). When the amount of **3-2a** is increased to 4 equivalents, the yield of product **3-3a** also decreased (49%, **3-3a**:**3-3a'** = 84:16; **Table 3-2**, entry 15). I found the formation of some yellow byproducts, which indicates the decomposition of **3-3a** is enhanced by increasing the amount of **3-2a**. When the amount of NaDT was decreased to 1 mol%, the yield of **3-3a** decreased to 59% (**Table 3-2**, entry 16). When the amount of NaDT was increased to 3 mol%, the product yield decreased to 64%, but the yield of **3-3a'** was increased (**Table 3-2**, entry 17).

The use of $^{n}Bu_4N[W_{10}O_{32}]$ (TBADT) as a catalyst also facilitated the reaction, but the yield and selectivity of **3-3a** were significantly lower compared to those achieved with NaDT (**Table 3-2**, entry 18), which attributed to the steric effect of tetrabutylammonium salt. Therefore, the optimal reaction conditions were determined: **3-1a** (0.200 mmol, 1.0 equiv) and fumaronitrile (**3-2a**; 0.600 mmol, 3.0 equiv) in the presence of NaDT (2 mol%) in MeCN/H_2O (80:1, 2.0 mL), irradiated at 405 nm for 12 h.



3-1a **3-3a** **3-3a'** **3-4**

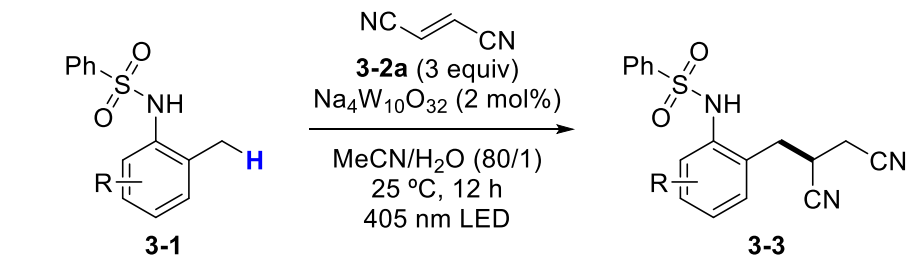
entry	$MeCN/H_2O$ (2.0 mL)	**3-2a** (equiv)	NaDT (mol%)	time (h)	light (nm)	GC yield of **3-3a** (%)[a]	**3-3a:3-3a'**[a]
1	10 : 1	3	2	16	365	15	91:9
2	20 : 1	3	2	16	365	21	92:8
3	40 : 1	3	2	16	365	25	93:7
4	80 : 1	3	2	16	365	30	95:5
5	100 : 1	3	2	16	365	23	96:4
6	80 : 1	3	2	12	365	40	93:7
7	80 : 1	3	2	8	365	43	89:11
8	80 : 1	3	2	4	365	40	87:13
9	80 : 1	3	2	12	390	57	90:10
10	**80 : 1**	**3**	**2**	**12**	**405**	**73**	**90:10**
11	80 : 1	3	2	12	456	4	84:16
12	80 : 1	3	2	6	405	50	88:12
13	80 : 1	3	2	14	405	66	91:9
14	80 : 1	2	2	12	405	57	84:16
15	80 : 1	4	2	12	405	49	84:16
16	80 : 1	3	1	12	405	59	88:12
17	80 : 1	3	3	12	405	64	78:22
18[b]	80 : 1	3	2	12	405	52	73:27

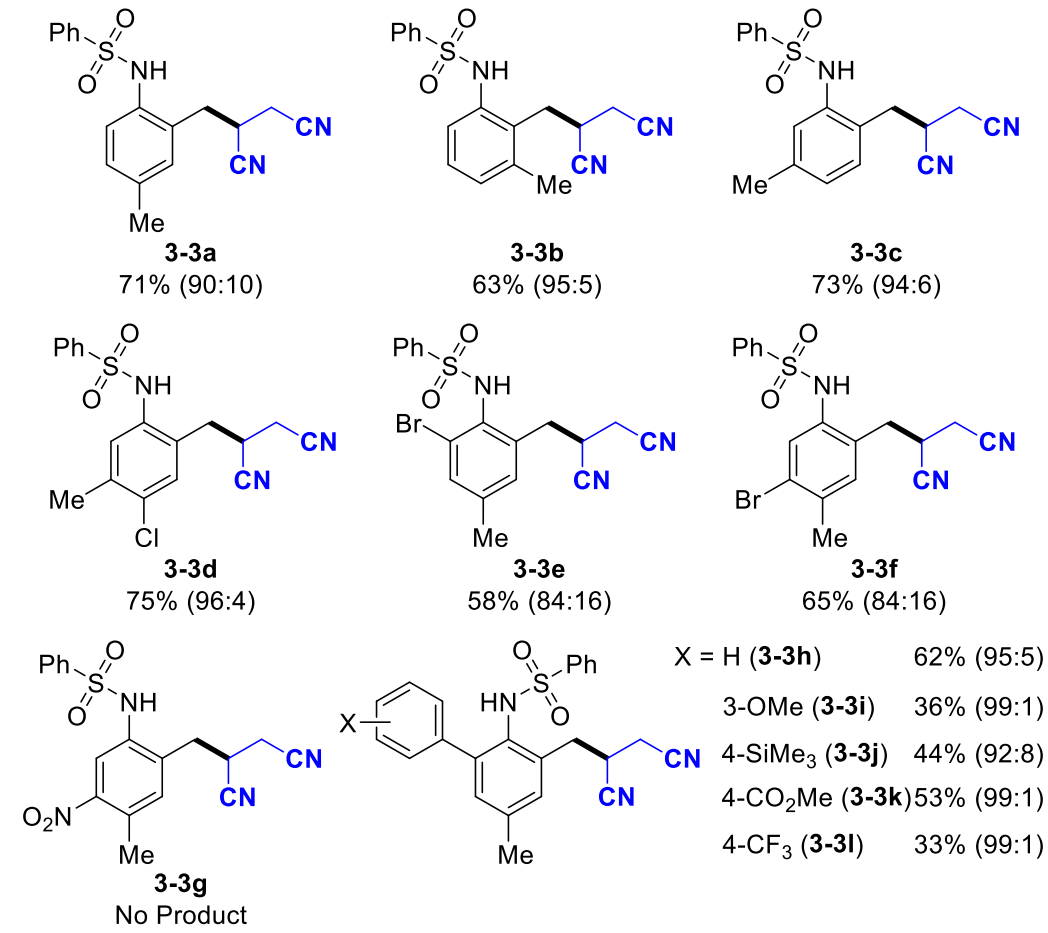
[a] Determined by GC. [b] $(^nBu_4N)W_{10}O_{32}$ instead of $Na_4W_{10}O_{32}$.

Table. 3-2 Optimization of reaction conditions

3.2.3 Scope of Sulfonamides and Alkenes

Under the optimized conditions, the sulfonanilide derivatives were investigated (**Schemes 3-4**, **3-5**, and **3-6**). Isolated yields of **3-3** and the selectivity (**3-3**:**3-3'**) were shown in the schemes. First, when the benzene ring containing a methyl group in addition to the proximal methyl group (**Scheme 3-4**), alkylation at proximal benzylic position selectively proceeded to afford **3-3a**, **3-3b**, and **3-3c** in high site-selectivity. Substrates **3-1d**–**1f** bearing chlorine or bromine atom also selectively formed the corresponding alkylated products **3-3d**–**3f**. However, when a strongly electron-withdrawing NO_2 group was present in the substrate (**3-1g**), the corresponding alkylated product **3-3g** was not detected at all. For other *ortho*-arylated substrates, *ortho*-phenyl sulfonanilide (**3-1h**), *ortho*-aryl sulfonanilides with an electron-donating group such as *ortho*-(3-methoxy)phenyl sulfonanilide (**3-1i**) and *ortho*-(4-trimethylsilyl)phenyl sulfonanilide (**3-1j**), and *ortho*-aryl sulfonanilides with an electron-withdrawing group such as *ortho*-(4-methoxycarbonyl)phenyl sulfonanilide (**3-1k**) and *ortho*-(4-trifluoromethyl)phenyl sulfonanilide (**3-1l**) were investigated. As a result, proximal alkylated products **3-3h**–**3l** were selectively produced. The DFT calculations of **3-1h** indicate that the *ortho*-aryl group may form π–π interaction with the phenyl group attached to the sulfur atom. As shown in **Figure 3-1**, this structure is more stable than other conformations. As a result, the N–H bond faces the *ortho*-methyl group and forms a hydrogen bond with decatungstate photocatalyst, abstracting a hydrogen atom from the *ortho*-methyl group and generating the corresponding radical. Therefore, the site-selectivity of *ortho*-aryl sulfonanilide substrates **3-3h**–**3l** was not decreased.





Scheme. 3-4 Scope of substrates

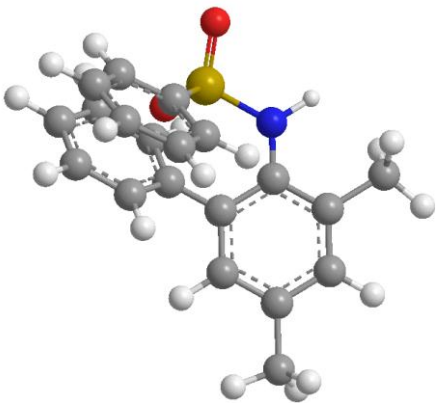
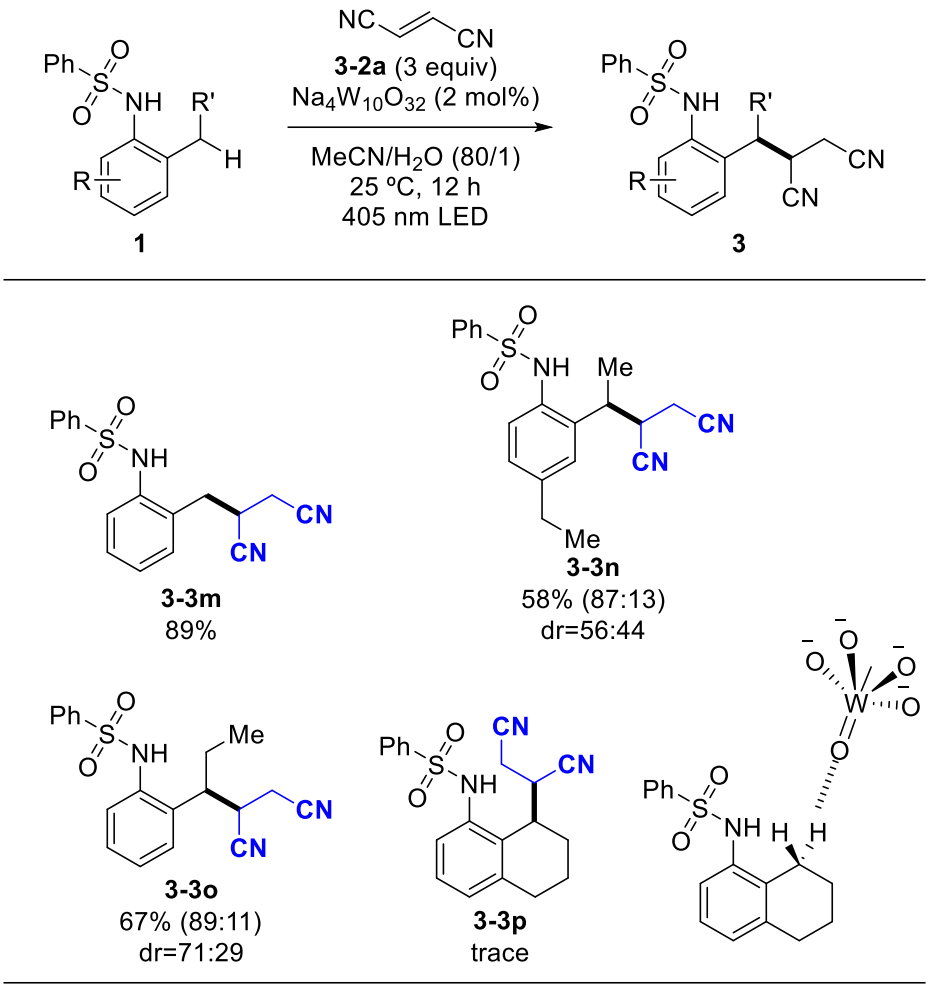


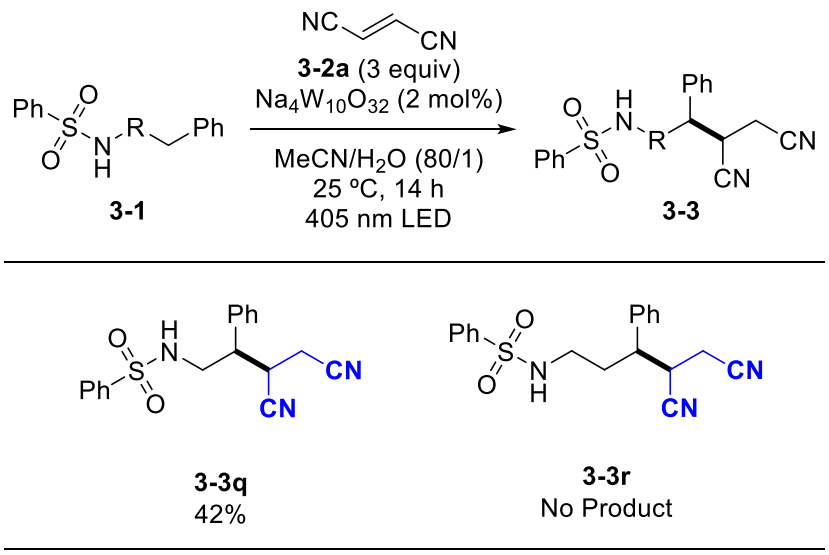
Figure 3-1. Conformation of **3-3h**

In the case of sulfonanilide **3-1m** having only an *ortho*-methyl group, the yield of alkylated product **3-3m** was 89% (**Scheme 3-5**). For sulfonanilide **3-1n** with both *ortho*- and *para*-ethyl groups, the C(sp^3)–H alkylation selectively occurred at the benzylic position of the *ortho*-ethyl group, yielding a mixture of diastereomers (**3-3m**, dr = 56:44). Similarly, when the *ortho*-position was substituted with a propyl group (**3-1o**), the reaction selectively took place at the benzylic position, affording a diastereomeric mixture of alkylated products (**3-3o**, dr = 71:29). For *N*-(5,6,7,8-tetrahydronaphthalen-1-yl)benzenesulfonamide (**3-1p**), only a trace amount of the product was formed and small amounts of other products were detected (almost no site-selectivity). Because the 6-membered ring (non-benzene ring) is rigid, due to the condensation with the benzene ring of **3-1p**, decatungstate was prevented to form hydrogen bond with the N–H bond of **3-1p** during abstracting the hydrogen atom to generate a benzylic radical. However, since the hydrogen atoms are located diagonally above and below the 6-membered ring, the degree of stabilization due to the conjugation effect with the π orbital of the benzene ring is weakened during hydrogen atom abstraction, making it difficult to generate a benzyl radical. These factors ultimately make it difficult for **3-1p** to form alkylated product at the benzylic position.



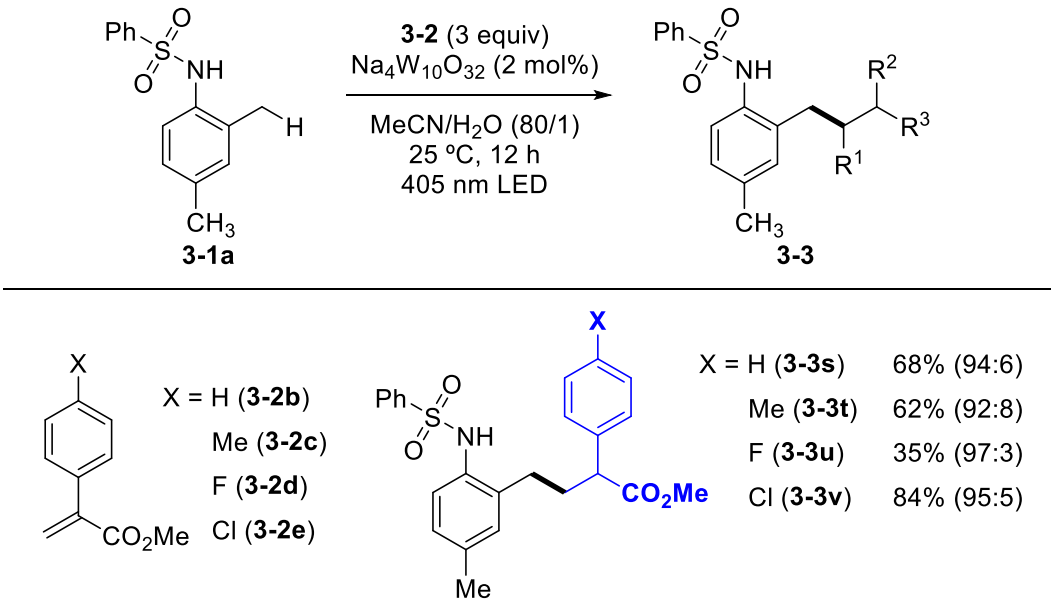
Scheme. 3-5 Scope of substrates

To investigate whether the reaction occurs at the benzylic and/or other position(s) of substrates other than sulfonanilides, *N*-phenethylbenzenesulfonamide (**3-1q**) and *N*-(3-phenylpropyl)benzenesulfonamide (**3-1r**) were subjected to the reaction under the optimized conditions (**Scheme 3-6**). The reaction also proceeded at the benzylic position of **3-1q**, and the corresponding alkylated product **3-3q** was obtained in 42% yield. However, for *N*-(3-phenylpropyl)benzenesulfonamide (**3-1r**), no any product peak was detected by GC-MS. The results indicate that the benzylic position exhibits higher reactivity than others; however, the reaction becomes significantly less favorable when it is distant from the sulfonamide group.



Scheme. 3-6 Scope of substrates

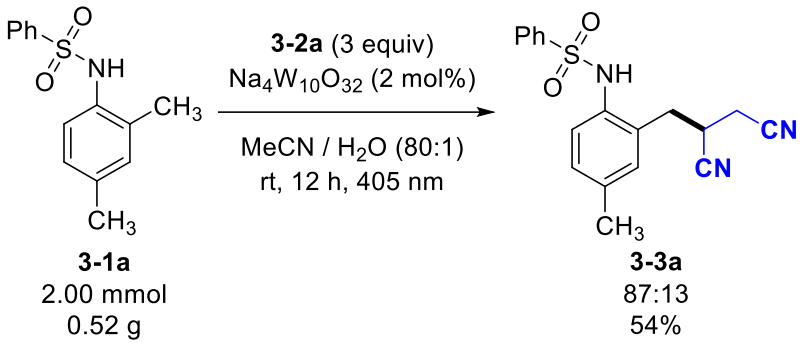
Alkenes other than fumaronitrile **3-2a** were investigated for the C(sp³)–H alkylation (**Scheme 3-7**). The results showed that α-aryl acrylates **3-2b**–**2e**, including methyl- or halogen-substituted aryl groups, reacted with **3-1a** to produce **3-3p**–**3s** with high selectivity.



Scheme. 3-7 Scope of alkenes

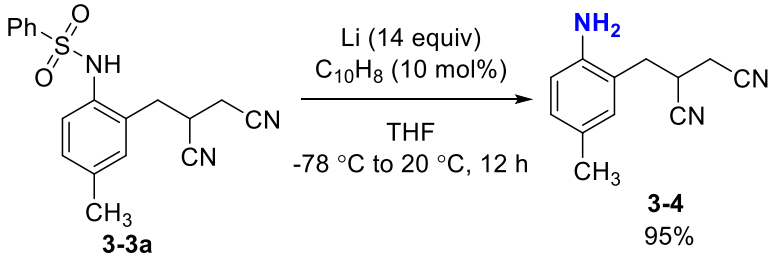
3.2.4 2 mmol-Scale Reaction and Deprotection of Sulfonyl Group

The 2 mmol-scale C(sp³)–H alkylation was conducted (**Scheme 3-8**). At the optimized conditions, a mixture of **3-1a** (2.00 mmol), **3-2a** , and NaDT in the mixture of MeCN/H_2O, yielding 0.366 g of alkylation product **3-3a** in 54% yield (**3-3a**:**3-3a'** = 87:13).



Scheme. 3-8 2 mmol scale reaction

The deprotection reaction of **3-3a** (68.8 mg, 0.200 mmol, 1.0 equiv) was proceeded. The alkylated product **3-3a** was treated with lithium and naphthalene in THF, the sulfonyl group was removed smoothly and the corresponding aniline derivative **3-4** was obtained in 95% yield (**Scheme 3-9**).[27]



Scheme 3-9. Deprotection reaction

3.2.5 Mechanistic Studies

First, to determine whether the NH group of **3-1a** can interact with decatungstate by hydrogen bond. I conducted titration experiments by ^{1}H NMR measurements of **3-1a** with

different amounts of $^{n}Bu_4N[W_{10}O_{32}]$ (TBADT) in CD_3CN. TBADT was used as a catalyst because it has better solubility in acetonitrile than NaDT which was used under the optimized reaction conditions. The following three sets of ^1H NMR analyses were performed for comparison.

Sample 1 (Only **3-1a**): **3-1a** (5.23 mg, 0.0200 mmol) was dissolved in CD_3CN (1.0 mL) and ^1H NMR spectrum of the solution was measured.

Sample 2 (**3-1a**:TBADT = 4:1): **3-1a** (5.23 mg, 0.0200 mmol, 1.0 equiv) and TBADT (16.6 mg, 0.00500 mmol, 0.25 equiv) were dissolved in CD_3CN (1.0 mL) and ^1H NMR spectrum of the solution was measured.

Sample 3 (**3-1a**:TBADT = 2:1:): **3-1a** (5.23 mg, 0.0200 mmol, 1.0 equiv) and TBADT (33.2 mg, 0.0100 mmol, 0.50 equiv) were dissolved in CD_3CN (1.0 mL) and ^1H NMR spectrum of the solution was measured.

The proton signal of NH group of sulfonanilide **3-1a** was observed at 7.27 ppm. Upon adding TBADT to the CD_3CN solution of **3-1a** at a ratio of 1:4, 1:2 and 1:1, the NH proton signal was shifted to 7.32 ppm (**3-1a**:TBADT = 4:1), 7.33 ppm (**3-1a**:TBADT = 2:1) and 7.33 ppm (**3-1a**:TBADT = 1:1), respectively. And other proton signals remain essentially unchanged (Experimental Section, **Figure 3-3**). The trend line of changes in the chemical shift of -NH proton with increasing TBADT content in the sample was obtained (**Figure 3-2**). As shown in **Figure 3-1**, with the increase in TBADT content, the chemical shift of the -NH proton of **3-1a** gradually shifted downfield. This shift reached its maximum when the **3-1a**:TBADT = 2:1. Upon further increase in TBADT content, the -NH chemical shift no longer changed. These results indicate the presence of hydrogen bond between the decatungstate catalyst and the NH bond of the sulfonamide group of substrates.

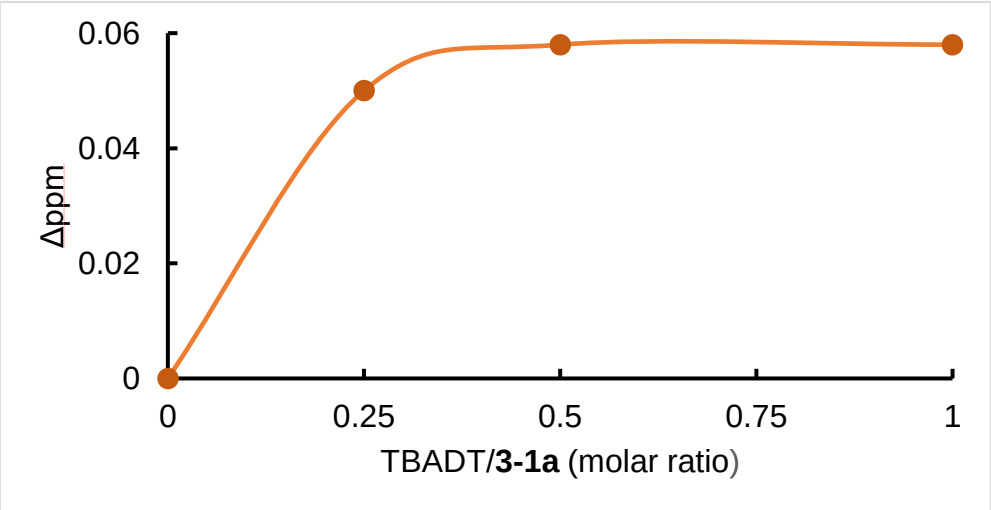
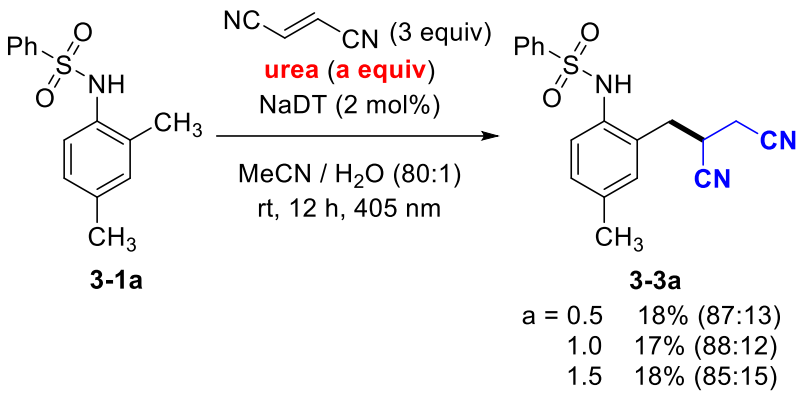


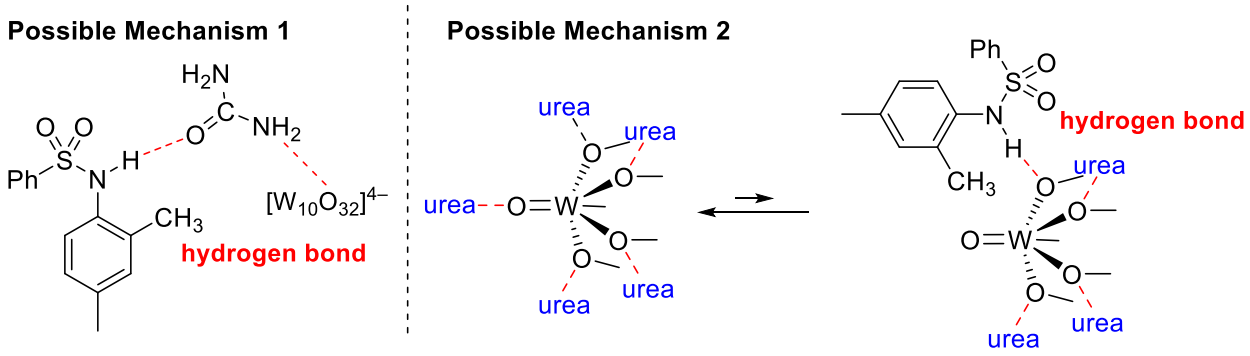
Figure 3-2. The changing trend of -NH proton chemical shift

Additionally, when optimizing the ratio of MeCN/H_2O as a solvent in **Table 3-2**, both the yield and siteselectivity decreased with an increasing proportion of water (increased polarity). This result also supports the hypothesis that hydrogen bond plays a critical role in promoting the site-selective C(sp^3)–H alkylation.

To further verify the importance of hydrogen bond, I added urea, a hydrogen bond inhibitor, into the reaction. Under the optimized conditions, 0.5, 1.0 or 1.5equivalent(s) of urea was added to the reaction mixture to investigate the effect of the hydrogen bond inhibitor. As a result, the yield of alkylated product **3-3a** was decreased to 17-18%, but the site-selectivity had rarely changed (**3-3a**:**3-3a'** = 87:13 compared to **3-3a**:**3-3a'** = 90:10 (w/o urea)) (**Scheme 3-10**). The results indicate that urea does disrupt the hydrogen bond between the **3-1a** and decatungstate. However, the nearly unchanged site-selectivity may be attributed to the following two possible reasons: 1) The oxygen atom of urea forms hydrogen bond with **3-1a**, while its hydrogen atom forms hydrogen bond with decatungstate. This causes decatungstate to still favor the proximal C(sp^3)–H bond for alkylation. Due to the increased distance between **3-1a** and catalyst, the yield decreases dramatically, while the site-selectivity remains unaffected; and 2) the addition of urea allows it to form hydrogen bonds with decatungstate, preventing the catalyst from forming hydrogen bond with **3-1a**. However, because the hydrogen bond is in equilibrium, when urea

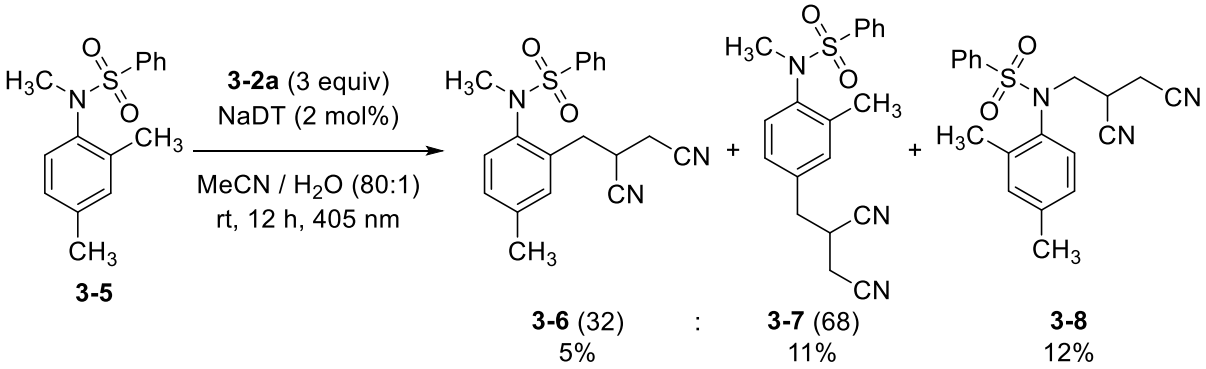
dissociates from decatungstate photocatalyst, the free oxygen atom of the photocatalyst forms a hydrogen bond with the N-H bond of the substrate, and the hydrogen atom is selectively abstracted from the *ortho*-methyl group. As a result, the yield of the product drops dramatically upon the addition of urea, but the site-selectivity remains almost unchanged.





Scheme. 3-10. The effect of urea

When a reaction was carried out using **3-5** in which the NH group of substrate **3-1a** was protected by a methyl group (formation of N–Me), three products **3-6**, **3-7**, and **3-8** were formed



Scheme. 3-11. Selectivity in the reaction of **3-5**

as shown in **Scheme 3-11**. In this reaction, *ortho*-selectivity is lost, and the reaction preferentially occurs at the *para*-benzylic position. This result further confirms that hydrogen bond plays a critical role in controlling the site-selectivity.

3.3 Conclusion

In conclusion, to address the poor site-selectivity reported in **Chapter 2** due to the weak hydrogen bond between phenylboronic acid substrates and decatungstate, I envisioned to enhance the hydrogen bond between substrates and decatungstate by introducing an electron-withdrawing functional group onto the NH_2 group of aniline derivatives. This modification enables proximal-selective benzylic C(sp^3)–H alkylation of sulfonanilides. The reaction showed good functional group tolerance, and the reaction maintained good yield and high site-selectivity even on 2 mmol scale. After the C(sp^3)–H alkylation, the sulfonyl group introduced on the nitrogen atom of the substrate can be deprotected to obtain the corresponding aniline derivatives. Mechanistic studies revealed that the site-selectivity of this reaction is governed by hydrogen bond between the substrate and the decatungstate photocatalyst.

3.4 Experimental Section

3.4.1 General

All reactions were carried out under nitrogen atmosphere unless otherwise noted. ^{1}H (400 MHz), ^{13}C (101 MHz) and ^{19}F (368 MHz) NMR spectra were recorded using a JEOL ECZ400 spectrometer, and ^{1}H (600 MHz) spectra were recorded using a JEOL JNM-ECA600 spectrometer. Proton chemical shifts are reported relative to residual solvent peak ($CDCl_3$ at δ 7.26 ppm and CD_3CN at 1.94 ppm). Carbon chemical shifts are reported relative to $CDCl_3$ at δ 77.0 ppm). High resolution mass spectra (HRMS) were recorded on JEOL JMS-700 (EI) and JEOL JMS-700 (FAB) spectrometer. Double-focusing mass spectrometer (DFMS) was used for the HRMS measurements. Kessil PR160L (λ = 390 nm) was used as a light source and set to 100% power as the emission spectrum. Controller 8332A (CCS) and LED light heads AC8361 (λ = 365 nm, CCS) were used as light sources and set to 100% power as the emission spectrum and controller 8332C (CCS) and LED light heads AC8375-405 (λ = 405 nm, CCS) were used as light sources and set to 80% power as the emission spectrum (the distance from light source to the irradiation vessel: <5 mm, Figure S1). The emission spectra of AC8361 and AC8375 are provided by CCS. Emission spectra were recorded on C9920-02 (Hamamatsu Photonics). Borosilicate Schlenk flasks with PTFE stopcock were used as irradiation vessel. The outer diameter of the 10 mL Schlenk flasks is 1.9 cm.

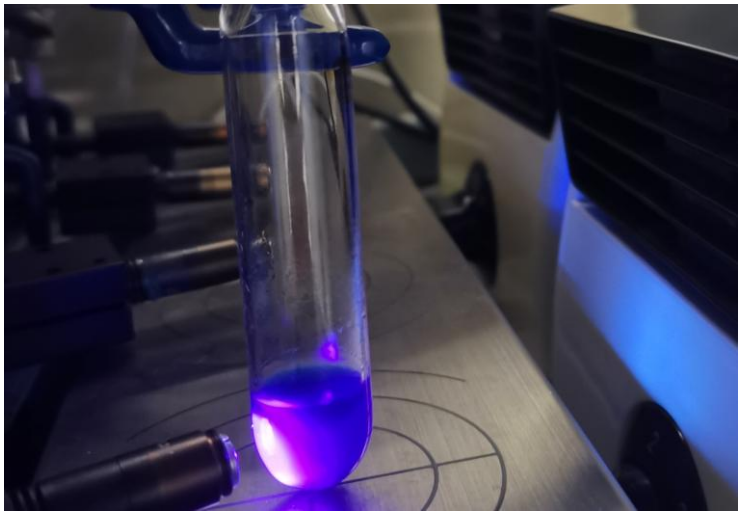


Figure S1. Reaction setup

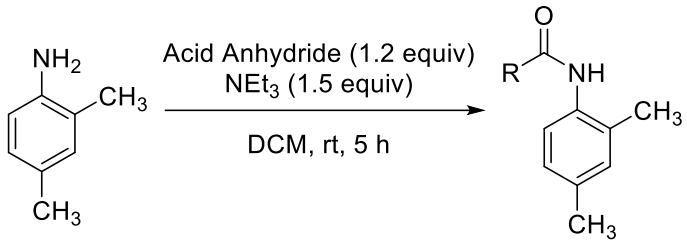
3.4.2 Materials

***Solvents, catalysts and reagents*:** Acetonitrile was distilled over calcium hydride and degassed prior to use. Distilled water was degassed prior to use. Decatungstate photocatalysts $Na_4W_{10}O_{32}$ and $(^nBu_4N_4)W_{10}O_{32}$ were prepared according to the reported procedure.[21] The other reagents were purchased from commercial sources and used without further purification.

Synthesis of decatungstate photocatalysts $Na_4W_{10}O_{32}$

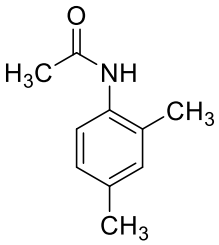
To a 3 L beaker containing a boiling solution (95 °C) of $Na_2WO_4{\cdot}2H_2O$ (33.0 g, 100 mmol) in deionized water (200 mL), a boiling aqueous solution (95 °C) of HCl (1.0 M, 200 mL) was added. The resulting solution was allowed to boil for 30 s, then rapidly cooled to 30 °C in a dry ice/methanol bath with stirring. Sodium chloride was added to near saturation, then the mixture was cooled to 0 °C. The precipitates were filtered, washed with cooled brine, and dried in vacuum overnight. The precipitate was suspended in hot acetonitrile (80 mL), then filtered, and the filtrate was placed in a freezer (–20 ºC) overnight. The crystal was filtered and dried in vacuum to afford $Na_4W_{10}O_{32}$ (12.2 g, 5.00 mmol, 50%) as a colorless solid.

Synthesis of amides[22]



General Procedure I: To a solution of 2,4-dimethylaniline (1.2 g, 3.00 mmol, 1.0 equiv) and Et_3N (455 mg, 4.50 mmol, 1.5 equiv) in CH_2Cl_2 (6.0 mL) was added acid anhydride (3.60 mmol, 1.2 equiv) dropwise at 0 °C. After addition, the mixture was stirred at room temperature for 5 h. The reaction was then quenched with H_2O and extracted with CH_2Cl_2 (5.0 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel.

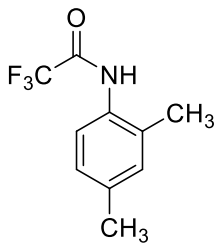
N-(2,4-Dimethylphenyl)acetamide (3-1A)[23]



3-1A

According to the *General Procedure I*, acetic anhydride (368 mg, 3.60 mmol, 1.2 equiv) was used. The crude residue was purified by recrystallization to give product **3-1A** (401 mg, 2.46 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.06 (brs, 1H), 7.01-6.96 (m, 2H), 2.27 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 135.2, 132.9, 131.1 (2C), 127.2, 124.0, 24.0, 20.8, 17.7.

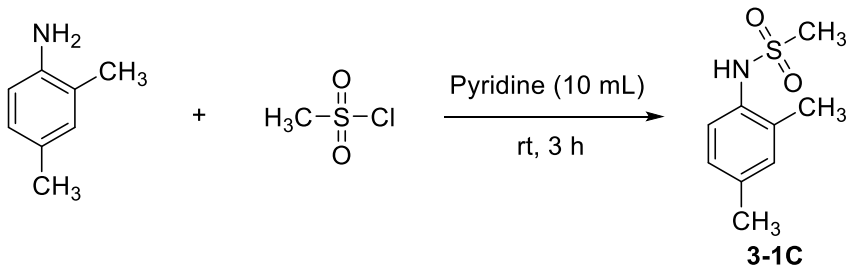
N-(2,4-Dimethylphenyl)-2,2,2-trifluoroacetamide (3-1B)



3-1B

According to the *General Procedure I*, trifluoroacetic anhydride (756 mg, 3.60 mmol, 1.2 equiv) was used. The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 6/1) to give product **3-1B** (593 mg, 2.73 mmol, 91%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (brs, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.06-7.05 (m, 2H), 2.32 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (q, *J* = 33.2 Hz), 137.1, 131.5, 130.2, 130.0, 127.6, 123.5, 115.8 (q, *J* = 282 Hz), 20.9, 17.3; ^{19}F NMR (368 MHz, $CDCl_3$) δ -75.5; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{10}H_{10}F_3NO$: 217.0714, Found: 217.0716.

N-(2,4-Dimethylphenyl)methanesulfonamide (3-1C)[24]

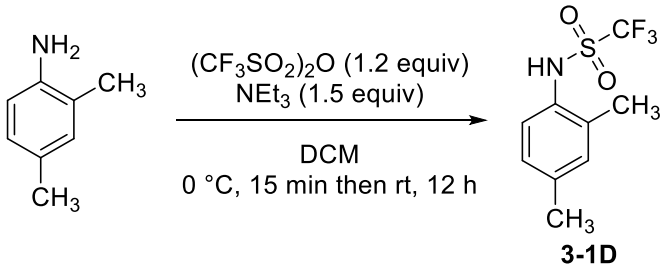


3-1C

A flask charged with the 2,4-dimethylaniline (242 mg, 2.00 mmol, 1.0 equiv) and pyridine (10 mL) cooled to 0 ºC, then methanesulfonyl chloride (252 mg, 2.20 mmol, 1.1 equiv) was

added dropwise. The mixture was warmed to room temperature and stirred for 3 h. The mixture was then added water (8.0 mL) and the aqueous phase extracted with DCM (3 × 4 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The product **3-1C** (400 mg, 2.00mmol, 100%) was obtained after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 1H), 7.05 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.29 (brs, 1H), 2.99 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 131.8 (2C), 131.4, 127.8, 124.0, 39.7, 20.8, 18.0.

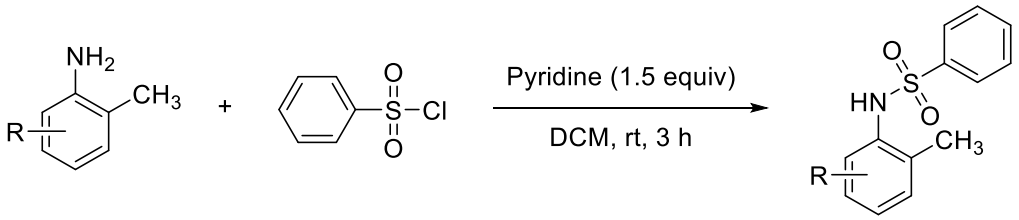
_N_-(2,4-Dimethylphenyl)-1,1,1-trifluoromethanesulfonamide (3-1D)[25]



3-1D

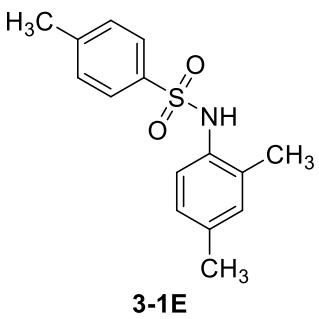
In a 50 mL round-bottom flask aniline 2,4-dimethylaniline (0.6 g, 5.00 mmol, 1.0 equiv), 10 mL dry DCM and dry Et_3N (750 mg, 7.50 mmol, 1.5 equiv) added. The reaction mixture cooled to 0 ºC and stir for 15 min. Then, $(CF_3SO_2)_2O$ (1.0 mL, 1.2 equiv) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion, the resulting reaction mixture was extracted with DCM (3 x 15 mL) and dried over $MgSO_4$. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (hexane/EtOAc = 10/1) gave the product **3-1D** (465 mg, 1.85 mmol, 37%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.8 Hz, 1H), 7.08 (s, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.76 (brs, 1H), 2.34 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 134.2, 131.9, 129.1, 127.7, 126.7, 119.7 (q, *J* = 323 Hz), 20.9, 17.7; ^{19}F NMR (368 MHz, $CDCl_3$) δ -75.9.

Synthesized of benzenesulfonamide[26]



General Procedure II: A flask charged with the aryl amine (3.00 mmol, 1.0 equiv), pyridine (356 mg, 3.00 mmol, 1.5 equiv), DCM (6.0 mL), and then benzenesulfonyl chloride (583 mg, 3.30 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at room temperature for 3 h. The mixture was then added water (8.0 mL) and the aqueous phase extracted with DCM (3 × 6.0 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography afforded the benzenesulfonamide.

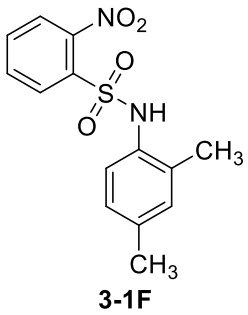
_N_-(2,4-Dimethylphenyl)-4-methylbenzenesulfonamide (3-1E)



3-1E

According to the *General Procedure II*, 2,4-dimethylaniline (364 mg, 3.00 mmol, 1.0 equiv) and 4-methylbenzenesulfonyl chloride (629 mg, 1.1 equiv, 3.30 mmol) were used to obtain product **3-1E** (529 mg, 1.92 mmol, 64%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.22 (brs, 1H), 2.39 (s, 3H), 2.25 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 136.8, 136.3, 131.9, 131.7, 131.4, 129.5, 127.5, 127.2, 125.1, 21.5, 20.8, 17.5; HRMS (EI-DFMS) m/z: $[M]^+$ Calcd for $C_{15}H_{17}NO_2S$: 275.0980, Found: 275.0980.

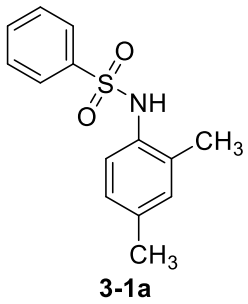
_N_-(2,4-Dimethylphenyl)-2-nitrobenzenesulfonamide (3-1F)



3-1F

According to the *General Procedure II*, 2,4-dimethylaniline (364 mg, 3.00 mmol, 1.0 equiv) and 2-nitrobenzenesulfonyl chloride (731 mg, 1.1 equiv, 3.30 mmol) were used to obtain product **3-1F** (916 mg, 2.99 mmol, 99%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.72 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.61 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.05-7.03 (m, 2H), 6.97 (s, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 2.27 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 137.3, 133.8, 133.7, 133.4, 132.6, 131.8, 131.4, 131.0, 127.4, 126.0, 125.2, 20.9, 17.7; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{14}N_2O_4S$: 306.0674, Found: 306.0671.

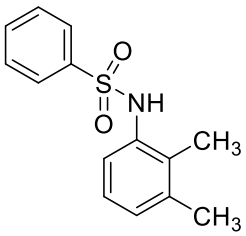
_N_-(2,4-Dimethylphenyl)benzenesulfonamide (3-1a)



3-1a

According to the *General Procedure II*, 2,4-dimethylaniline (364 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1a** (784 mg, 3.00 mmol, 100%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.90 (s, 1H), 6.37 (s, 1H), 2.26 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 136.5, 132.8, 132.2, 131.5 (2C), 128.9, 127.5, 127.1, 125.3, 20.8, 17.4; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}NO_2S$: 261.0824, Found: 261.0822.

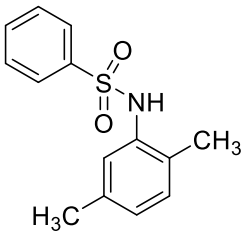
_N_-(2,3-Dimethylphenyl)benzenesulfonamide (3-1b)



3-1b

According to the *General Procedure II*, 2,3-dimethylaniline (364 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1b** (784 mg, 3.00 mmol, 100%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.70 (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.41 (m, 2H), 7.05-6.99 (m, 3H), 6.36 (brs, 1H), 2.21 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 137.9, 133.9, 132.8, 131.7, 128.9, 128.4, 127.2, 126.0, 123.4, 20.6, 13.7; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}NO_2S$: 261.0824, Found: 261.0821.

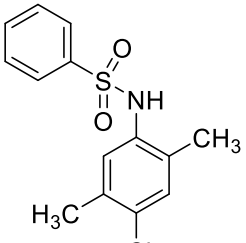
_N_-(2,5-Dimethylphenyl)benzenesulfonamide (3-1c)



3-1c

According to the *General Procedure II*, 2,5-dimethylaniline (364 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1c** (784 mg, 3.00 mmol, 100%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.71 (m, 2H), 7.57-7.53 (m, 1H), 7.45-7.41 (m, 2H), 7,14 (s, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.25 (brs, 1H), 2.27 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 136.8, 134.0, 132.9, 130.5, 128.9, 128.1, 127.2, 127.1, 125.3, 21.0, 17.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}NO_2S$: 261.0824, Found: 261.0821.

_N_-(4-Chloro-2,5-dimethylphenyl)benzenesulfonamide (3-1d)

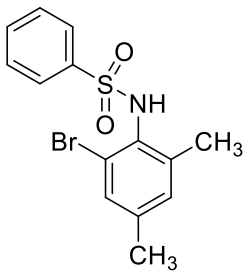


3-1d

According to the *General Procedure II*, 4-chloro-2,5-dimethylaniline (467 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1d** (887 mg, 3.00 mmol, 100%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.70 (m, 2H), 7.59-7.55 (m, 1H), 7.47-7.43 (m, 2H), 7.19 (s, 1H), 7.05 (s, 1H), 6.38 (brs, 1H), 2.28 (s, 3H), 1.87 (s, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 139.4, 134.6, 133.1, 132.6, 132.1, 130.8 (2C), 129.1, 127.4, 127.0, 19.6, 16.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}ClNO_2S$: 295.0434, Found: 295.0433.

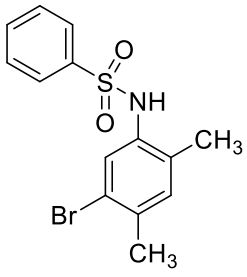
_N_-(2-Bromo-4,6-dimethylphenyl)benzenesulfonamide (3-1e)



3-1e

According to the *General Procedure II*, 2-bromo-4,6-dimethylaniline (600 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1e** (765 mg, 2.25 mmol, 75%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 6/1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.08 (s, 1H), 7.04 (s, 1H), 6.17 (brs, 1H), 2.50 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 139.7, 139.0, 133.0, 131.8, 130.8, 130.0, 128.9, 127.7, 123.1, 20.6, 20.2; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}BrNO_2S$: 338.9929, Found: 338.9928.

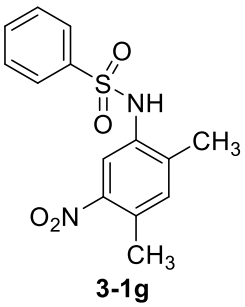
_N_-(5-Bromo-4,6-dimethylphenyl)benzenesulfonamide (3-1f)



3-1f

According to the *General Procedure II*, 5-bromo-4,6-dimethylaniline (600 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1f** (1.02 g, 3.00 mmol, 100%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 6/1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.48-7.43 (m, 3H), 6.95 (s, 1H), 6.36 (brs, 1H), 2.29 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 136.2, 133.1, 132.9, 132.6, 131.2, 129.1, 128.6, 127.1, 121,9, 22.2, 17.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}BrNO_2S$: 338.9929, Found: 338.9926.

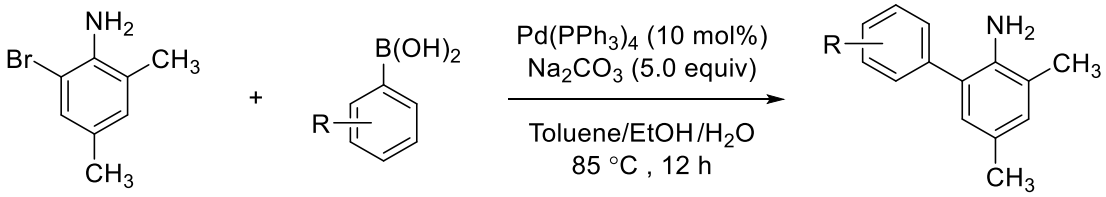
_N_-(2,4-Dimethyl-5-nitrophenyl)benzenesulfonamide (3-1g)



3-1g

According to the *General Procedure II*, 2,4-dimethyl-5-nitroaniline (499 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1g** (919 mg, 3.00 mmol, 100%) as a pale yellow solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (3, 1 H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.62-7.58 (m, 1H), 7.51-7.48 (m, 2H), 7.08 (s, 1H), 6.60 (s, 1H), 2.52 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 139.0, 137.7, 134.9, 133.5, 133.0, 131.6, 129.3, 127.2, 120.4, 20.2, 17.7; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}N_2O_4S$: 306.0674, Found: 306.0676.

Synthesis of amine by Suzuki-Miyaura cross-coupling

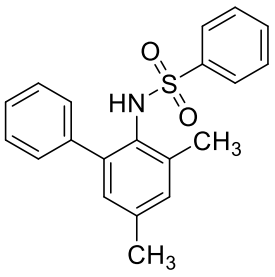


General Procedure III: To a 200 mL two-necked flask with a reflux condenser, $Pd(PPh_3)_4$ (578 mg, 0.500 mmol, 10 mol%), Na_2CO_3 (2.64 g, 25.0 mmol, 5.0 equiv), 2-bromo-4,6-dimethylaniline (1.00 g, 5.00 mmol, 1.0 equiv), arylboroinc acid (5.00 mmol, 1.0 equiv), toluene (25 mL), H_2O (15 mL), and EtOH (15 mL) were added. The resulting mixture was refluxed for 12 h. After cooling to room temperature, the organic materials were extracted with EtOAc (3 x 40 mL). The combined organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the amine.

_N_-(3,5-Dimethyl-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-1h)

According to the *General Procedure III*, phenylboronic acid (610 mg, 5.00 mmol, 1.0 equiv) was used to get 3,5-dimethyl-[1,1'-biphenyl]-2-amine (789 mg, 4.00 mmol, 80%) as a

pale brown oil after purification by column chromatography on silica gel (hexane/EtOAc = 20/1).

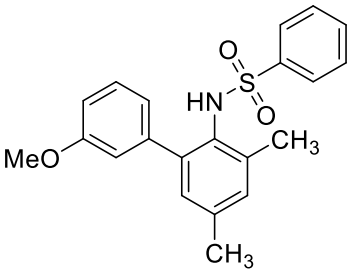


3-1h

According to the *General Procedure II*, 3,5-dimethyl-[1,1'-biphenyl]-2-amine (592 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1h** (1.01 g, 3.00 mmol, 100%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 1H), 7.24-7.09 (m, 8H), 6.78-6.75 (m, 3H), 6.45 (brs, 1H), 2.52 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 139.6, 139.0, 138.6, 137.4, 132.1, 131.6, 139.1, 128.7, 128.4, 128.3, 128.2, 126.9, 126.8, 20.9, 19.7; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{19}NO_2S$: 337.1137, Found: 337.1135.

***N*-(3'-Methoxy-3,5-dimethyl-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-1i)**

According to the *General Procedure III*, (3-methoxyphenyl)boronic acid (760 mg, 5.00 mmol, 1.0 equiv) was used to get methyl 3'-methoxy-3,5-dimethyl-[1,1'-biphenyl]-2-amine (977 mg, 4.30 mmol, 86%) as a pale brown oil after purification by column chromatography on silica gel (hexane/EtOAc = 7/1).



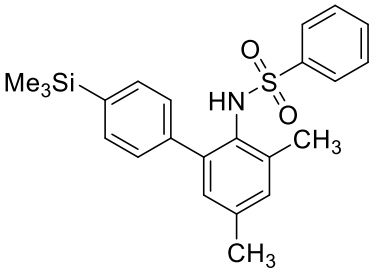
3-1i

According to the *General Procedure II*, 3'-methoxy-3,5-dimethyl-[1,1'-biphenyl]-2-amine (682 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1i** (948 mg, 2.58 mmol, 86%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.2 Hz, 1H), 7.27-7.25 (m, 2H), 7.18 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.10-7.05 (m, 2H), 6.78 (s, 1H), 6.70 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.56 (s, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 6.20 (dd, *J* = 2.0, 1.8 Hz, 1H), 3.72 (s, 3H), 2.53 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 140.3, 140.0, 139.6, 138.7, 137.4, 132.1, 131.6, 129.3, 128.9, 128.5, 128.2, 126.9, 120.4, 114.2, 112.4, 55.0, 20.9, 19.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{21}NO_3S$: 367.1242, Found: 367.1244.

_N_-(3,5-Dimethyl-4'-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-1j)

According to the *General Procedure III*, (4-(trimethylsilyl)phenyl)boronic acid (971 mg, 5.00 mmol, 1.0 equiv) was used to get 3,5-dimethyl-4'-(trimethylsilyl)-[1,1'-biphenyl]-2-amine (1.35 g, 5.00 mmol, 100%) as a pale brown oil after purification by column chromatography on silica gel (hexane/EtOAc = 10/1).

According to the *General Procedure II*, 3,5-dimethyl-4'-(trimethylsilyl)-[1,1'-biphenyl]-2-amine (808 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1j** (1.06 g, 2.58 mmol, 86%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 1H), 7.26-7.20 (m, 4H), 7.15-7.11 (m, 3H), 6.78-6.73 (m, 3H), 6.50 (brs, 1H), 2.55 (s, 3H), 2.31 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 139.6, 139.3, 138.8, 138.5, 137.5, 133.4, 132.0, 131.6, 129.1, 128.6, 128.2, 127.5, 126.8, 20.9, 19.8, -1.1; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{27}NO_2SSi$: 409.1532, Found: 409.1531.

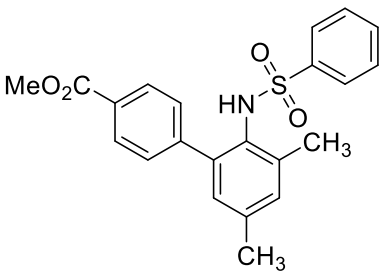


3-1j

Methyl 3',5'-Dimethyl-2'-(phenylsulfonamido)-[1,1'-biphenyl]-4-carboxylate (3-1k)

According to the *General Procedure III*, (4-(methoxycarbonyl)phenyl)boronic acid (900 mg, 5.00 mmol, 1.0 equiv) was used to get methyl 2'-amino-3',5'-dimethyl-[1,1'-biphenyl]-4-carboxylate (1.09 g, 4.25 mmol, 85%) as a pale brown oil after purification by column chromatography on silica gel (hexane/EtOAc = 10/1).

According to the *General Procedure II*, methyl 2'-amino-3',5'-dimethyl-[1,1'-biphenyl]-4-carboxylate (766 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1k** (1.14 g, 2.88 mmol, 96%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.6



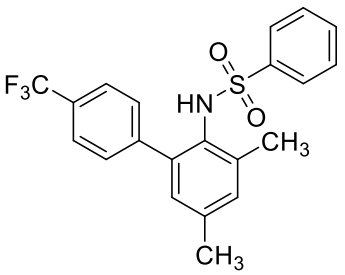
3-1k

Hz, 1H), 7.26-7.24 (m, 2H), 7.15 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.12 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 6.49 (s, 1H), 3.95 (s, 3H), 2.46 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 144.0, 139.9, 139.7, 139.0, 137.9, 132.2, 132.0, 129.4, 129.0, 128.7, 128.6, 128.3, 128.1, 126.8, 52.2, 20.9, 19.5; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{22}H_{21}NO_4S$: 395.1191, Found: 395.1186.

_N_-(3,5-dimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-1l)

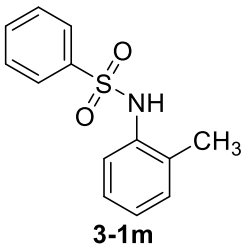
According to the *General Procedure II*, (4-(trifluoromethyl)phenyl)boronic acid (950 mg, 5.00 mmol, 1.0 equiv) was used to get 3,5-dimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-amine (1.15 g, 4.33 mmol, 87%) as a pale brown oil after purification by column chromatography on silica gel (hexane/EtOAc = 15/1).

According to the *General Procedure II*, 3,5-dimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-amine (796 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1l** (808 mg, 1.99 mmol, 66%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 16.4, 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27-7.25 (m, 3H), 7.19-7.15 (m, 2H), 7.02 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.81 (s, 1H), 6.31 (s, 1H), 2.48 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 139.8, 139.6, 139.3, 138.2, 132.3, 132.1, 130.1 (q, *J* = 40.6 Hz), 129.2, 128.9, 128.7 (d, *J* = 1.0 Hz, 2C), 128.1, 126.6, 125.0 (q, *J* = 3.8 Hz, 2C), 119.6 (q, *J* = 329 Hz), 21.0, 19.5; ^{19}F NMR(368 MHz,$CDCl_3$) δ -62.4; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{18}F_3NO_2S$: 405.1010, Found: 405.1010.



3-1l

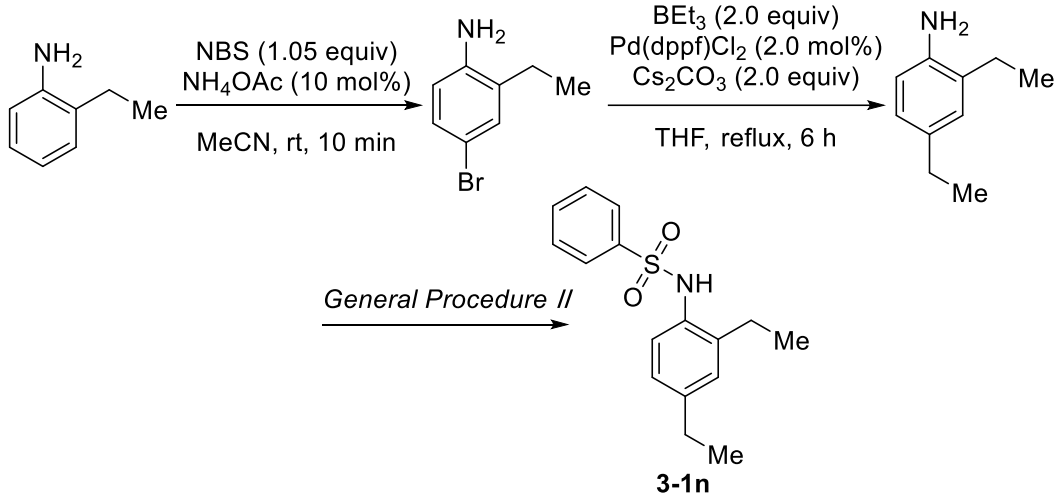
N-(*o*-Tolyl)benzenesulfonamide (3-1m)



3-1m

According to the *General Procedure II*, 2-methylaniline (321 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1m** (743 mg, 3.00 mmol, 100%%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.72 (m, 2H), 7.57-7.53 (m, 1H), 7.45-7.41 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.17-7.12 (m, 1H), 7.09-7.07 (m, 2H), 6.41 (brs, 1H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 134.3, 132.9, 131.5, 130.8, 129.0, 127.1, 127.0, 126.4, 124.5, 17.5; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{13}NO_2S$: 247.0667, Found: 247.0665.

N-(2,4-Diethylphenyl)benzenesulfonamide (3-1n)[19]



3-1n

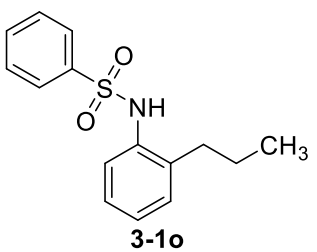
To a 300 mL two-necked flask, 2-ethylaniline (2.42 g, 20.0 mmol, 1.0 equiv), NH_4OAc (0.154 g, 2.00 mmol, 10 mol%), N-bromosuccinimide (3.74 g, 21.0 mmol, 1.05 equiv) and MeCN (100 mL, degassed) were added and the resulting mixture was stirred at room temperature. After 10 min, the volatiles were removed under reduced pressure. Water (100 mL) was added and the organic materials were extracted with EtOAc (3 x 100 mL), dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was

purified by column chromatography on silica gel to afford 4- bromo-2-ethylaniline (3.5 g, 18.0 mmol, 90%).

To a 200 mL two-necked flask with a reflux condenser, $Pd(dppf)Cl_2$ (0.146 g, 0.200 mmol, 2.0 mol%), Cs_2CO_3 (6.52 g, 20.0 mmol, 2.0 equiv), 4- bromo-2-ethylaniline (2.0 g, 10.0 mmol, 1.0 equiv), and triethylborane (1.0 M in THF, 20 mL, 20.0 mmol, 2.0 equiv) were added and refluxed for 6 h. The mixture was cooled to 0 ℃ and 30% H_2O_2 (5 mL) and 10% aq. NaOH (15 mL) were added. The mixture was further stirred for 30 min at room temperature. The resulting mixture was acidified by 1N aq. HCl, and the organic materials were extracted with Et_2O (3 x 70 mL). The combined organic layer was washed with saturated aqueous solution of $FeSO_4$ and brine, dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to afford 2,4-diethylaniline (478 mg, 3.20 mmol, 32%) as a brownish red oil.

According to the *General Procedure II*, 2,4-diethylaniline (448 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1n** (469 mg, 1.62 mmol, 54%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 6.8 Hz, 1H), 7.43 (dd, *J* = 7.6, 6.8 Hz, 2H), 7.16-7.14 (m, 1H), 6.96-6.95 (m, 2H), 6.30 (brs, 1H), 2.58 (q, *J* = 7.6 Hz, 2H), 2.33 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.01 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 139.7, 137.8, 132.8, 131.0, 128.9, 128.4, 127.2, 126.1, 125.2, 28.3, 23.7, 15.4, 14.2; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{16}H_{19}NO_2S$: 289.1137, Found: 289.1135.

N-(2-Propylphenyl)benzenesulfonamide (3-1o)

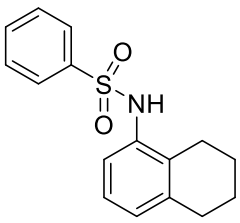


3-1o

According to the *General Procedure II*, 2-propylaniline (406 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1o** (644 mg, 2.34 mmol, 78%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.72 (m, 2H), 7.54 (dd, *J* = 8.0, 7.6, 1H), 7.45-7.41 (m, 2H), 7.35-7.33 (m, 1H), 7.16-7.07 (m, 3H), 6.45 (brs, 1H), 2.27 (t, *J* = 7.6 Hz, 2H),

1.43-1.33 (m, 2H), 0.83 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 135.5, 133.8, 132.9, 129.8, 129.0, 127.1, 126.8, 126.3, 124.4, 32.6, 23.0, 13.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{17}NO_2S$: 275.0980, Found: 275.0980.

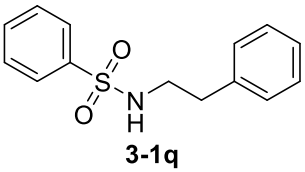
N-(5,6,7,8-Tetrahydronaphthalen-1-yl)benzenesulfonamide (3-1p)



3-1p

According to the *General Procedure II*, 5,6,7,8-tetrahydronaphthalen-1-amine (442 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1p** (837 mg, 2.91 mmol, 97%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.51 (s, 1H), 2.68 (t, *J* = 6.0 Hz, 2H), 2.31 (t, *J* = 6.0 Hz, 2H), 1.64-1.61 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 138.5, 134.1, 132.8, 130.3, 128.9, 127.2, 127.1, 125.9, 121.3, 29.6, 24.2, 22.6, 22.3; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{17}NO_2S$: 287.0980, Found: 287.0980.

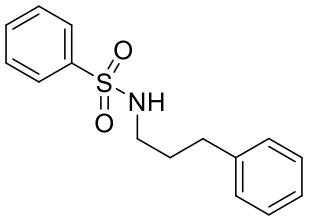
N-Phenethylbenzenesulfonamide (3-1q)



3-1q

According to the *General Procedure II*, 2-phenylethan-1-amine (364 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1q** (533 mg, 2.04 mmol, 68%) as a white solid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* =7.6, 7.4 Hz, 1H), 7.50 (dd, *J* = 7.6, 7.4 Hz, 2H), 7.29-7.21 (m, 3H), 7.07 (d, *J* = 7.4 Hz, 2H), 4.35 (brt, *J* = 5.4 Hz, 1H), 3.25 (td, *J* = 6.8, 5.4 Hz, 2H), 2.77 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 132.6, 129.1, 128.8, 128.7, 127.0, 126.9, 126.8, 44.2, 35.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}NO_2S$: 261.0824, Found: 261.0826.

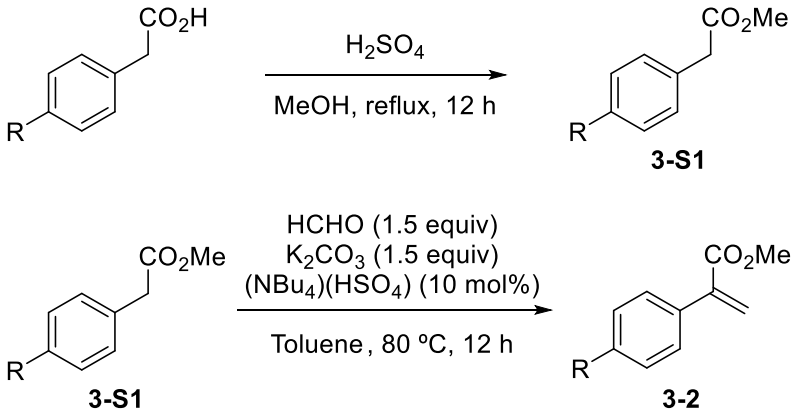
N-(3-Phenylpropyl)benzenesulfonamide (3-1r)



3-1r

According to the *General Procedure II*, 3-phenylpropan-1-amine (406 mg, 3.00 mmol, 1.0 equiv) was used to obtain product **3-1r** (446 mg, 1.62 mmol, 54%) as a colorless liquid after purified by flash column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.61-7.56 (m, 1H), 7.54-7.49 (m, 2H), 7.27-7.23 (m, 2H), 7.20-7.16 (m, 1H), 7.08 (d, *J* = 6.8 Hz, 2H), 4.49 (brt, *J* = 6.0 Hz, 1H), 2.99 (q, *J* = 6.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.83-1.76 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 139.9, 132.6, 129.1, 128.5, 128.3, 127.0, 126.1, 42.7, 32.7, 31.2; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{13}NO_2S$: 275.0980, Found: 275.0982.

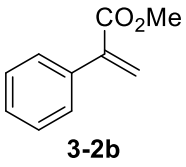
Synthesis of 3-2b–3-2e[19]



General Procedure IV: To a 300 mL two-necked flask with a reflux condenser, H_2SO_4 (12.0 mL) and MeOH (90 mL) were added. To the mixture, a phenylacetic acid derivative (30.0 mmol) was added dropwise at 0 ℃, and the resulting mixture was refluxed for 12 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. Water (150 mL) was added and the organic materials were extracted with EtOAc (3 x 150 mL). The combined organic layer was washed with saturated aqueous solution of $NaHCO_3$ and brine (200 mL), dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford a methyl phenylacetate detivative **3-S1b-e**.

To a 300 mL two-necked flask with reflux condenser, paraformaldehyde (1.35 g, 45.0 mmol, 1.5 equiv), K_2CO_3 (6.22 g, 45.0 mmol, 1.5 equiv), tetrabutylammonium hydrogensulfate (1.02 g, 3.00 mmol, 10 mol%) and **3-S1** (30.0 mmol, 1.0 equiv), were added. This mixture was resolved in toluene and stirred at 80 °C for 12 h. After cooling to room temperature, water (200 mL) was added and the organic materials were extracted with Et_2O (3 x 50 mL). the combined organic layer was washed with brine (100 mL), dried over $MgSO_4$ filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane) to afford alkene **3-2**.

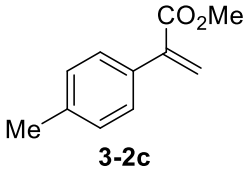
Methyl 2-phenylacrylate (3-2b)



3-2b

According to the *General Procedure IV*, the product **3-2b** (3.26 g, 20.1 mmol, 67%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 6.37 (d, *J* = 1.2 Hz, 1H), 5.90 (d, *J* = 1.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 141.2, 136.7, 128.3, 128.2, 128.1, 127.0, 52.2.

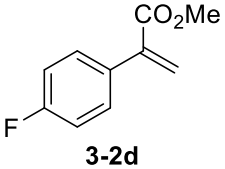
Methyl 2-(*p*-tolyl)acrylate (3-2c)



3-2c

According to the *General Procedure IV*, the product **3-2c** (1.85 g, 10.5 mmol, 35%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 6.31 (d, *J* = 1.2 Hz, 1H), 5.86 (d, *J* = 1.2 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 142.1, 137.7, 134.3, 128.8, 127.8, 126.1, 51.9, 21.1.

Methyl 2-(4-fluorophenyl)acrylate (3-2d)

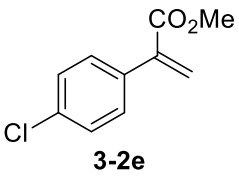


3-2d

According to the *General Procedure IV*, the product **3-2d** (3.14 g, 17.4 mmol, 58%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 2H), 7.06-7.00 (m, 2H), 6.35 (d, *J* = 1.2 Hz, 1H), 5.86 (d, *J* = 1.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 164.3 (d, *J* = 252 Hz), 140.2, 132.7 (d, *J* = 12 Hz), 130.1 (d, *J* = 31 Hz), 127.0, 115.0 (d, *J* = 84 Hz), 52.3.

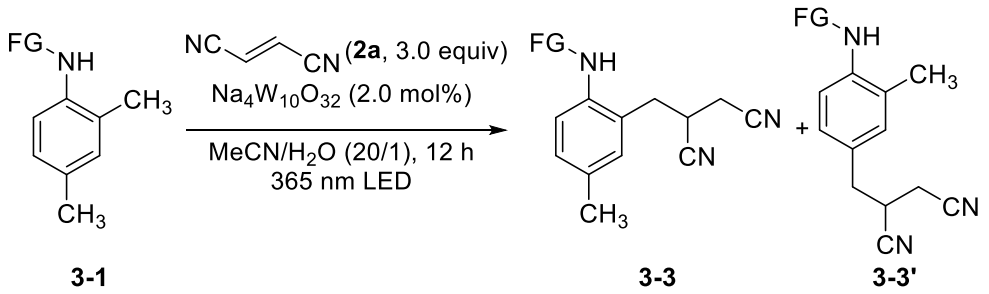
Methyl 2-(4-chlorophenyl)acrylate (3-2e)

According to the *General Procedure IV*, the product **3-2e** (1.18 g, 6.00 mmol, 20%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 6.39 (d, J = 1.2 Hz, 1H), 5.90 (d, J = 1.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 140.1, 135.9, 133.9, 129.7, 128.3, 127.4, 52.3.



3-2e

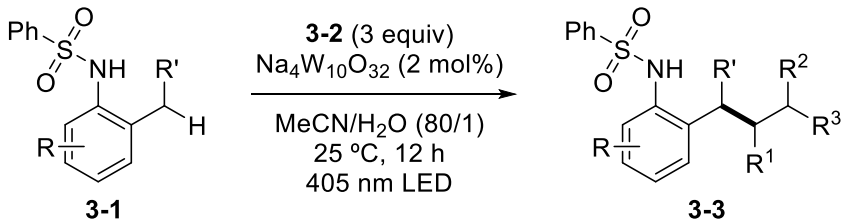
3.4.3 Screening of Functional Groups (Table 3-1)



3-1 **3-3** **3-3'**

To a Schlenk tube, **3-1A**–**3-1F**, **3-1a** (0.200 mmol, 1.0 equiv), fumaronitrile (**3-2a**, 46.8 mg, 0.600 mmol, 3.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%), and MeCN/H_2O (20/1, 2.0 mL) were added, and the resulting mixture was stirred at room temperature for 12 h under irradiation of UV (365 nm). After the reaction, the resulting mixture was analyzed by GC to determine the site-selectivity and then 1,2-dichloroethane was added to determine the yield of **3-3** and **3-3'** by ^{1}H NMR.

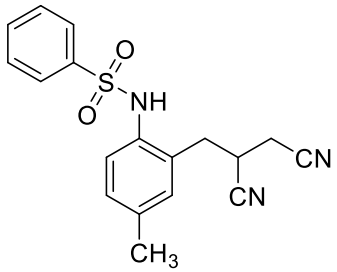
3.4.4 Site-Selective C(sp^3)–H Alkylation of Sulfonanilides (Schemes 3-4, 3-5, 3-6, 3-7)



3-1 **3-3**

General procedure V: To a Schlenk tube, a *N*-(o-tolyl)benzenesulfonamide derivative (**3-1**, 0.200 mmol, 1.0 equiv), fumaronitrile (**3-2a**, 46.8 mg, 0.600 mmol, 3.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%), and MeCN/H_2O (80/1, 2.0 mL) were added, and the resulting mixture was stirred at room temperature for 12 h under irradiation of UV (405 nm). After the reaction, the volatiles were removed under reduced pressure, the resulting mixture was purified by column chromatography on silica gel **3-3**.

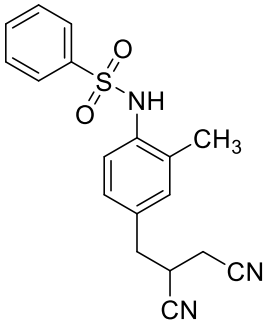
***N*-(2-(2,3-Dicyanopropyl)-4-methylphenyl)benzenesulfonamide (3-3a)**



3-3a

According to the *General procedure V*, the reaction was carried out using **3-1a** (52.3 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3a** (48.2 mg, 71%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.19 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.44 (s, 1H), 3.39-3.32 (m, 1H), 3.26 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.11 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.82-2.70 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.6, 134.1, 133.4, 132.0, 131.0, 129.4, 129.2, 128.5, 127.5, 118.9, 115.7, 33.0, 29.3, 21.0, 21.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{17}N_3O_2S$: 339.1041, Found: 339.1042.

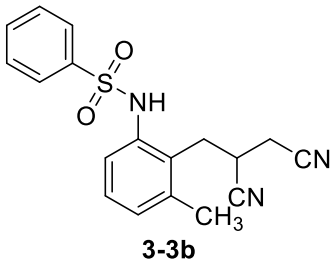
***N*-(4-(2,3-Dicyanopropyl)-2-methylphenyl)benzenesulfonamide (3-3a')**



3-3a'

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.45 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.40 (brs, 1H), 3.14-3.07 (m, 1H), 3.00 (d, *J* = 6.8 Hz, 2H), 2.64 (d, *J* = 6.4 Hz, 2H), 2.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 134.4, 133.2, 132.3, 132.1, 131.5, 129.1, 127.6, 127.0, 124.7, 118.2, 115.3, 36.4, 30.0, 20.2, 17.5; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{17}N_3O_2S$: 339.1041, Found: 339.1041.

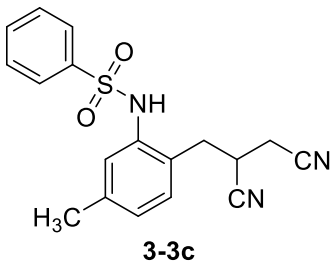
_N_-(2-(2,3-Dicyanopropyl)-3-methylphenyl)benzenesulfonamide (3-3b)



3-3b

According to the *General procedure V*, the reaction was carried out using **3-1b** (52.3 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3b** (42.8 mg, 63%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.50 (dd, *J* = 8.0, 7.2 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.98 (dd, *J* = 8.0, 7.2 Hz, 1H), 6.63 (brs, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 3.49-3.42 (m, 1H), 3.33-3.25 (m, 2H), 2.85-2.84 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.7, 134.4, 133.4, 133.3, 131.1, 129.2, 128.1, 127.6, 126.3, 118.9, 115.8, 29.6, 28.5, 21.3, 20.2; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{17}N_3O_2S$: 339.1041, Found: 339.1042.

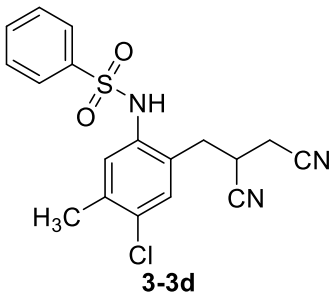
_N_-(2-(2,3-Dicyanopropyl)-5-methylphenyl)benzenesulfonamide (3-3c)



3-3c

According to the *General procedure V*, the reaction was carried out using **3-1c** (52.3 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3c** (49.6 mg, 73%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.51 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.84 (brs, 1H), 6.50 (s, 1H), 3.30-3.23 (m, 1H), 3.18 (dd, *J* = 13.4, 5.5 Hz, 1H), 3.05 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.78-2.67 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 138.6, 133.6, 133.4, 131.1, 130.2, 129.2, 129.1, 128.7, 127.5, 119.0, 115.9, 32.6, 29.3, 20.8 (2C); HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{17}N_3O_2S$: 339.1041, Found: 339.1042.

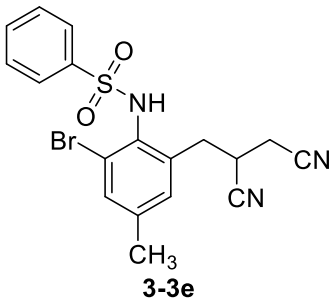
N-(4-Chloro-2-(2,3-dicyanopropyl)-5-methylphenyl)benzenesulfonamide (3-3d)



3-3d

According to the *General procedure V*, the reaction was carried out using **3-1d** (59.2 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3d** (56.1 mg, 75%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.53 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.35 (s, 1H), 6.60 (brs, 1H), 6.51 (s, 1H), 3.32-3.25 (m, 1H), 3.17 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.05 (dd, *J* = 13.8, 9.8 Hz, 1H), 2.82-2.71 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 137.0, 134.5, 133.6, 132.9, 132.2, 131.4, 130.7, 129.3, 127.5, 118.6, 115.6, 32.4, 29.2, 20.9, 19.6; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{16}ClN_3O_2S$: 373.0652, Found: 373.0649.

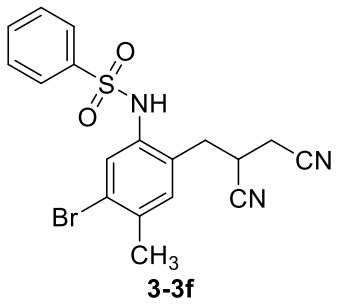
N-(2-Bromo-6-(2,3-dicyanopropyl)-4-methylphenyl)benzenesulfonamide (3-3e)



3-3e

According to the *General procedure V*, the reaction was carried out using **3-1e** (68.1 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3e** (48.2 mg, 58%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.60 (m, 3H), 7.45 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.26 (s, 1H), 7.22 (s, 1H), 6.34 (brs, 1H), 3.62 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.55-3.49 (m, 1H), 3.28 (dd, *J* = 14.0, 10.6 Hz, 1H), 2.87-2.75 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 138.5, 137.0, 133.6, 133.2, 131.6, 130.0, 129.1, 127.8, 123.8, 118.8, 115.6, 34.6, 29.1, 21.3, 20.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{16}BrN_3O_2S$: 417.0147, Found: 417.0149.

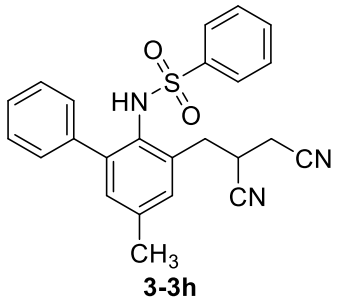
_N_-(5-Bromo-2-(2,3-dicyanopropyl)-4-methylphenyl)benzenesulfonamide (3-3f)



3-3f

According to the *General procedure V*, the reaction was carried out using **3-1f** (68.1 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3f** (54.4 mg, 65%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.53 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.23 (s, 1H), 6.92 (brs, 1H), 6.79 (s, 1H), 3.33-3.27 (m, 1H), 3.18 (dd, *J* = 13.8, 5.0 Hz, 1H), 3.03 (dd, *J* = 13.8, 9.8 Hz, 1H), 2.83-2.71 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 138.1, 133.6, 133.0, 132.9, 132.5, 131.8, 129.3, 127.4, 124.0, 118.8, 115.9, 32.5, 29.1, 22.4, 20.9; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{16}BrN_3O_2S$: 417.0147, Found: 417.0145.

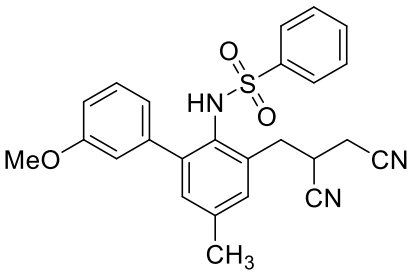
_N_-(3-(2,3-Dicyanopropyl)-5-methyl-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-3h)



3-3h

According to the *General procedure V*, the reaction was carried out using **3-1h** (67.5 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3h** (51.5 mg, 62%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.2 Hz, 1H), 7.29 (s, 1H), 7.21-7.18 (m, 3H), 7.14-7.09 (m, 4H), 6.89 (s, 1H), 6.74 (s, 1H), 6.63 (d, *J* = 7.2 Hz, 2H), 3.63-3.51 (m, 2H), 3.41 (dd, *J* = 12.8, 9.6 Hz, 1H), 2.85-2.84 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 138.6, 138.4, 138.0, 135.7, 132.6, 131.4, 131.2, 128.9, 128.8, 128.1, 127.9, 127.1, 127.0, 119.2, 115.8, 34.3, 29.6, 21.3, 21.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{21}N_3O_2S$: 415.1354, Found: 415.1351.

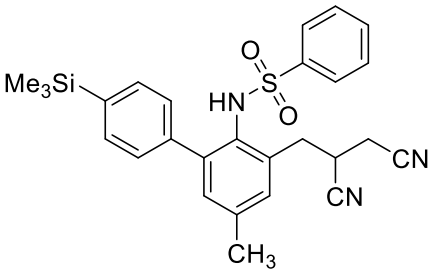
_N_-(3-(2,3-Dicyanopropyl)-3'-methoxy-5-methyl-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-3i)



3-3i

According to the *General procedure V*, the reaction was carried out using **3-1i** (73.5 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3i** (32.1 mg, 36%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 6.2 Hz, 1H), 7.28 (s, 1H), 7.19 (m , 4H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.89 (s, 1H), 6.82 (s, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.33 (d, *J* = 6.8 Hz, 1H), 6.04 (br, 1H), 3.72 (s, 3H), 3.63-3.53 (m, 2H), 3.39 (dd, *J* = 12.8, 9.6 Hz, 1H), 2.85-2.83 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 140.7, 139.3, 138.6, 138.4, 135.7, 132.6, 131.3, 131.2, 129.6, 128.7, 128.2, 127.0, 120.0, 119.2, 115.8, 114.1, 112.6, 55.0, 34.3, 29.5, 21.3, 21.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{25}H_{23}N_3O_3S$: 445.1460, Found: 445.1462.

_N_-(3-(2,3-Dicyanopropyl)-5-methyl-4'-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-3j)

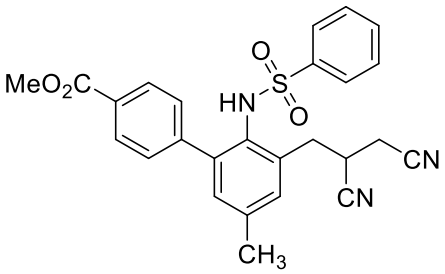


3-3j

According to the *General procedure V*, the reaction was carried out using **3-1j** (81.9 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3j** (42.9 mg, 44%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 6.0 Hz, 1H), 7.30 (s, 1H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.14 (m, 4H), 6.89 (s, 1H), 6.78 (s, 1H), 6.63 (d, *J* = 7.2 Hz, 2H), 3.64-3.53 (m, 2H), 3.41 (dd, *J* = 12.6, 9.8 Hz, 1H), 2.87-2.85 (m, 2H), 2.36 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 139.2, 138.6, 138.5,

138.3, 135.9, 133.6, 132.5, 131.3, 131.2, 128.8, 128.1, 127.2, 126.9, 119.3, 115.8, 34.2, 29.5, 21.3, 21.0, -1.2; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{27}H_{29}N_3O_2SSi$: 487.1750, Found: 487.1752.

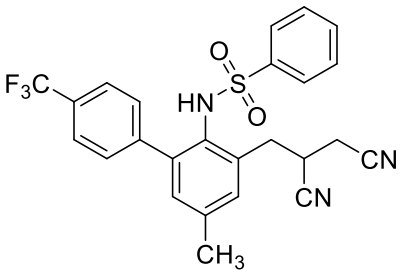
Methyl 3'-(2,3-dicyanopropyl)-5'-methyl-2'-(phenylsulfonamido)-[1,1'-biphenyl]-4-carboxylate (3-3k)



3-3k

According to the *General procedure V*, the reaction was carried out using **3-1k** (79.1 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3k** (50.2 mg, 53%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.46-7.44 (m, 1H), 7.31 (s, 1H), 7.17-7.14 (m, 4H), 6.91 (s, 1H), 6.82 (s, 1H), 6.78 (d, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 3.58-3.50 (m, 2H), 3.40 (dd, *J* = 14.2, 11.8 Hz, 1H), 2.97-2.86 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 142.8, 140.6, 139.1, 138.6, 136.6, 132.6, 131.7, 131.2, 129.7, 128.9, 128.7, 128.2, 128.0, 126.8, 119.2, 115.9, 52.3, 34.1, 29.6, 21.2, 21.0; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{26}H_{23}N_3O_4S$: 473.1409, Found: 473.1410.

***N*-(3-(2,3-Dicyanopropyl)-5-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)benzenesulfonamide (3-3l)**

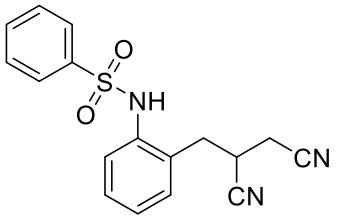


3-3l

According to the *General procedure V*, the reaction was carried out using **3-1l** (81.1 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3l** (31.9 mg, 33%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 4.0 Hz, 1H), 7.33-7.30 (m, 3H), 7.18-7.17 (m, 4H), 6.92 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 2H),

6.80 (s, 1H), 3.57-3.50 (m, 2H), 3.46-3.40 (m, 1H), 2.89-2.88 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 140.4, 139.3, 138.8, 136.8, 132.7, 131.9, 131.3, 129.1 (q, J = 24.0 Hz), 129.0, 128.6 (q, J = 1.0 Hz, 2C), 128.0, 126.7, 125.3 (q, J = 7.5 Hz, 2C), 118.0 (q, J = 304 Hz), 119.2, 115.8, 34.0, 29.7, 21.2, 21.1; ^{19}F NMR (368 MHz,$CDCl_3$) δ -62.5; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{25}H_{20}F_3N_3O_2S$: 483.1228, Found: 483.1228.

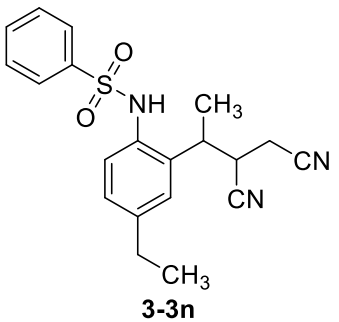
_N_-(2-(2,3-Dicyanopropyl)phenyl)benzenesulfonamide (3-3m)



3-3m

According to the *General procedure V*, the reaction was carried out using **3-1m** (49.5 mg, 0.200 mmol), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3m** (57.9 mg, 89%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.51 (dd, J = 7.8, 7.2 Hz, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.29 (dd, J = 7.2, 7.2 Hz, 1H), 7.13 (dd, J = 7.2, 7.2 Hz, 1H), 6.79 (brs, 1H), 6.67 (d, J = 7.2 Hz, 1H) 3.35-3.26 (m, 2H), 3.14 (dd, J = 12.6, 9.8 Hz, 1H), 2.81-2.70 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 133.9, 133.5, 131.4, 129.3, 128.8, 128.7, 128.2, 127.5 (3C), 118.9, 115.7, 33.0, 29.2, 20.9; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{17}H_{15}N_3O_2S$: 325.0885, Found: 325.0884.

_N_-(2-(3,4-Dicyanobutan-2-yl)-4-ethylphenyl)benzenesulfonamide (3-3n)



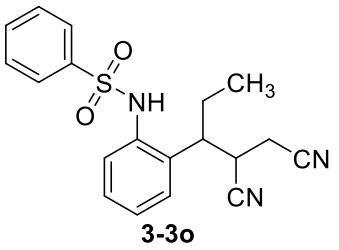
3-3n

According to the *General procedure V*, the reaction was carried out using **3-1n** (57.8 mg, 0.200 mmol, 1.0 equiv), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). A mixture of diastereomers of **3-3n** (42.6 mg, 0.12 mmol, 58%, dr = 56:44) was obtained as a colorless liquid after purification by column chromatography on silica gel (hexane/EtOAc = 4/1). The diastereomers could be

partially separated by column chromatography on silica gel (hexane/EtOAc = 4/1). *Major diastereomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.52 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.20 (s, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 6.39 (brs, 1H), 3.78-3.72 (m, 1H), 3.21 (q, *J* = 7.1 Hz, 1H), 2.65-2.60 (m, 4H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 140.2, 138.8, 133.3, 130.2, 129.2, 128.9, 127.7, 127.6, 126.4, 118.3, 116.2, 35.4, 34.4, 28.5, 20.0, 18.2, 15.2; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{21}N_3O_2S$: 367.1354, Found: 367.1354. *Minor diastereomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 7.4 Hz, 2H), 7.36 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.59 (brs, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 3.96-3.90 (m, 1H), 3.19 (q, *J* = 7.3 Hz, 1H), 2.66-2.61 (m, 3H), 2.54 (dd, *J* = 16.8, 8.4 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.22 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 139.2, 138.8, 133.2, 130.8, 129.1, 128.8, 127.8, 127.6, 126.7, 118.3, 116.3, 35.6, 33.5, 28.5, 19.2, 19.1, 15.1; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{21}N_3O_2S$: 367.1354, Found: 367.1352.

_N_-(2-(1,2-Dicyanopentan-3-yl)phenyl)benzenesulfonamide (3-3o)

According to the *General procedure V*, the reaction was carried out using **3-1o** (49.5 mg, 0.200 mmol), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). A mixture of diastereomers of **3-3o** (47.4 mg, 0.15 mmol, 67%, dr = 71:29) was obtained as a colorless liquid after purification by column chromatography on silica gel (DCM/Et_2O = 25/1). The diastereomers could be partially separated by column chromatography on silica gel (DCM/Et_2O = 25/1). *Major diastereomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.52 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.10 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.49 (brs, 1H), 3.64-3.59 (m, 1H), 3.30-3.25 (m, 1H), 2.78-2.66 (m, 2H), 2.10-2.00 (m, 1H), 1.86-1.75 (m, 1H), 0.70 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 138.3, 134.1,

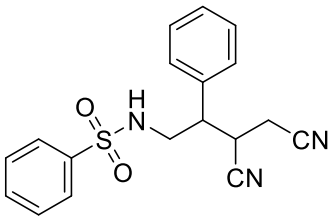


3-3o

133.5, 129.3, 129.2, 128.3, 128.2, 127.5, 127.2, 118.6, 116.3, 40.9, 34.6, 25.5, 20.1, 11.1; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{19}N_3O_2S$: 353.1198, Found: 353.1198. *Minor diastereomer*: ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 2H), 7.64-7.58 (m, 2H), 7.50 (dd, *J* = 7.8, 7.6 Hz, 2H), 7.35 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.10 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.63 (s, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 3.76 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.35 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.67 (dd, *J* = 17.2, 5.8 Hz, 1H), 2.50 (dd, *J* = 17.2, 9.2 Hz, 1H), 1.98-1.87 (m, 1H), 1.85-1.74 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 137.6, 134.2, 133.4, 129.2, 129.1, 128.4 (2C), 127.7, 127.6, 118.1, 116.5, 39.7, 33.5, 27.1, 19.1, 11.5; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{19}N_3O_2S$: 353.1198, Found: 353.1198.

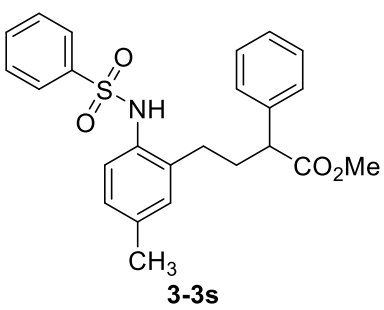
_N_-(2-(2,3-Dicyanopropyl)phenyl)benzenesulfonamide (3-3q)

According to the *General procedure V*, the reaction was carried out using **3-1q** (52.3 mg, 0.200 mmol), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2a** (46.8 mg, 0.60 mmol, 3.0 equiv) for 14 h under irradiation of UV (405 nm). The product **3-3q** (28.5 mg, 42%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.40-7.39 (m, 3H), 7.11 (d, *J* = 6.8 Hz, 2H), 4.37 (brt, *J* = 5.4 Hz, 1H), 3.65-3.59 (m, 1H), 3.41-3.34 (m, 1H), 3.19-3.09 (m, 2H), 2.60 (dd, *J* = 17.6, 3.6 Hz, 1H), 2.37 (dd, *J* = 17.6, 6.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 134.8, 133.2, 130.0, 129.4, 129.3, 127.9, 127.1, 117.6, 115.0, 46.7, 45.8, 31.7, 19.7; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{17}N_3O_2S$: 339.1041, Found: 339.1041.



3-3q

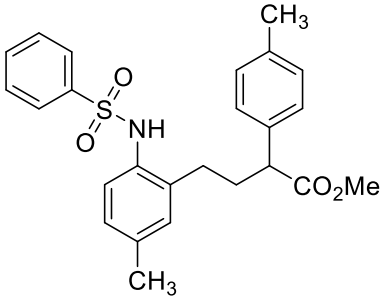
Methyl 4-(5-methyl-2-(phenylsulfonamido)phenyl)-2-phenylbutanoate (3-3s)



3-3s

According to the *General procedure V*, the reaction was carried out using **3-1a** (52.3 mg, 0.200 mmol), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2b** (97.3 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3s** (57.6 mg, 68%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.0 Hz, 1H), 7.39-7.27 (m, 6H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.03 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 3.73 (s, 3H), 3.55-3.47 (m, 1H), 2.25 (s, 3H), 2.22-1.99 (m, 3H), 1.81-1.74 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 139.7, 138.5, 136.1, 134.8, 132.6, 131.5, 130.3, 128.8, 128.7, 127.9, 127.6, 127.4, 127.0, 125.4, 52.4, 50.7, 34.3, 29.0, 20.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{25}NO_4S$: 423.1504, Found: 423.1505.

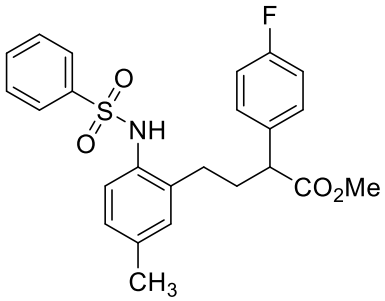
Methyl 4-(5-methyl-2-(phenylsulfonamido)phenyl)-2-(*p*-tolyl)butanoate (3-3t)



3-3t

According to the *General procedure V*, the reaction was carried out using **3-1a** (52.3 mg, 0.200 mmol), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2c** (105.7 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3t** (54.3 mg, 62%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 2H), 7.08 (d, *J* = 7.3 Hz, 2H), 7.03-6.96 (m, 2H), 6.83 (s, 1H), 3.73 (s, 3H), 3.44 (dd, *J* = 8.4, 5.6 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 2.19-1.96 (m, 3H), 1.79-1.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 139.8, 137.2, 136.1, 135.5, 134.7, 132.6, 131.6, 130.3, 129.5, 128.7, 127.9, 127.5, 127.0, 125.3, 52.4, 50.3, 34.3, 29.0, 21.0, 20.8; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{25}H_{27}NO_4S$: 437.1661, Found: 437.1662.

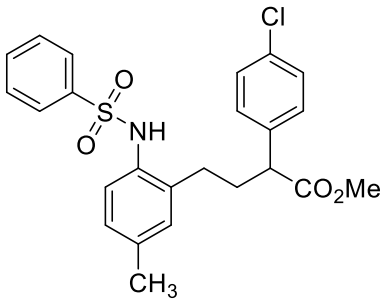
Methyl 2-(4-fluorophenyl)-4-(5-methyl-2-(phenylsulfonamido)phenyl)butanoate (3-3u)



3-3u

According to the *General procedure V*, the reaction was carried out using **3-1a** (52.3 mg, 0.200 mmol), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2d** (108.1 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3u** (30.9 mg, 35%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 8.0, 7.6 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.18-7.15 (m, 2H), 7.02-6.95 (m, 3H), 6.91 (s, 1H), 6.84 (s, 1H), 3.74 (s, 3H), 3.47 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.25 (s, 3H), 2.29-1.98 (m, 3H), 1.79-1.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 162.1 (d, *J* = 247 Hz), 139.8, 136.3, 134.9, 134.3, 132.7, 131.5, 130.4, 129.2 (d, *J* = 7.6 Hz, 2C), 128.8, 128.0, 127.1, 125.5, 115.7 (d, *J* = 22.3, 2C), 52.5, 50.0, 34.4, 29.1, 20.8; ^{19}F NMR (368 MHz, $CDCl_3$) δ -115; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{24}FNO_4S$: 441.1410, Found: 441.1410.

Methyl 2-(4-chlorophenyl)-4-(5-methyl-2-(phenylsulfonamido)phenyl)butanoate (3-3v)



3-3v

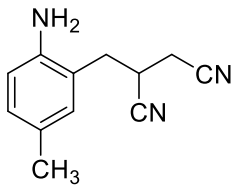
According to the *General procedure V*, the reaction was carried out using **3-1a** (52.3 mg, 0.200 mmol), $Na_4W_{10}O_{32}$ (9.77 mg, 0.0040 mmol, 2.0 mol%) and **3-2e** (118.0 mg, 0.60 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3v** (76.9 mg, 84%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.39 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.30-7.24 (m, 3H), 7.13 (d, *J* = 7.0 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H), 6.84 (s, 1H), 3.74 (s, 3H), 3.47 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.25 (s, 3H), 2.21-1.98 (m, 3H), 1.79-1.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 139.8, 137.0, 136.3, 134.8, 133.4, 132.7, 131.5, 130.4, 129.0, 128.9, 128.8, 128.0, 127.1, 125.5, 52.6, 50.2,

34.2, 29.1, 20.9; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{24}ClNO_4S$: 457.1115, Found: 457.1114.

2 mmol Scale reaction

According to the *General procedure V*, the reaction was carried out using **3-1a** (523 mg, 2.00 mmol), $Na_4W_{10}O_{32}$ (97.7 mg, 0.0400 mmol, 2.0 mol%) and **3-2a** (468 mg, 6.00 mmol, 3.0 equiv) for 12 h under irradiation of UV (405 nm). The product **3-3a** (0.366 g, 54%; **3-3a**:**3-3a'** = 87:13) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1).

2-(2-Amino-5-methylbenzyl)succinonitrile (3-4)[27]



3-4

To a 10 mL pressure reaction tube, **3-3a** (68.8 mg, 0.200 mmol, 1.00 equiv) (solved in 1.0 mL THF) was dropwise to the lithium (19.4 mg, 2.80 mmol, 14.0 equiv) and naphthalene (2.58 mg, 0.020 mmol, 10 mol%) in dehydrated THF (4.0 mL) under nitrogen atmosphere at -78 ºC for 1 h and then warm to 20 ºC for 12 h. The resulting mixture were quenched by water and extracted by EtOAc (5.0 mL x 3). The combined organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to afford **3-4**[19] (37.9 mg, 0.190 mmol, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.54 (br, 2H), 3.41-3.34 (m, 1H), 3.04 (dd, *J* = 14.4, 11.0 Hz, 1H), 2.90 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.69 (dd, *J* = 17.6, 6.0 Hz, 1H), 2.62 (dd, *J* = 17.6, 6.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 131.3, 129.8, 129.0, 119.6, 119.1, 117.2, 116.0, 33.5, 27.2, 20.3, 20.1.

3.4.5 Mechanism Study

^{1}H NMR analysis of a mixture of 3-1a and (^{n}Bu$_4$N)W$_{10}$O$_{32}$

Three kinds of mixture of **3-1a** and (^{n}Bu$_4$N)W$_{10}$O$_{32}$ (TBADT) were analyzed by ^{1}H NMR in CDCN. 1) **3-1a** (5.23 mg, 0.0200 mmol); 2) **3-1a** (5.23 mg, 0.0200 mmol, 1.0 equiv) and TBADT (16.6 mg, 0.00500 mmol, 0.25 equiv) (**3-1a**/TBADT = 4:1); 3) **3-1a** (5.23 mg, 0.0200 mmol, 1.0 equiv) and TBADT (33.2 mg, 0.0100 mmol, 0.50 equiv) (**3-1a**/TBADT = 2:1); 4) **3-1a** (5.23 mg, 0.0200 mmol, 1.0 equiv) and TBADT (66.4 mg, 0.0200 mmol, 0.50 equiv) (**3-1a**/TBADT = 1:1).The chemical shift of NH proton in ^{1}H NMR spectra: 7.32 ppm (**3-1a**/TBADT = 4:1, molar ratio) and 7.34 ppm (**3-1a**/TBADT = 2:1, molar ratio), compared to **3-1a** (δ 7.27 ppm) (**Figure 3-3**) NH proton signals are obviously shifted by adding decatungstate. These results suggest that hydrogen bond exists between the decatungstate catalyst and the NH bond of the sulfonamide group of the substrate.

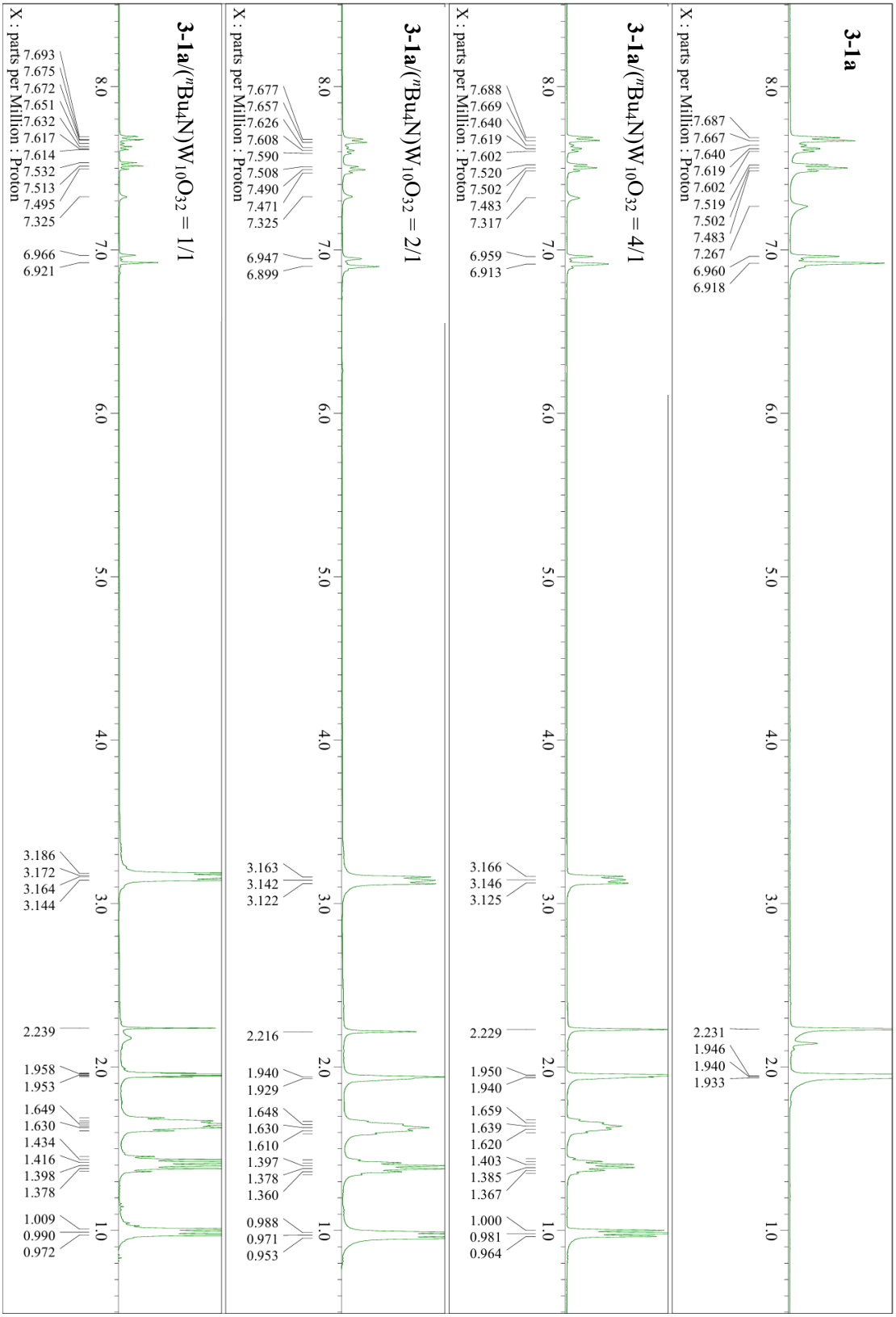
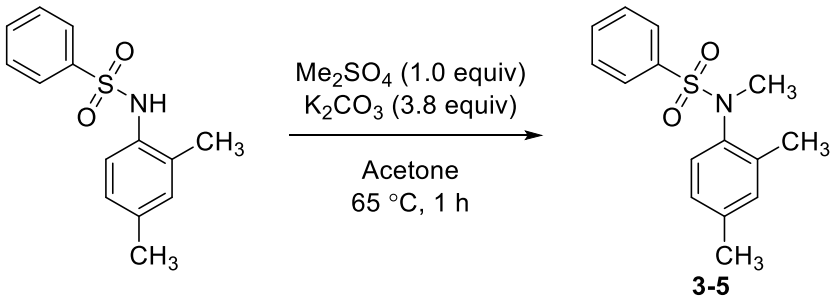


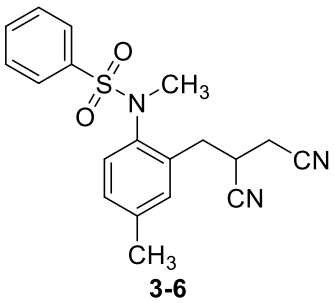
Figure 3-3. ^{1}H NMR spectra of **3-1a** and 1:4, 1:2 and 1:1 mixtures of **3-1a** and (^{n}Bu$_4$N)[$W_{10}O_{32}$] in CD_3CN

***N*-(2,4-dimethylphenyl)-*N*-methylbenzenesulfonamide (5)**[28]



A mixture of **3-1a** (261 mg, 1.00 mmol), Me_2SO_4 (126 mg, 1.00 mmol) and anhyd K_2CO_3 (524 mg) in dry acetone (10 mL) was refluxed at 65 ºC for 1 h. The mixture was cooled, filtered and the solvent was removed. The residual mass was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to afford the compound **3-5** (248 mg, 90%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.09 (s, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 3.13 (s, 3H), 2.35 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 138.2, 138.1, 137.6, 132.6, 132.1, 128.8, 127.9, 127.0, 126.6, 39.0, 21.0, 18.2.

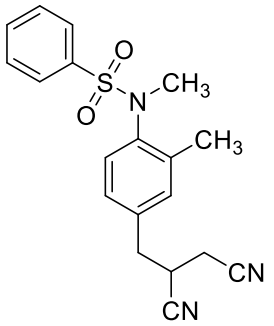
***N*-(2-(2,3-dicyanopropyl)-4-methylphenyl)-*N*-methylbenzenesulfonamide (3-6)**



According to the *General procedure V*, the mixture isomer product **3-6** (3.53 mg, 5%) with ratio of 60:40 was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). The NMR of mixture product **3-6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 3H), 7.55 (t, *J* = 7.2 Hz, 2H), 7.33 (s, 0.6H), 7.23 (s, 0.4H), 6.95 (t, *J* = 8.4 Hz, 1H), 6.31 (t, *J* = 8.4 Hz, 1H), 3.65-3.51 (m, 1.4H), 3.33-3.09 (m, 1.6H), 3.13 (s, 3H), 2.88-2.80 (m, 1.6H), 2.70 (dd, *J* = 16.8, 5.6 Hz, 0.4H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 139.2, 138.3, 137.8, 136.2, 135.9, 135.0, 133.4, 133.2, 132.7, 131.4, 129.6, 129.3, 129.0, 128.5, 128.3,

126.4, 119.3, 115.7, 40.0, 40.0, 34.1, 32.8, 29.7, 28.4, 21.6, 21.1, 21.1, 20.6. HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{19}N_3O_2S$: 353.1198, Found: 353.1200.

_N_-(4-(2,3-dicyanopropyl)-2-methylphenyl)-_N_-methylbenzenesulfonamide (3-7)



3-7

According to the *General procedure V*, the product **3-7** (7.78 mg, 11%) was obtained as a colorless oil after purification by column chromatography on silica gel (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.53 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.19 (s, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 7.2 Hz, 1H), 3.16-3.10 (m, 1H), 3.13 (s, 3H), 3.08-3.01 (m, 2H), 2.69 (d, *J* = 6.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 140.0, 137.8, 134.5, 132.9, 132.1, 129.0, 127.9, 127.7, 127.2, 118.2, 115.3, 38.9, 36.5, 29.9, 20.3, 18.4; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{19}N_3O_2S$: 353.1198, Found: 353.1199.

3.5 References

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Chapter 4.

Since this research is unpublished, the relevant research data will not be made public.

Chapter 5. Conclusion

In summary, this thesis describes the researches on decatungstate-catalyzed benzylic C(sp^3)–H alkylation assisted by hydrogen bond. Site-selective C–H transformations are significantly important in synthetic organic chemistry. Although a large amount of researches have been published in site-selective C–H transformations, challenges remain particularly for site-selective C(sp^3)−H transformations compared to C(sp^2)–H transformations. Our group focuses on developing "*non-covalent method"* for site-selective C–H transformations, and have successfully achieved proximal-selective C(sp^3)–H alkylation controlled by electrostatic interaction between cationic anilinium salts and anionic decatungstate. I envisioned that the electron-rich decatungstate could form hydrogen bond with a hydrogen bond-donating functional group of substrates and unpublished content for Chapter 4 to achieve site-selective C(sp^3)−H transformations.

In **Chapter 2**, I chose boronic acids as the hydrogen bond donors because boronic acid derivatives are indispensable molecules in synthetic organic chemistry and the B−O−H bonds have the potential to form hydrogen bond with oxygen-rich decatungstate. In this research, benzylic C(sp^3)−H alkylation of phenylboronic acids assisted by hydrogen bond was achieved. However, when substrates with two reaction sites, such as 2,4-dimethylphenylboronic acid, were employed, the site-selectivity was low. I attribute this to the weak hydrogen bond between the aryl boronic acids and decatungstate.

In **Chapter 3**, I propose that enhancing hydrogen bond between the substrate and the catalyst can enable site-selective C(sp^3)–H transformations. By introducing an electron-withdrawing functional group on the NH_2 group of *ortho*-toluidine derivatives, the hydrogen bond between substrates and catalysts was modulated, achieving proximal-selective C(sp^3)–H alkylation of *N*-(*ortho*-tolyl)benzenesulfonamide derivatives. This strategy was also successfully applied to the proximal-selective C(sp^3)–H alkylation of *N*-(3,4-dicyano-2-phenylbutyl)benzenesulfonamide.

In **Chapter 4**, unpublished content.

Overall, the study emphasizes the potential of non-covalent interaction-assisted methods in advancing C(sp^3)–H transformations, providing new perspectives and methodologies that expand these reactions.

Publication List

1. Boronyl-Group-Assisted Decatungstate-Catalyzed Benzylic C(sp^3)–H Alkylation

   Jiang, H., Torigoe, T., Kuninobu, Y. *Organic Letters*, **2024**, *26*, 4853−4856.

2. Hydrogen Bond-Controlled Site-Selective C(sp^3)−H Alkylation of Sulfonamides

   Jiang, H., Sekine, K., Kuninobu, Y. *The Journal of Organic Chemistry*, **2025**, *90*, 3454−3467.

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Throughout my doctoral research, I have acquired new knowledge, overcome numerous obstacles, and experienced significant growth. These years have been invaluable and filled with profound learning experiences. While this thesis cannot fully encapsulate my personal growth, every detail of the scientific journey and accomplishments documented within reflects the perseverance and dedication I have poured into my work. As the saying goes, “Life leaves traces everywhere, like wild geese leaving footprints on snowy ground.” Both time and the people around me have left indelible marks on my heart. Therefore, I am deeply grateful to everyone who has accompanied and supported me in my work and life.

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I hope to maintain a spirit of eternal youth, enthusiasm, and positivity, staying true to my original aspirations and continuing to move forward.

2024/12

Hui JIANG