Development of synthetic methods for complex molecular frameworks via 1,2-rearrangement reactions

March 2025

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Contents

Chapter 1. General introduction

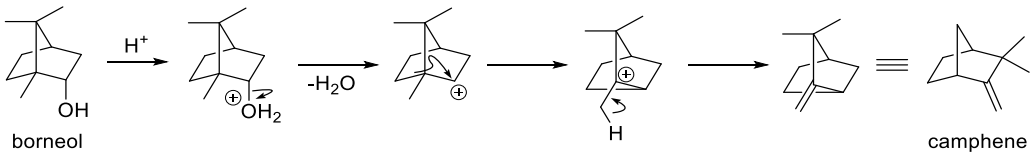
1-1. Introduction

Rearrangement reactions are crucial in organic reactions, defining the shift of a substituent from one atom to another atom within the same molecule. These reactions are essential tools for constructing complex carbon skeletons including quaternary carbons and polycyclic structures. Various types of rearrangement reactions include 1,2-rearrangement, sigmatropic rearrangement, and anionic rearrangement. In this paper, the author focuses on 1,2-rearrangement.

1-2. 1,2-Rearrangement

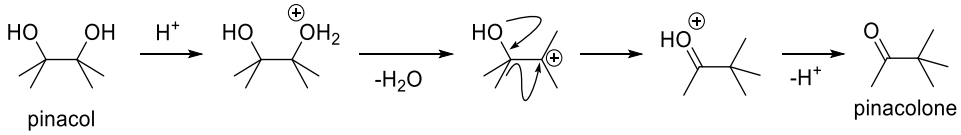
1,2-Rearrangement reactions are the most prevalent type of rearrangement reactions, characterized by a 1,2-migration of a carbon, hydrogen or other heteroatoms from one carbon center to an adjacent carbon center.

Wagner–Meerwein rearrangement is the most fundamental 1,2-rearrangement reaction and is well-known in or frequently observed in biosynthesis pathways. In 1899, Wagner discovered that borneol could be converted to camphene (Scheme 1).[1] Afterwards, in 1914, Meerwein revealed the mechanism of the conversion, which proceeds through a 1,2-rearrangment.[2] By exposing borneol to a strong acid, it undergoes protonation of hydroxy group followed by dehydration, resulting in the formation of a carbocation. This intermediate undergoes a 1,2-rearrangement generating a more stable tertiary carbocation. The final step is E1-elimination, leading to the formation of an alkene, which ultimately produces camphene. This type of 1,2-rearrangement, proceeding through the generation of a more stable carbocation, is now broadly recognized as Wagner–Meerwein rearrangement.



Scheme 1. Wagner–Meerwein rearrangement

The 1,2-rearrangement reaction was pioneered in 1860 by Fittig, who discovered pinacol-pinacolone rearrangement (Scheme 2).[3] This reaction converts pinacol into pinacolone by the aid of a strong Brønsted acid. The mechanism of this reaction is as follows: 1) Protonation of Pinacol by a strong Brønsted acid. 2) Generation of a tertiary carbocation by the elimination of water. 3) 1,2-Migration of a methyl group from the carbon atom bonded to oxygen to the carbocation forming a carbonyl group.



Scheme 2. Pinacol-pinacolone rearrangement

Semi-pinacol rearrangement, which is a subclass of pinacol rearrangement, was described and defined by Tiffeneau and co-worker in 1923.[4] According to them, the semi-pinacol rearrangement was defined to the selectivity opposite to the pinacol rearrangement. However, it is currently recognized differently (Figure 1).[5] Specifically, the formation of a carbonyl group accompanying the migration to an electron-deficient carbon is defined as a semi-pinacol rearrangement. The semi-pinacol rearrangements are mainly divided into four types. Type I semi-pinacol rearrangement occurs in alcohols with a good leaving group (such as OTs, OMs, Br, I, SR) on the β-carbon. The rearrangement proceeds with the formation of a carbonyl group through a 1,2-shift involving the elimination of a leaving group. Type II semi-pinacol rearrangement proceeds in allyl alcohols by activating the double bond with an electrophile (such as SeR), causing a substituent on the α-carbon of the hydroxy group to migrate to the activated alkene. Type III semi-pinacol rearrangement occurs when an epoxide is activated by a Lewis acid, causing a substituent on one carbon of the epoxide to migrate to the other carbon, resulting in the formation of a ketone. Type IV semi-pinacol rearrangement uses α-hydroxyketones and imines. As with previous cases, a substituent on the α-carbon of the hydroxy group migrates to the electron-deficient carbon center, resulting in the formation of a carbonyl group.

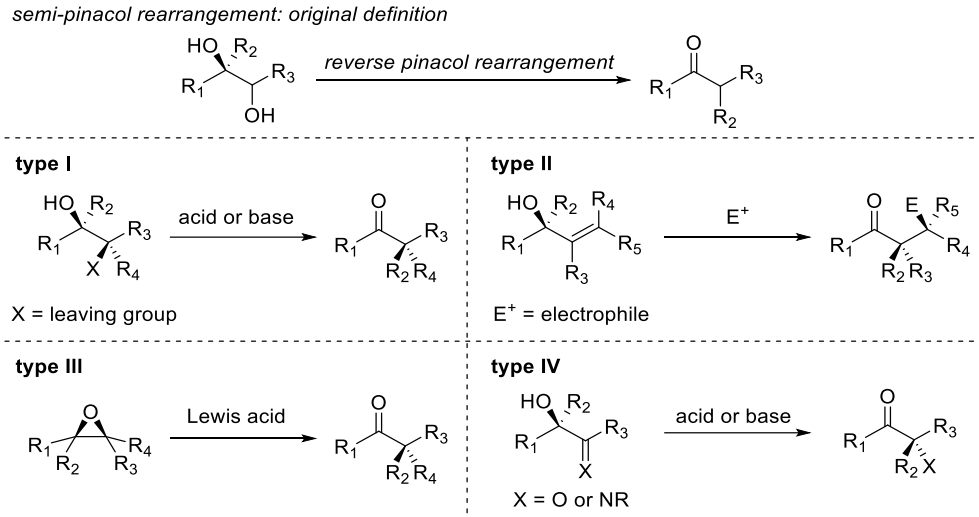
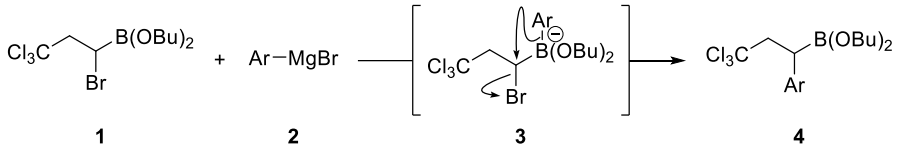


Figure 1. Various types of semi-pinacol rearrangement

Thus, the semi-pinacol rearrangement reactions are a useful method since these reactions can synthesize various aliphatic ketones with highly substitution at the α-position.[6] The author was fascinated by such rearrangement reactions which can synthesize complex compounds and particularly wanted to synthesize complex compounds using two rearrangement reactions.

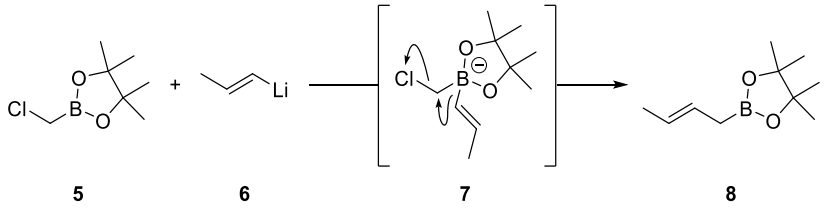
1-3. 1,2-metallate rearrangement

A 1,2-metallate rearrangement is a powerful method for synthesizing highly substituted alkylborones.[7] This reaction involves the formation of a boronate complex from an alkylboronic acid and an organometallic reagent, followed by the migration of a substituent on the boron to the adjacent cationic carbon. In this context, the metallate rearrangement reaction of alkylboronic acids with a leaving group at the α-position is specifically referred to as the Matteson-type metallate rearrangement. Matteson and co-worker reported a reaction called Matteson homologation (Scheme 3).[8] First, α-bromoboronic ester **1** was converted to the ate-complex **3** with an aryl Grignard reagent **2**. Then, through 1,2-metallate rearrangement of an aryl group on the boronate complex **3** to the adjacent carbon with elimination of bromide anion, a secondary alkylboronic ester **4** was obtained.



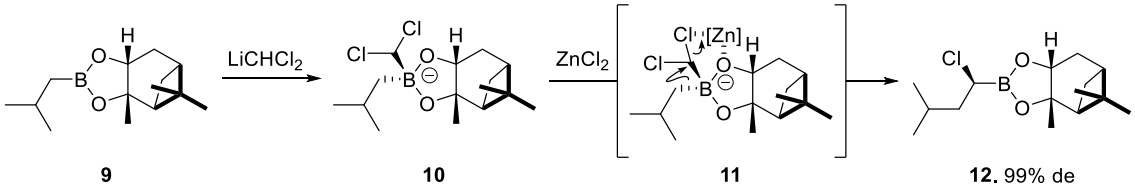
Scheme 3. Original Matteson homologation

Harris and co-workers also reported that a 1,2-metallate rearrangement of a α-chloroboronic acid pinacol ester **5** using vinyllithium **6** occurred via the 1,2-shift of a vinyl group with retention of stereochemistry, successfully achieving Matteson homologation (Scheme 4).[9]



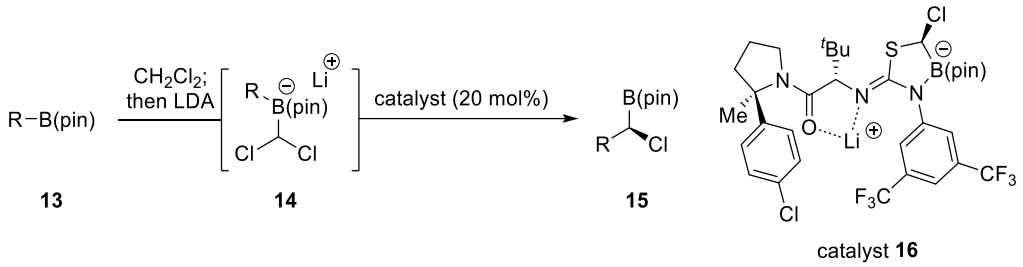
Scheme 4. Matteson homologation by Harris and co-workers

Matteson and co-worker have developed a diastereoselective 1,2-metallate rearrangement using boronic acid pinanediol ester **9** as chiral auxiliary, yielding chiral alkylborones **12** (Scheme 5).[10] Boronic ester **9** was converted to boronate complex **10** with lithium dichloromethide. Zinc chloride coordinated with the sterically less hindered oxygen atom of the boronic ester and one of the two prochiral chlorine atoms of **10** to promote the diastereoselective 1,2-metallate rearrangement, resulting in the synthesis of alkylboronic ester **12** with a chiral center at the α-position.



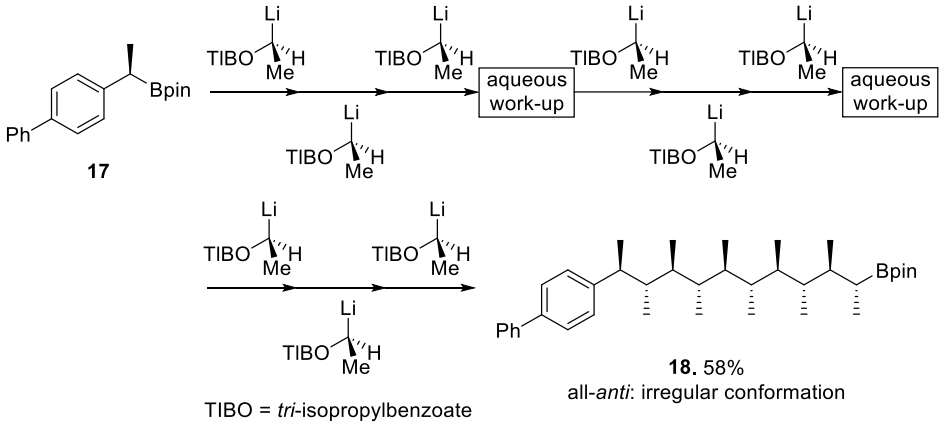
Scheme 5. Matteson homologation using chiral auxiliary by Matteson and co-worker

Recently, Jacobsen and co-workers have achieved an enantioselective catalytic 1,2-metallate rearrangement reaction using lithium-thiourea-boronate complex catalyst **16** (Scheme 6).[11] Throught the selective chelation of one of the two prochiral chlorine atoms by the lithium ion of catalyst **16**, an enantioselective 1,2-metallate reaction proceeded, resulting in the synthesis of a chiral α-chloroboronic ester **15**.



Scheme 6. Enantioselective catalytic 1,2-metallate rearrangement reaction by Jacobsen and co-workers

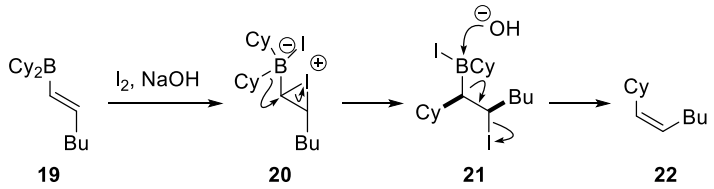
Aggarwal has achieved remarkable accomplishments in this field in recent years. In 2011, he and co-workers reported assembly-line synthesis using sequential 1,2-metallate rearrangement by boronic ester **17** and chiral α-lithiumethyl *tri*-isopropylbenzoate (Scheme 7).[12] This sequential 1,2-metallate rearrangement reactions proceeded stereospecifically, allowing for the perfect control of nine new consecutive stereocenters. Thus, the 1,2-metallate rearrangement reactions are highly advantageous, as it enables the sophisticated construction of alkyl chains due to its specific reaction.



Scheme 7. Assembly-line synthesis using sequential 1,2-metallate rearrangement by Aggarwal and co-workers

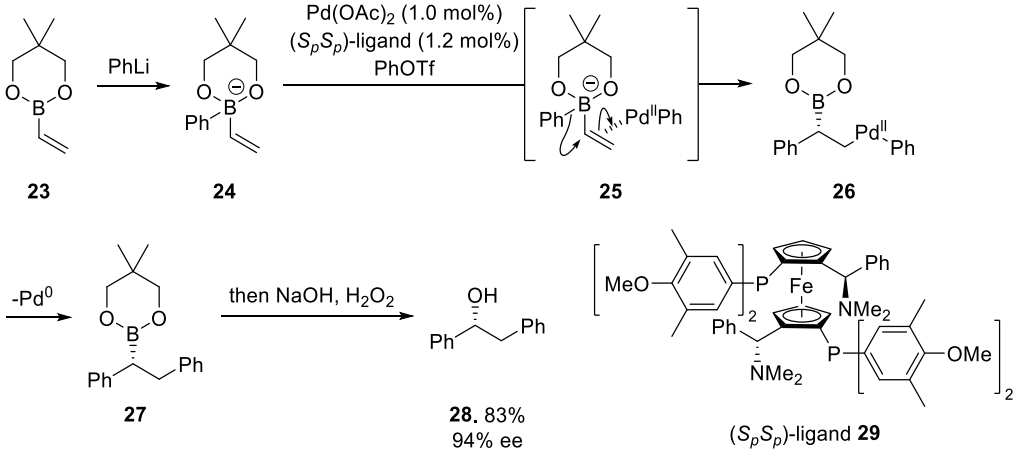
Another type of 1,2-metallate rearrangement uses vinylboronic esters. A 1,2-metallate rearrangement of vinylboronic esters is regarded as a 1,2-functionalization of alkenes that proceeds by applying an electrophile to the vinylboronic ester ate-complex generated by vinylboronic ester with organometallic reagents. When the double bond is activated by an electrophile, a substituent on the boron atom migrates to the vicinal cationic carbon, forming a new two bonds. As pioneering research, in 1967, Zweifel and co-workers reported a reaction

which is called Zweifel olefination (Scheme 8).[13] After vinylborane **19** was generated from dicyclohexylborane and hex-1-yne, the addition of iodine and sodium hydroxide led to the formation of a halonium ion intermediate **20**, then a 1,2-metallate rearrangement of which proceeded to give **21**. Finally, *anti*-elimination of **21** proceeded with the aid of sodium hydroxide, leading to the formation of *Z*-alkene **22**.



Scheme 8. Zweifel olefination by Zweifel and co-workers

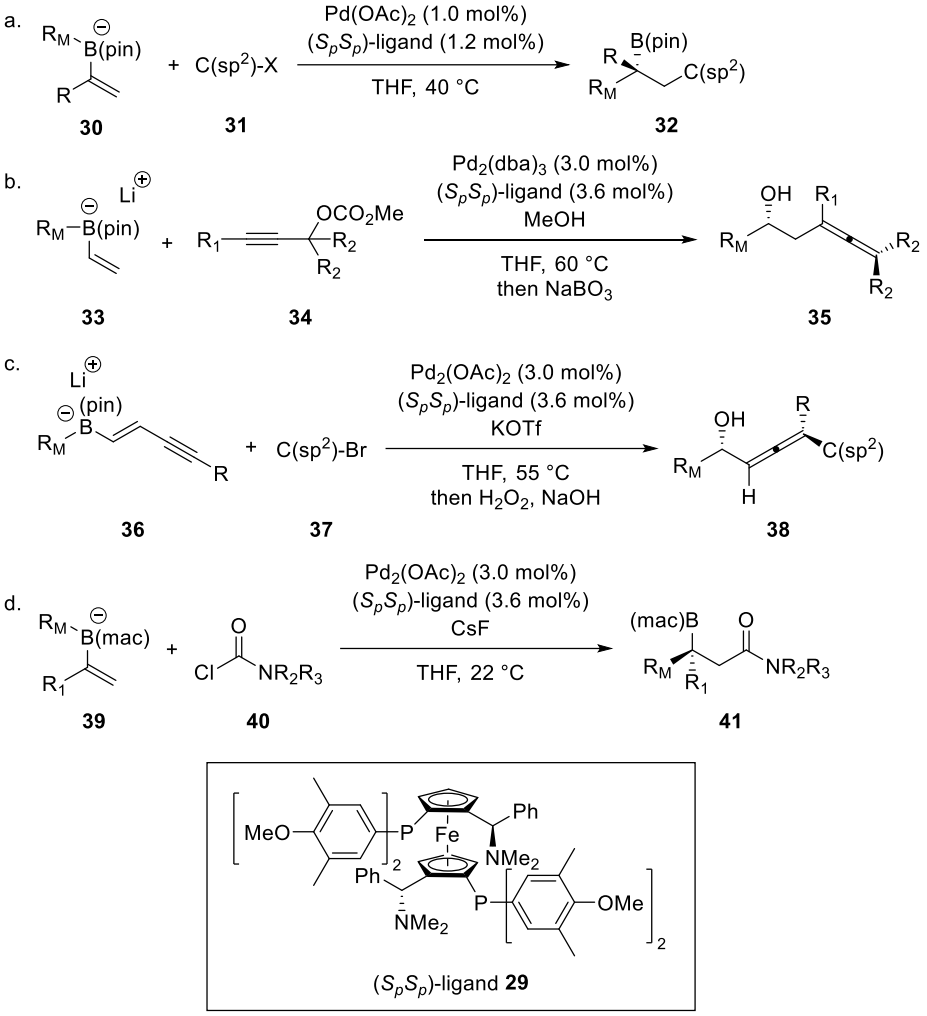
By using a carbon electrophile for the 1,2-metallate rearrangement of vinylboronic esters, two new carbon–carbon bonds can be formed. Morken and co-workers utilized organometallic catalysts to achieve Pd-catalyzed enantioselective 1,2-metallate rearrangement (Scheme 9).[14] Vinylboronate **24**, generated from phenyllithium and vinylboronic ester **23**, underwent a 1,2-metallate rearrangement induced by an electrophilic palladium(II) complex that was synthesized by the oxidative addition of phenyl triflate with a chiral palladium(0) complex. Subsequent reductive elimination formed an additional carbon–carbon bond to give chiral boronic acid **27**. Oxidation of boronic ester **27** yielded a chiral secondary alcohol **28**. The 1,2-metallate rearrangement of vinylboronate is a highly useful method that links three components while forming two carbon–carbon bonds.



Scheme 9. Metal-induced 1,2-metallate rearrangement reaction by Morken and co-workers

Building on their findings, they have reported various Pd-catalyzed enantioselective 1,2-metallate rearrangement reactions (Scheme 10). Initially, it was reported that the 1,2-metallate rearrangement could proceed with *gem*-substituted vinylboronic esters ate-complex **30**, leading to the synthesis of alkylborone compounds **32** with quaternary carbons (Scheme 10a).[15] Subsequently, in 2019, β-boryl allenes were obtained through Pd-catalyzed enantio- and

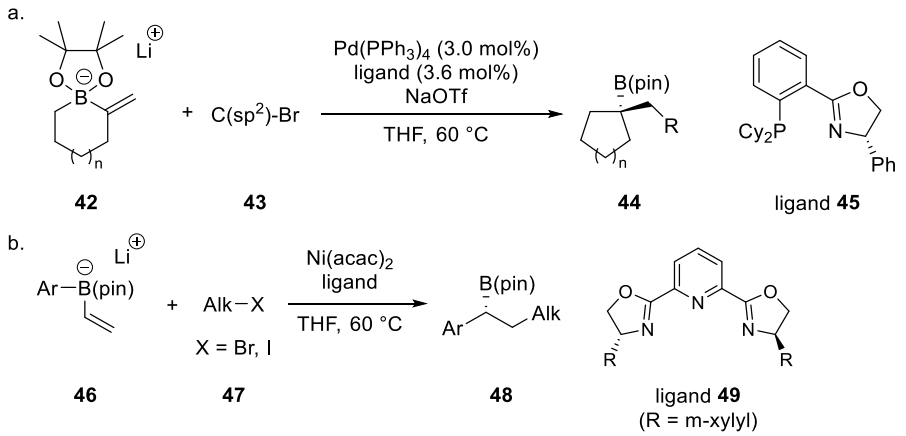
diastereoselective conjunctive coupling of vinylboronate **33** with propargyl carbonates **34**. Subsequent oxidation yielded the corresponding β-allenols **35** (Scheme 10b).[16] Additionally, this reaction enables the synthesis of α-allenols **38** through the 1,4-addition of enyne-derived boronate complexes **36** and carbon electrophiles **37** (Scheme 10c).[17] Carbamoyl chloride **40** can be employed as a carbon electrophile, facilitating the formation of β-*tert*-boryl amides **41** via the enantioselective 1,2-metallate rearrangement of a vinylboronic ester ate-complex **39** (Scheme 10d).[18]



Scheme 10. Pd-catalyzed enantioselective 1,2-metallate rearrangement by Morken and co-workers

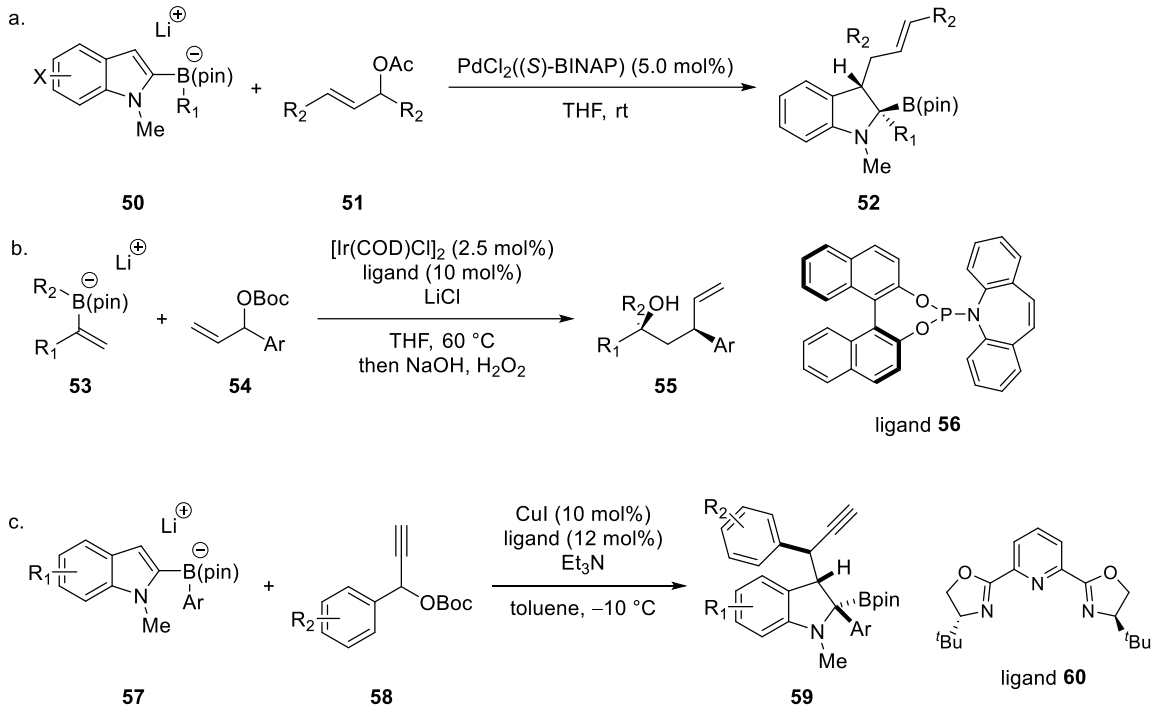
This type of reaction is applicable not only to acyclic vinylboronic esters but also to cyclic vinylboronic esters (Scheme 11a).[19] With cyclic vinylboronic ester ate-complexes **42** that have an *exo*-methylene group, a PHOX-ligated Pd-catalyzed enantioselective ring-contraction metallate rearrangement gave the corresponding cyclopentylboronic esters **44**. Carbon electrophiles that were used hitherto have predominantly been C(sp^2)–Pd species, such as aryl or vinyl groups, making the formation of C(sp^3)–C(sp^2) bonds. The use of a Ni catalyst enabled

the incorporation of alkyl groups, facilitating the formation of $C(sp^3)$–$C(sp^3)$ bonds during the coupling process (Scheme 11b).[20]



Scheme 11. Ring contraction metallate rearrangement and Ni-catalyzed metallate rearrangement by Morken and co-workers

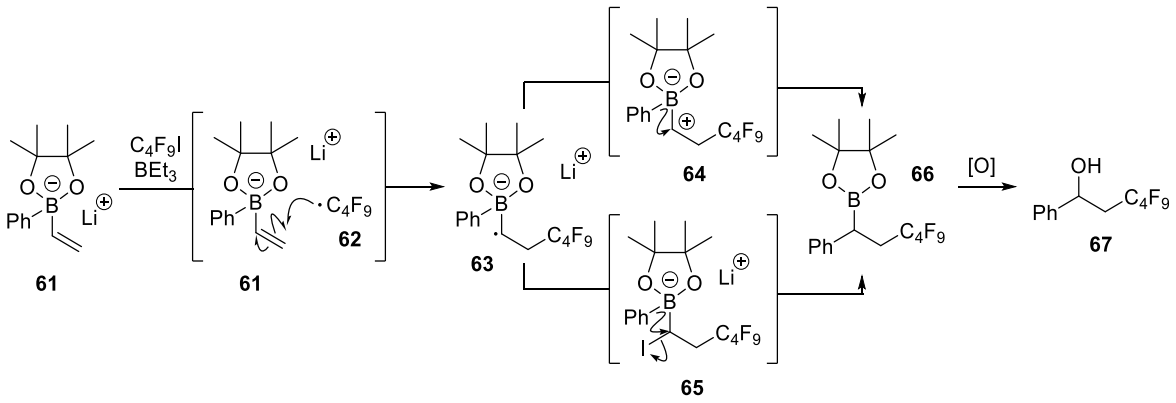
The use of π-allyl metals as carbon electrophiles has also been reported (Scheme 12). In 2017, Ready and co-workers achieved an enantioselective 1,2-metallate rearrangement with 2-indolylboronates **50** using π-allyl palladium complexes which were generated by allyl acetates **51** and a chiral Pd catalyst as carbon electrophiles (Scheme 12a).[21] The corresponding chiral indolines **52** were obtained. In 2021, Ready and co-workers also reported that vinylboronate complexes **53** underwent 1,2-metallate rearrangement with π-allyl iridium complexes which were synthesized from a chiral iridium complex and allylic carbonates **54**. Subsequent oxidation of the 1,2-metallate rearrangement products gave tertiary alcohols **55** (Scheme 12b).[22] Brown and co-workers found that the 1,2-metallate rearrangement reaction of 2-indolylboronates **57** could also be promoted using Cu-allenylidene complexes as electrophiles, to give the corresponding indolines **59** (Scheme 12c).[23]



Scheme 12. 1,2-Metallate rearrangement using π-allyl metals as carbon electrophiles

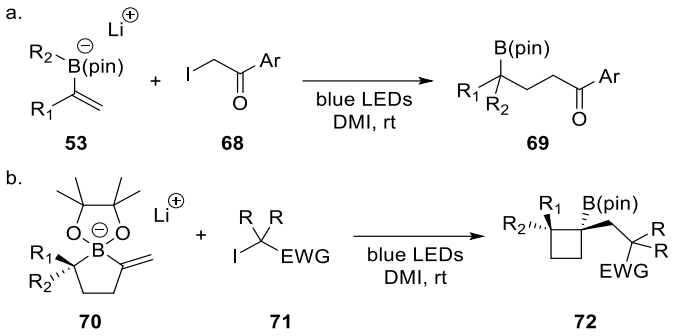
The 1,2-metallate rearrangement using organometallics as carbon electrophiles is highly useful not only for forming two carbon–carbon bonds but also for achieving asymmetric reactions due to the chiral metal complexes involved.

In addition to methods using transition metal complexes, 1,2-metallate rearrangements could also be promoted by radical species. Studer and co-workers reported a method utilizing a carbon radical as a carbon electrophile (Scheme 13).[24] An alkyl radical **62** generated by triethylborane and alkyl iodide underwent radical addition to vinyl boronate **61**, forming an α-boryl radical **63**. Subsequently, 1,2-metallate rearrangement of **63** gave alkylboronic ester **66**. For this 1,2-metallate rearrangement, two mechanisms were proposed: the formation of carbocation **64** via single-electron oxidation followed by 1,2-metallate rearrangement, or the radical addition to alkyl iodide forming α-iodoboronate **65**, which underwent a Matteson-type metallate rearrangement. Oxidation of **66** produced a secondary alcohol **67**.



Scheme 13. 1,2-metallate rearrangement using alkyl radical by Studer and co-workers

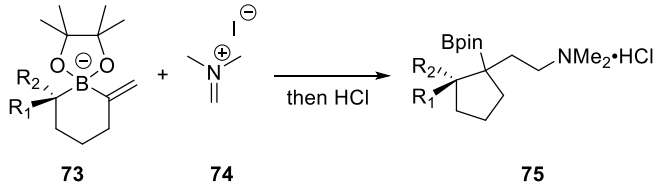
Aggarwal and co-workers discovered a 1,2-metallate rearrangement of vinylboronate complex **53** using α-carbonyl radicals generated from α-iodoketones **68** under blue light irradiation, synthesizing γ-carbonyl boronic esters **69** (Scheme 14a).[25] They also applied this reaction to cyclic boronic esters **70** which have an *exo*-methylene group, achieving a method to construct cyclobutylboronic ester **72** through a ring contraction metallate rearrangement (Scheme 14b).[26]



Scheme 14. 1,2-metallate rearrangement using alkyl radical by Aggarwal and co-workers

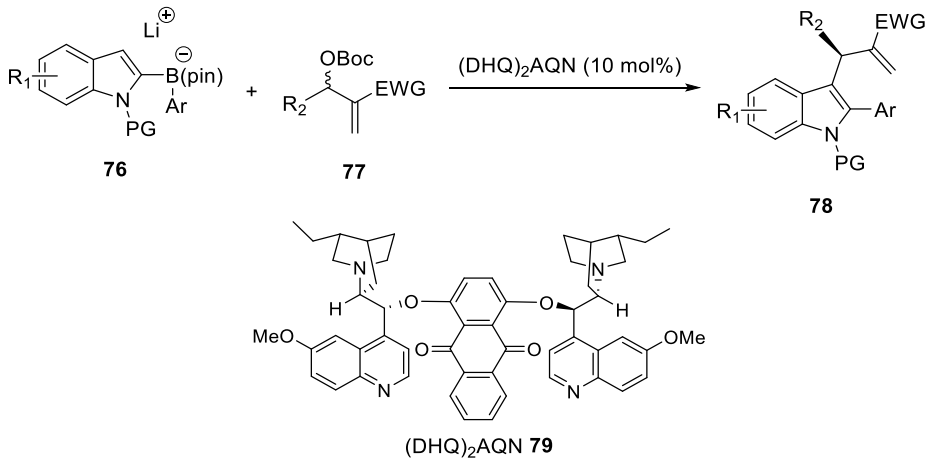
Finally, the author introduces the 1,2-metallate rearrangement of vinylboronate using carbon electrophiles without the use of transition metals or alkyl radicals.

Aggarwal and co-workers reported a 1,2-metallate rearrangement using iminium ions, a different type of carbon electrophile (Scheme 15).[27] When Eschenmoser's salt **74** was applied to cyclic boronate, a ring contraction metallate rearrangement occurred, resulting in the formation of a cyclopentane ring **75**.



Scheme 15. Ring contraction metallate rearrangement using iminium salt by Aggarwal and co-workers

Very recently, Aggarwal and a co-workers reported Lewis base catalyzed, a cinchona alkaloid-based organocatalytic **79**, asymmetric 1,2-metallate rearrangement, involving 2-indolylboronates **76** and Morita-Baylis-Hillman carbonates **77** (Scheme 16).[28]

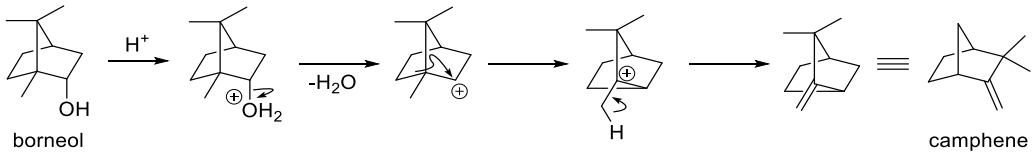


Scheme 16. Lewis base catalyzed asymmetric 1,2-metallate rearrangement by Aggarwal and co-workers

In this way, the 1,2-metallate rearrangement reaction is a multi-component coupling reaction and an excellent method for synthesizing complex alkylborone compounds from simple boronic esters.

1-4. Skeletal rearrangement

As introduced at the beginning of this chapter, rearrangement reactions can often change the molecular framework. For example, borneol is converted to camphene via the Wagner–Meerwein rearrangement (Scheme 17). These types of rearrangement reactions are known as skeletal rearrangement reactions and are recognized as effective methods for constructing complex frameworks in synthetic organic chemistry.[29]

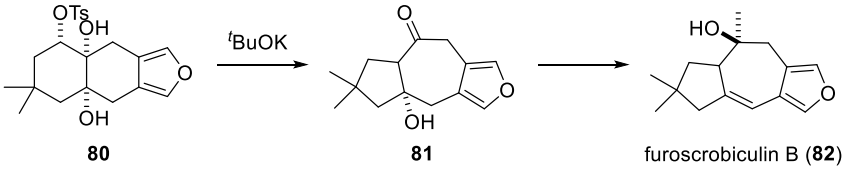


Scheme 17. Wagner–Meerwein rearrangement-type skeletal rearrangement

In the case of the construction of complex polycyclic frameworks, intermolecular reactions often encounter some issues that are caused by steric hindrance. On the other hand, skeletal rearrangement reactions include intramolecular movement of bonds from designed positions within the molecule to desired locations, making it easier to construct the target polycyclic frameworks. Therefore, the skeletal rearrangement reactions are highly important for the development of methods to construct complex frameworks through simple or well-established frameworks.

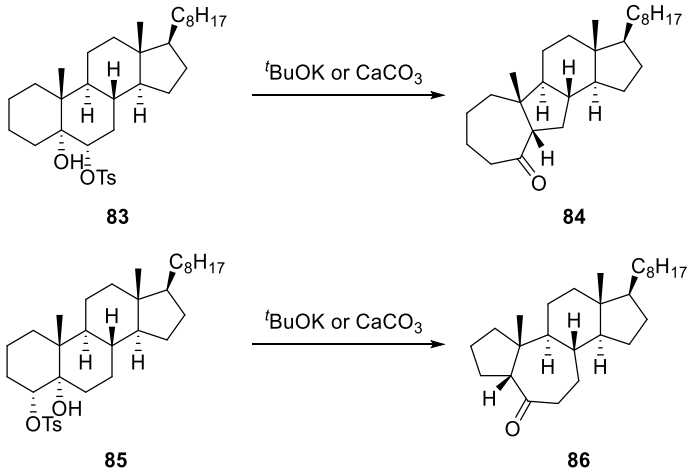
In 1994, Kanematsu and co-workers achieved total synthesis of furoscrobiculin B (**82**) through semi-pinacol-type skeletal rearrangement as a key reaction (Scheme 18).[30] Treatment of ^{t}BuOK to a tricyclic tertiary alcohol **80** with a tosyloxy group adjacent to the tertiary hydroxy

group resulted in the semipinacol-type skeletal rearrangement that constructed a [5.7.5] tricyclic framework **81**. Subsequent functional group transformations led to the total synthesis of **82**. [6.6] Bicyclic framework is one of the most common fused ring systems, and their construction methods have been well studied. Therefore, the author believes that the use of the [6.6] bicyclic compounds for the transformation into other structures through skeletal rearrangement is an effective strategy for the construction of complex frameworks.



Scheme 18. Total synthesis of furoscrobiculin B (**82**) by Kanematsu and co-workers

Similarly, Mazur and co-workers reported the construction of two-type unusual steroids **84**, **86** framework through the semi-pinacol-type skeletal rearrangement (Scheme 19).[31] The use of ^{t}BuOK or $CaCO_3$ as a base induced a semi-pinacol rearrangement, constructing [7.5.6.5] and [5.7.6.5] tetracyclic skeletons. In this way, changing the position of the leaving group resulted in significantly different tetracyclic skeletons after the skeletal rearrangement reaction.

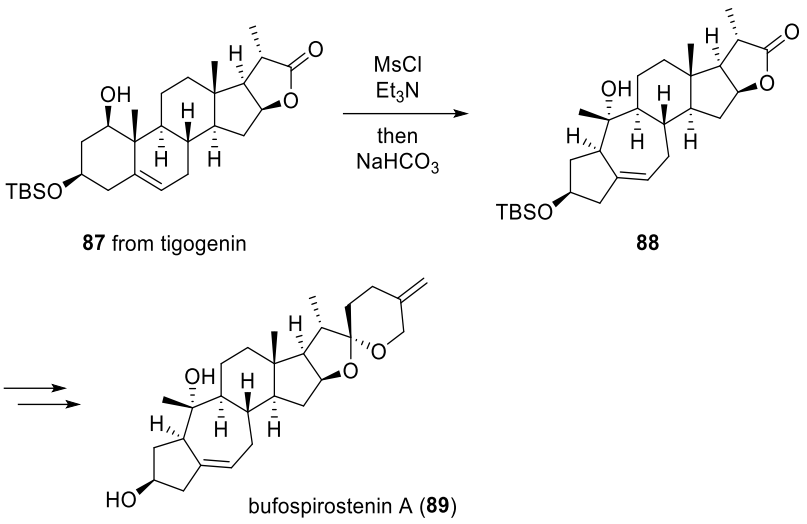


Scheme 19. Two skeletal rearrangements for the synthesis of steroids by Mazur and co-workers

Steroids are some of the most well-known natural groups of compounds. Most of them have a [6.6.6.5] tetracyclic framework, but some have different frameworks. Semi-synthesis, a method of synthesizing new compounds by partially chemically transforming natural products, is a powerful strategy for constructing various polycyclic skeletons based on the skeletal rearrangement of readily available [6.6.6.5] tetracyclic steroids.

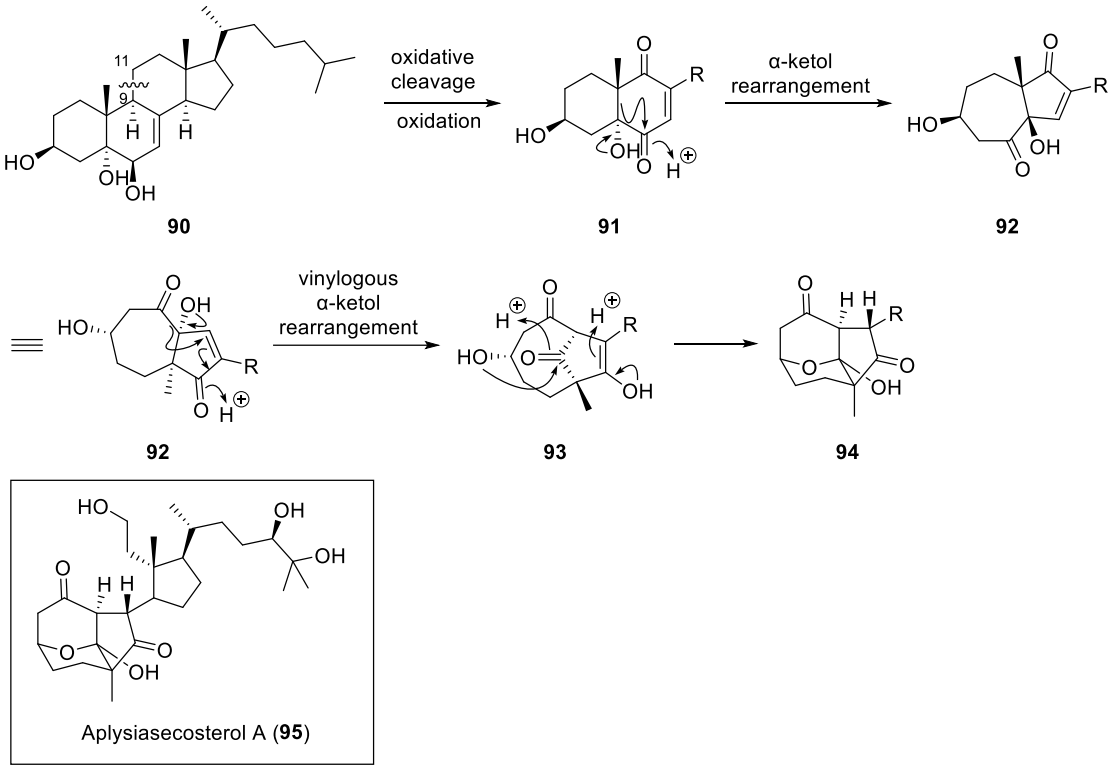
For example, Gui and co-workers achieved semi-synthesis of bufospirostenin A (**89**) through Wagner–Meerwein-type skeletal rearrangement (Scheme 20).[32] After mesylation of alcohol **87** which was derived from tigogenin, heating in the presence of a weak base promoted a Wagner–Meerwein-type skeletal rearrangement with the elimination of the mesylate, resulting

in the construction of a [5.7.6.5.5] pentacyclic steroid skeleton **88**. Subsequent derivatization gave bufospirostenin A (**89**). Thus, the use of readily available naturally occurring compounds for the skeletal rearrangement reactions is the most powerful tool.



Scheme 20. Semi-synthesis of bufospirostenin A (**89**) by Gui and co-workers

Rearrangement reactions are frequently observed in biosynthesis, where enzymatic substrate-specific reactions can sometimes construct highly complex polycyclic framework. For example, Kigoshi and co-workers reported the isolation of aplysiasecosterol A (**95**), a new 9,11-*seco*-steroid with an unprecedented tricyclic γ-diketone (Scheme 21).[33] The biosynthetic pathway for this unique skeleton was proposed as follows. First, the C9–C11 bond of the steroid skeleton **90** was oxidatively cleaved, and the hydroxy group at the C6 position was oxidized, producing 1,4-diketone **91**. 1,4-Diketone **91** underwent an α-ketol rearrangement, transforming the skeleton and producing α-hydroxyketone **92**, followed by a vinylogous α-ketol rearrangement to give bicyclo[5.2.1]decane **93**. Finally, the formation of a hemiacetal, which proceeded via the attack of the hydroxyl group to ketone, and subsequent tautomerization led to the construction of the tricyclic γ-diketone **94**.



Scheme 21. Proposed biosynthetic pathway of aplysiasecosterol A (**95**) by Kigoshi and co-workers

Thus, in biosynthesis, some complex polycyclic skeletons are constructed through skeletal rearrangement reactions. The construction of fused ring skeletons is particularly challenging in synthetic organic chemistry, making such skeletal rearrangement reactions a highly effective method for skeleton construction.

Biosynthetic pathways provide scientists with beneficial synthetic routes, and synthetic methods that mimic these biosynthetic pathways, known as biomimetic synthesis, have been reported. As an example, Baran and co-workers reported biomimetic synthesis of ingenol.[34] They proposed that ingenol is biosynthesized through a skeletal rearrangement from the tigliane skeleton to the ingenane skeleton (Figure 2).

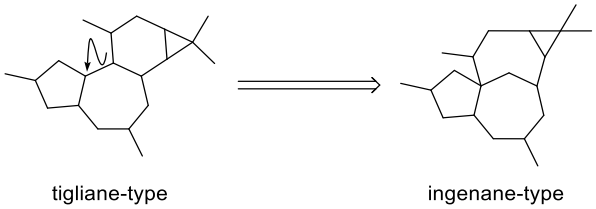
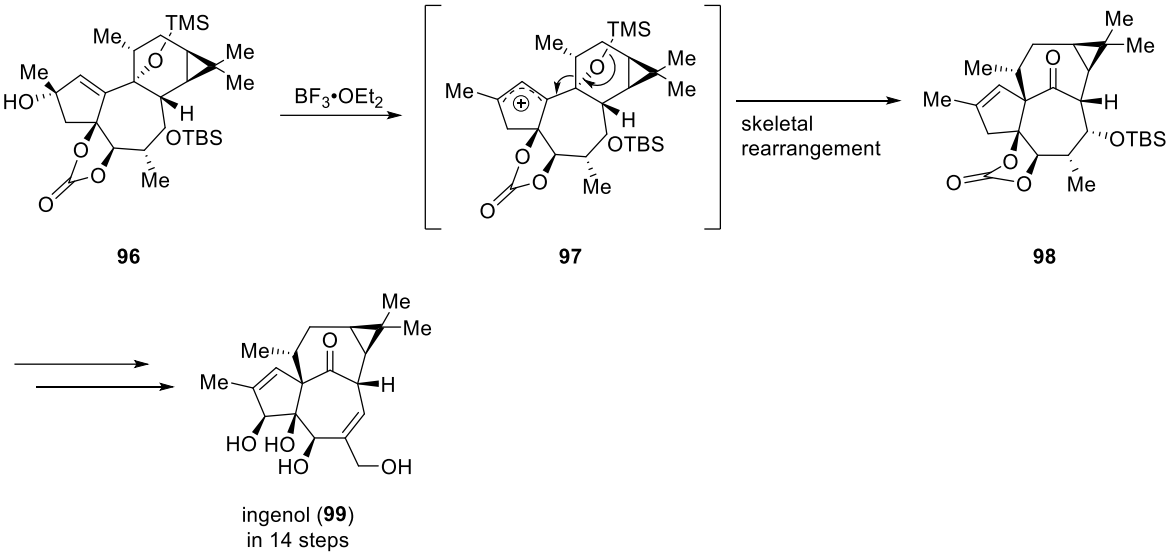


Figure 2. Proposed biosynthetic pathway of ingenane structure

By mimicking this proposed biosynthetic pathway, they employed a Lewis acid on allyl alcohol **96** possessing the tigliane skeleton (Scheme 22). This resulted in the formation of an allyl cation **97**, which underwent a pinacol-type skeletal rearrangement, thereby constructing ingenane skeleton **98**. Subsequently, the total synthesis of ingenol (**99**) was achieved. Ingenol

possesses a highly strained skeleton due to its trans-fused bicyclic rings, making its construction particularly challenging. Prior to this report, three total syntheses of ingenol (**99**) had been reported, each requiring 37-44 steps.[35] Baran and co-workers achieved the total synthesis in only 14 steps by biomimetic synthesis. This was achieved by constructing the strained bicyclic rings through a skeletal rearrangement that transferred the completely unstrained [7.6] bicyclic trans-fused skeleton.



Scheme 22. Biomimetic synthesis of ingenol (**99**)by Baran and co-workers

1-5. Proposed

Impressed by the 1,2-rearrangement reactions introduced so far, the author considered developing novel rearrangement reactions and utilize them to achieve the construction of complex skeletons.

In Chapter 2, the author describes a novel 1,2-metallate rearrangement reaction. As described in Chapter 1, the 1,2-metallate rearrangement of vinylboronic ester ate-complexes was induced by carbon electrophiles. However, most of these reactions involve transition metal catalysts or radical species, and the use of carbon electrophiles is very limited. The author believes that discovering a new class of carbon electrophiles could reveal new possibilities for this 1,2-metallate rearrangement field. The author considered that carbon electrophiles enabling 1,2-metallate rearrangement must be highly reactive and therefore focused on arynes (Figure 3). Arynes are a highly reactive aromatic species possessing a strained triple bond. Therefore, it was considered that the double bond of vinylboronic ester ate-complexes would nucleophilically attack the triple bond of the arynes. This process would generate an aryl anion, a new active species. By reacting this active species with another electrophile, an additional covalent bond can be formed. Thus, a coupling reaction involving four components, vinylboronic esters, nucleophiles, arynes, and electrophiles, forming up to three carbon–carbon bonds, provides an effective method for synthesizing complex alkylborone compounds.

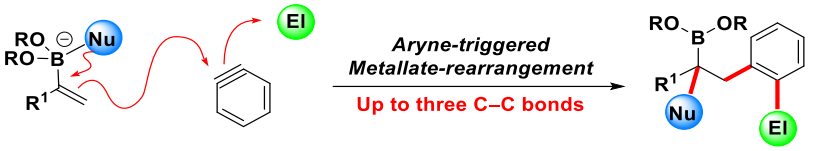


Figure 3. Aryne-triggered 1,2-metallate rearrangement

Additionally, the author was interested in the grayanane skeleton, aiming to construct complex polycyclic skeletons using skeletal rearrangement reactions as a key strategy (Figure 4). Grayanane skeleton which possess [5.7.6.5] tetracyclic framework bearing bicyclo[3.2.1]octane ring is proposed to be constructed via skeletal rearrangement from the kaurane skeleton which has [6.6.6.5] tetracyclic framework in their biosynthetic pathways. Therefore, the author hypothesized that grayanane skeleton could be constructed via the biomimetic strategy, by modifying the Wagner–Meerwein rearrangement to a pinacol-type rearrangement through the appropriate placement of hydroxy group. Based on this working hypothesis, Chapter 3 describes the development of a method for the rapid construction of a *ent*-kaurane-type tetracyclic skeleton including bicyclo[3.2.1]octane ring. Chapter 4 details the challenges and efforts in constructing the grayanane skeleton through skeletal rearrangement reactions of the synthesized *ent*-kaurane-type tetracyclic skeleton.

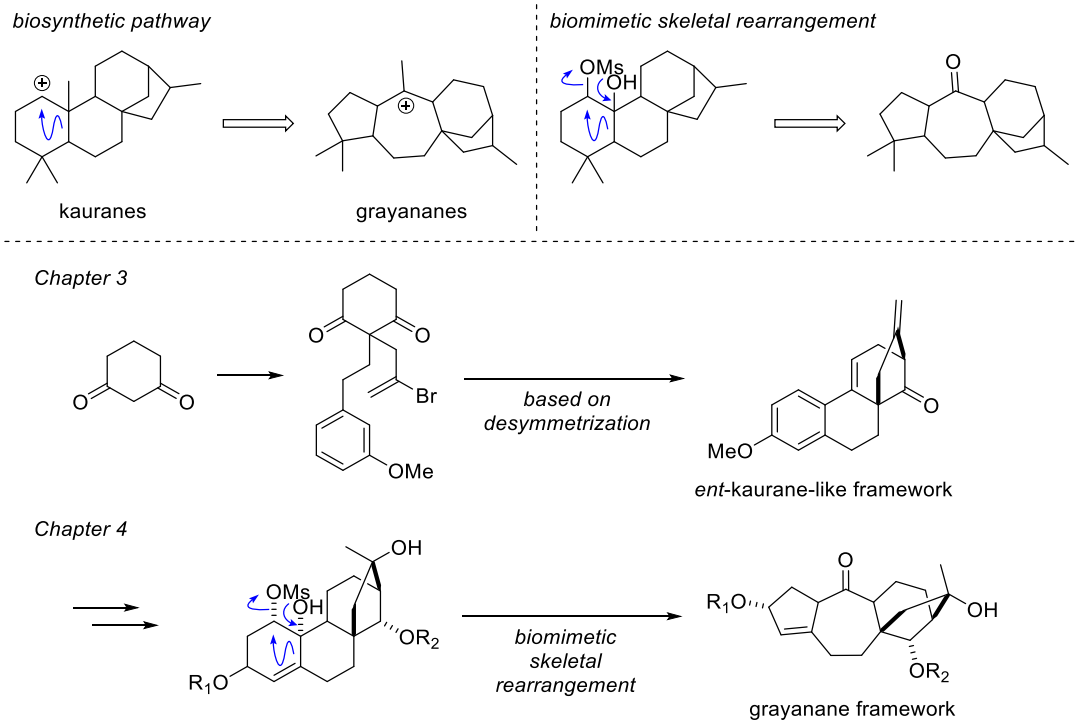


Figure 4. Synthetic plan for the biomimetic construction of grayanane skeleton

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Chapter 2. Annulative coupling of vinylboronic esters: aryne-triggered 1,2-metallate rearrangement

2-1. Abstract

1,2-Metallate rearrangement of vinylboronates using arynes as a new class of carbon electrophiles has developed. This annulative coupling including 1,2-metallate rearrangement resulted in the formation of a borinic ester ate-complex, characterized by the creation of two carbon–carbon bonds and one carbon–boron bond. This compound enabled the synthesis of a variety of complex alkylboronic acids and their derivatives through oxidation, halogenation, and direct coupling reactions.

2-2. Introduction

Organoboron compounds are an important class of molecules in modern organic synthesis. Due to their ability to undergo various transformations, such as the Suzuki–Miyaura coupling, which converts carbon–boron bonds into carbon–carbon bonds and other types of bonds, they have been widely utilized as crucial building blocks in the synthesis of bioactive compounds (Figure 1).[1]

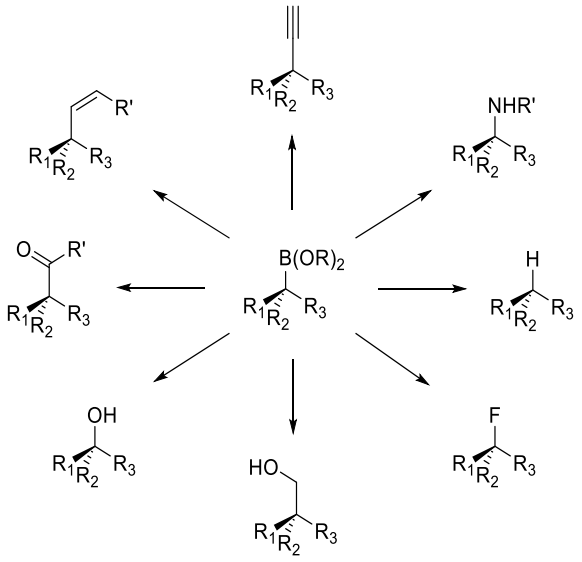


Figure 1. Summary of transformation of boronic esters

Recently, some boron-based pharmaceuticals have been developed (Figure 2). For example, Bortezomib has anti-cancer activity and Tavaborole has anti-fungal activity. These advancements not only increase the value of organoboron molecules themselves but also drive the demand for further development of their synthesis methods.

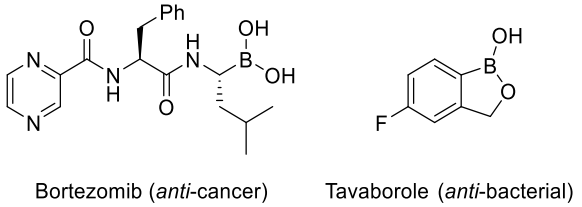
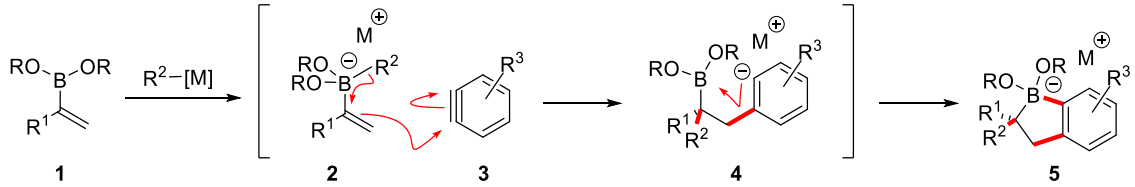


Figure 2. boron-based pharmaceuticals

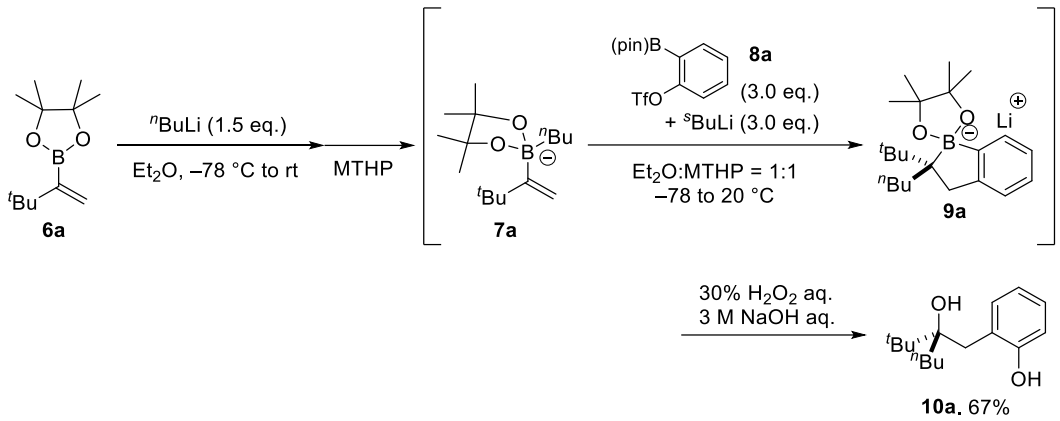
As described in Chapter 1, the 1,2-metallate rearrangement of vinylboronic esters is an effective method for synthesizing complex highly substituted alkylboronic acids. This method is particularly useful when carbon electrophiles are used, as it can form two carbon–carbon bonds. However, such carbon electrophiles are almost limited to organometallics and carboradical species. To address this limitation, the author has considered using arynes[2] as a new type of carbon electrophiles for the 1,2-metallate rearrangement. Thus, the author explains the synthetic plan of the 1,2-metallate rearrangement using vinylboronic esters and arynes (Scheme 1). First, boronic ester **1** is converted to boronic ester ate-complex **2** with an organolithium reagent. The vinyl group of **2** undergoes a nucleophilic attack on the aryne **3** which is generated *in situ*, promoting the 1,2-shift of the alkyl group on the vinylboronic ester ate-complex. The generated aryl anion would react with the boron center to cyclize, resulting in the formation of a cyclic borinic ester ate-complex **5**. The borinic ester ate-complex **5**, possessing two different carbon–boron bonds, is considered capable of undergoing various transformations. Therefore, the author decided to develop a process to synthesize complex alkylborone compounds from simple vinylboronic esters.



Scheme 1. Designed aryne-triggered 1,2-metallate rearrangement

2-3. Results and discussions

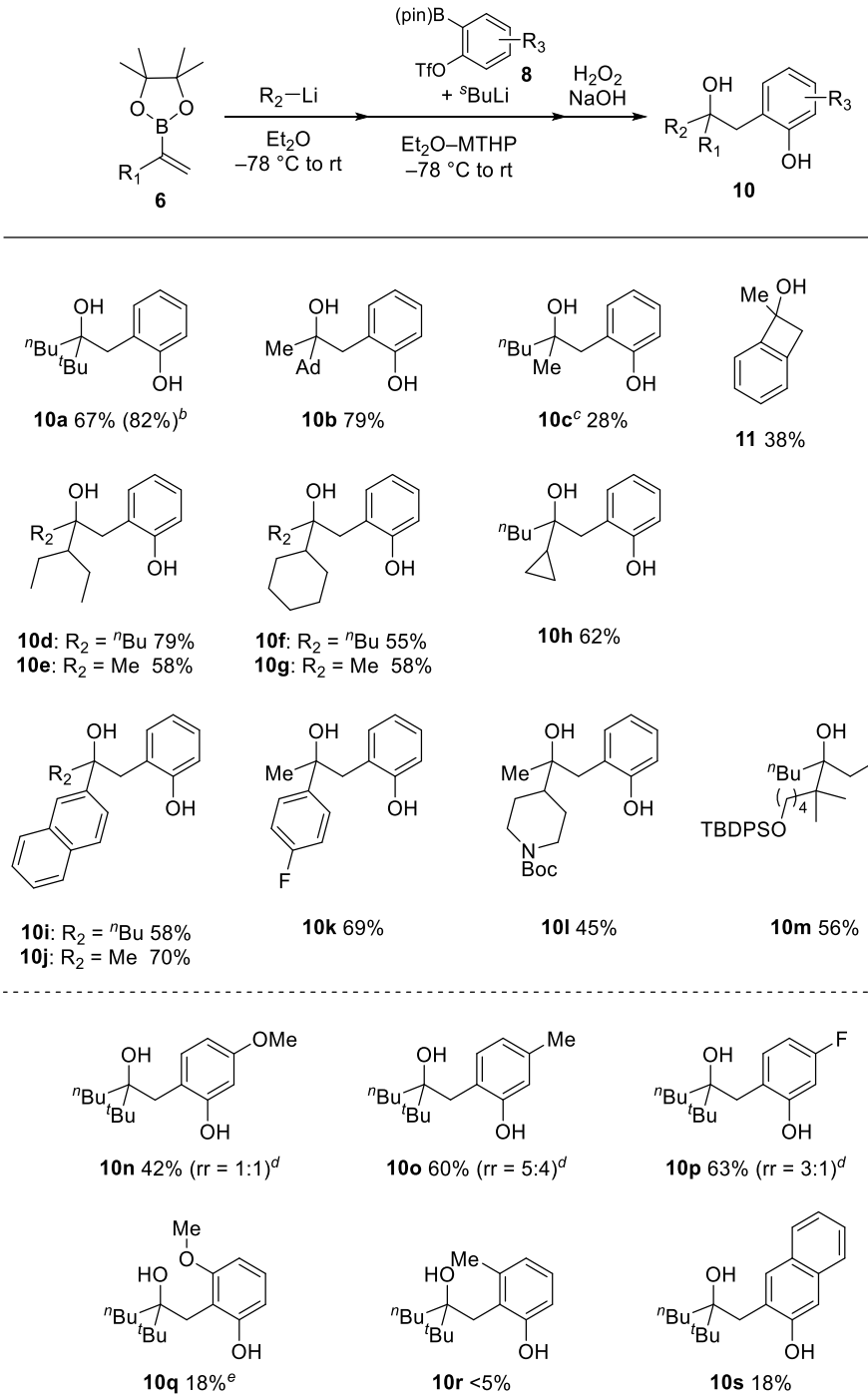
The investigation commenced with an exploration of the reaction conditions to promote the desired annulation reaction. After screening various conditions, the author found that the vinylboronic ate-complex **7a** proceeded 1,2-metallate rearrangement with benzyne, followed by an oxidation process. Upon treatment with H_2O_2, hydroxyphenol **10a** was obtained in 67% yield (Scheme 2). In detail, *tert*-butyl substituted vinylboronic ester **6a** was converted to vinylboronate **7a** with *n*-butyllithium in Et_2O. Since the vinylboronic ester ate-complex **7a** was insoluble, the solvent was *in situ* changed to 4-methyltetrahydropyran (MTHP)[4], which dissolved the ate-complex. The 1,2-metallate rearrangement of the vinylboronate **7a** was triggered by benzyne, which generated *in situ* from Hosoya's aryne precursor[3] and *s*-butyllithium, resulting in the formation of borinic ester ate-complex **9a**. Finally, treatment with H_2O_2 and NaOH oxidized the two C–B bonds, yielding hydroxyphenol **10a**.



Scheme 2. Optimized reaction conditions for aryne-triggered 1,2-metallate rearrangement

With the optimal conditions for the novel 1,2-metallate rearrangement of vinylboronic esters using arynes, the author next explored the reaction scope (Scheme 3). Initially, the reaction was confirmed to be easily scalable, yielding product **10a** in 82% yield in a 1 mmol scale. A combination of bulky adamanthyl vinylboronic ester **6b** and methyllithium as a small and poor migratory group[5] proceeded efficiently with the annulative coupling, followed by oxidative process, yielding **10b** in 79% yield. On the other hand, a combination of methyl vinylboronic ester **6c** and butyllithium showed poor performance in the 1,2-metallate rearrangement, producing hydroxyphenol **10c** in 28% yield and benzocyclobetene **11** in 38% yield as a side product due to cyclization of the aryl anion to the carbocation rather than the 1,2-metallate rearrangement. These results indicate that the size of the substituent on the vinylboronic ester significantly affects the 1,2-metallate rearrangement. The author also found that secondary alkyl substituted vinylboronic esters underwent the 1,2-metallate rearrangement efficiently. Coupled product **10d-10h** was obtained from vinylboronic esters with 3-penthyl, cyclohexyl, and cyclopropyl groups. Aryl substituted vinylboronic esters, such as naphthyl and 4-fluorophenyl groups, also performed well, yielding the desired hydroxyphenol **10i-10k**. Finally, the author investigated *N*-Boc protected amine and silyl ether as functional groups substituted on vinylboronic esters, coupled products **10l**,**10m** was obtained.

The scope of application of arynes was also explored. It was found that the steric hindrance of substituents is crucial for the scope of application of arynes. The 1,2-metallate rearrangement using 4-methoxy, 4-methyl, and 4-fluoro substituted aryne yielded the coupled product **10n-10p** efficiently although there are no regioselectivity.[6,7] However, for arynes with 2-methoxy and 2-methyl groups, the resulting hydroxyphenol **10q**,**10r** was obtained in low yield. This is likely due to the steric hindrance near the reacting triple bond. Similarly, 2,3-naphthalyne afforded the corresponding product **10s** in low yield.

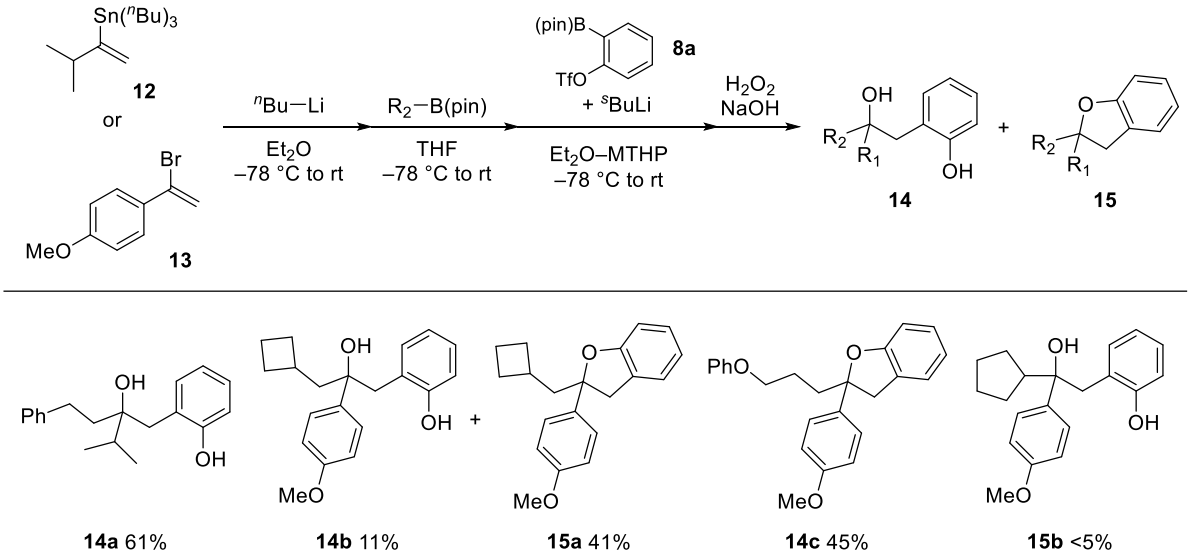


[a]Unless otherwise noted, all reactions were consucted using 0.2 mmol or 0.25 mmol or **6**, 1.5 eq of alkyllithium, 3.0 eq of **8**, and 3.0 eq of [s]BuLi. All yields refer to isolated yield of pure material. [b]1 mmol scale reaction. [c]0.5 mmol of vinylboronic ester was used. [d]rr = regioisomeric ratio of 5-substituted isomer and 4-substituted isomer. [e]Yield of the acetylated derivative at phenolic hydroxy group.

Scheme 3. Scope and limitations of vinylboronic esters, organolithiums, and aryne precursors.

To date, the substrate scope of vinylboronic esters and arynes have been reported. However, only methyllithium and butyllithium were used as organolithium reagents, indicating a limitation in the nucleophiles employed. Therefore, the author attempted to expand the scope

of this reaction by generating an ate-complex using vinyllithium and organoboron compounds (Scheme 4). Using isopropyl substituted vinyltin **12** and 4-methoxyphenyl substtuted vinylbromide **13** as a substrate, the reaction was first involved the generation of an ate-complex through lithiation and borylation, followed by an aryne-triggered 1,2-metallate rearrangement using a benzyne precursor and ^{s}BuLi. As a result, when phenethylboronic ester was used, the corresponding hydroxyphenol **14a** was obtained in good yield. Regarding cyclobutylmethylboronic ester, it was confirmed that the 1,2-metallate rearrangement proceeded well, but after purification, most of hydroxyphenol **14b** were found to have been converted to dihydrobenzofuran **15a**.[8] Similarly, only dihydrobenzofuran **14c** was obtained from boronic ester with a phenoxy group. When cyclopentylboronic ester was used, due to steric hindrance, hydroxyphenol **15b** was obtained in trace amounts.

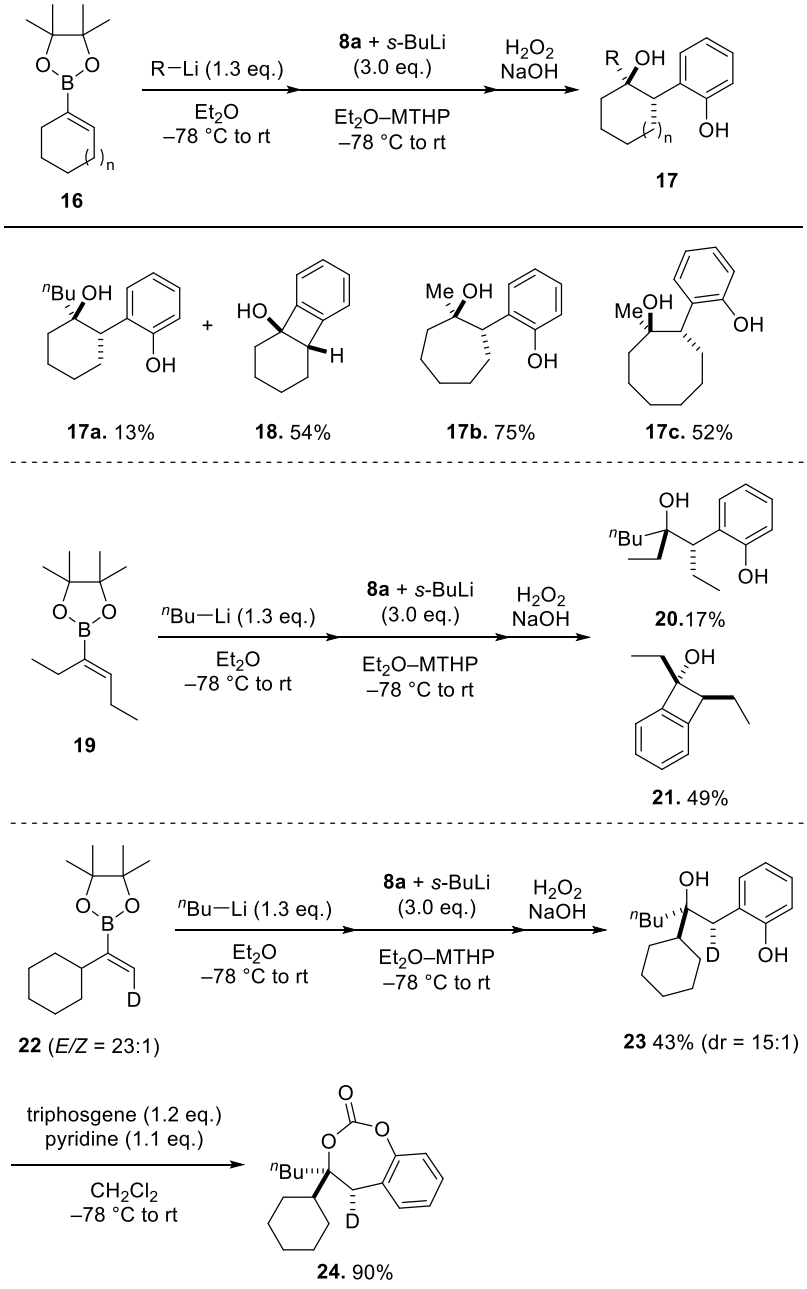


[a]Unless otherwise noted, all reactions were conducted using 0.2 mmol of **12** or **13**, 1.1 eq. of ^{n}BuLi, 1.5 eq. of boronic ester, 3.0 eq. of **8**, and 3.0 eq. of ^{s}BuLi. All yields refer to isolated yield of pure material.

Scheme 4. Scope and limitation of the migrating group

The author next investigated annulative coupling using cyclic vinylboronic esters **16** with internal alkenes (Scheme 5). The annulative coupling of cyclohexylboronic ester **16** with benzyne via a 1,2-metallate rearrangement afforded the corresponding coupling product **17a** in 13% yield and benzocyclobutane **18** as a byproduct in 54% yield. When using seven- and eight-membered cyclic vinylboronic esters, the 1,2-metallate rearrangement proceeded selectivity, yielding the corresponding hydroxyphenols **17b**,**17c**. These products were obtained as single diastereomers. Therefore, vinylboronic ester **19**, which contains an acyclic *Z*-alkene, was also investigated. As a result, hydroxyphenol **20** and the [2+2] cycloadduct **21** were obtained as single diastereomers, suggesting that the 1,2-metallate rearrangement occurs in a stereoselective manner. To determine the relative stereochemistry, annulative coupling was performed using cyclohexyl vinylboronic ester **22**, in which deuterium was selectively

introduced into the vinyl group. A stereoselective 1,2-metallate rearrangement proceeded, yielding hydroxyphenol **23**. **23** was converted into cyclic carbonate **24** using triphosgene, and its relative stereochemistry was determined through analysis by 2D NMR. The results suggested that the reaction with benzyne and 1,2-rearrange ment of the butyl group proceeded on the same face of the alkene.[9]



Scheme 5. 1,2-Metallate rearrangement using boronic esters possessing internal alkenes and a deuterated vinylboronic ester

Figure 3 showed the reaction mechanism of the annulative coupling based on the determined stereochemistry. First, the vinylboronic ester **I** was converted to the vinylboronic ester ate-complex **II** with organolithium. Benzyne approached **II**, avoiding the steric hindrance of the pinacol moiety, undergoing nucleophilic attack by the vinyl group, which occurred coupling

reaction to form arylithium **III**. The stereoselectivity of this reaction was attributed to the lithium ion chelating with one of the oxygens in the pinacol group, which fixes the conformation. The R_2 group on the boron atom underwent the 1,2-metallate rearrangement to the carbocation, followed by the nucleophilic attack of the carbon–lithium bond on the boron, leading to the formation of borinic ester ate-complex.

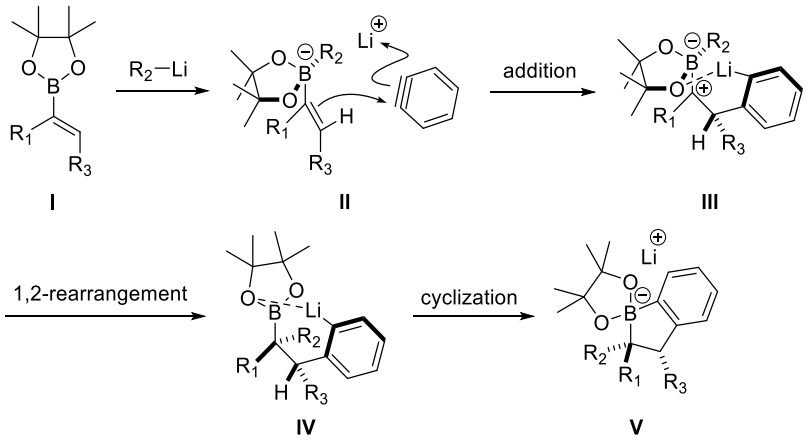
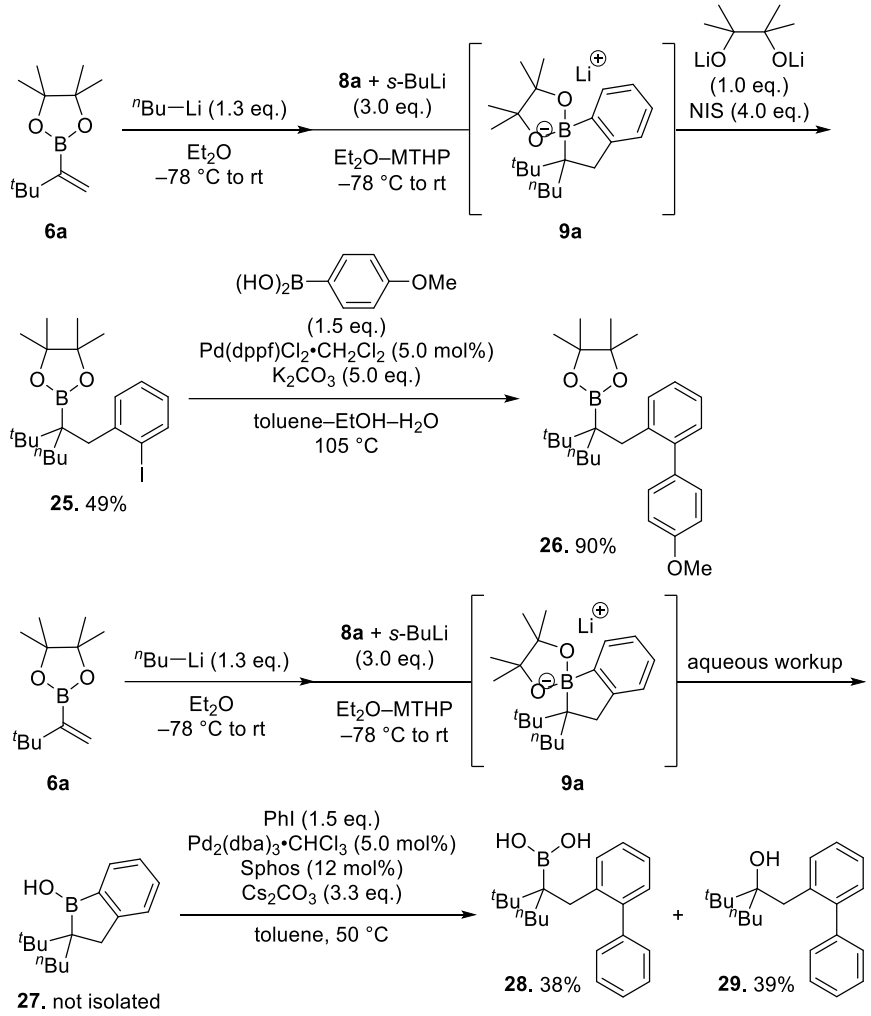


Figure 3. Proposed reaction mechanism

Up to this point, the reaction has been concluded by oxidizing the boron to obtain hydroxyphenol. Therefore, to demonstrate the utility of the intermediate borinic ester ate-complex, the author explored methods other than oxidation. This borinic ester ate-complex contains both C(sp^3)–B and C(sp^2)–B bonds, allowing for selective conversion reactions to synthesize complex alkylborone compounds, which could subsequently undergo further transformations at the boron site. First, the author attempted the iodination of the borinic ester ate-complex (Scheme 6). By adding the dianion of pinacol to the borinic ester ate-complex **9a** generated from vinylboronic ester **6a** with a *tert*-butyl substituent, butyllithium, and benzyne, and then applying NIS, the C(sp^2)–B was iodinated to yield iodoarene **25** in 49% yield. It was considered that the boronic ester ate-complex was partially converted to boronic acid in the system, making it important to add the dianion of pinacol to form more of the boronic ester ate-complex. **25** readily underwent a Suzuki–Miyaura coupling reaction with 4-methoxyphenylboronic acid to afford biphenyl **26**. Next, a direct Suzuki–Miyaura coupling of the borinic ester ate-complex **9a** was attempted. By treating the boronic acid esterate complex with an aqueous system, borinic ester **27** was obtained. However, as this boronic ester **27** could not be isolated, a coupling reaction was carried out using the crude mixture of **27**, resulting in the formation of a compound containing a biaryl boronic acid **28** and an oxidized derivative **29**.



Scheme 6. Application of birinic ester ate-complex

2-4. Conclusion

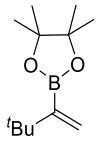
The author has developed a novel methodology employing arynes as a new carbon electrophile in the 1,2-metallate rearrangement reaction. The borinate complex, formed by reacting vinylboronic esters, nucleophiles, and arynes, was discovered to be a versatile intermediate. Despite its structure involving multiple bond formations, this intermediate can undergo various transformations, including oxidation, halogenation, and direct coupling reactions.

2-5. Experimental section: General Experimental Information

IR spectra were recorded on a SHIMADZU FTIR-8400 spestrometer. ^{1}H spectra were measured on a JEOL JNMECZ600R spectrometer (600 MHz), a Varian NMR System 600 PS600 spectrometer (600 MHz), a Varian 400-MR ASW spectrometer (400 MHz), and a Varian Mercury-300 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in pp, from the solvent resonance employed as the internal standard ($CHCl_3$ at 7.26 ppm) on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; pent = pentet/quintet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a JEOL JNMECZ600R spectrometer (150* MHz), a Varian NMR System 600 PS600 spectrometer (150 MHz), a Varian 400-MR ASW spectrometer (100 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.16 ppm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Kanto Chemical Co., Inc. silica gel 60 N (spherical, neutral), Fuji Silysia Chemical PSQ100B, and Kanto Chemical Co., Inc. silica gel 60 N (spherical) NH_2 were used. High- and low-resolution mass spectral analysis (HRMS) was measured on a JEOL JMS-700Mstation (FAB) and a Bruker micrOTOF II (ESI) at Chemical Instrument Facility, Okayama University. Dry toluene, tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), dimethyl sulfoxide (DMSO), methanol (MeOH), diethyl ether (Et_2O), ethyl acetate (EtOAc) and chloroform ($CHCl_3$) were purchased from Kanto Chemical Co., Inc. or Wako Pure Chemical Industries Ltd. As the ‘‘anhydrous’’ and stored under nitrogen. Cyclopentyl methyl ether (CPME), 1,2-dimethoxyethane (DME), and 4-methyltetrahydropyran (MTHP) were purchased from Kanto Chemical Co., Inc., TCI Co., LTD or Wako Oure Chemical Industries Ltd. And distilled from sodium/benzophenone ketyl prior to use. Other materials were obtained from commercial supplies and used without further purification. All reactions were conducted in flame dried glassware inder nitrogen atmosphere, otherwise noted.

2-5-1. Preparation of substrates

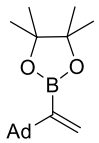
2-(3,3-dimethylbut-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6a)



6a

6a was prepared according to a reported procedure.[10]

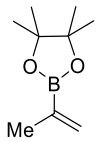
2-(1-(adamantan-1-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6b)



6b

6b was prepared according to a reported procedure.[11]

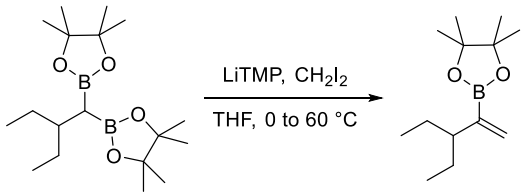
4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (6c)



6c

Commercially available

2-(3-ethylpent-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6d)

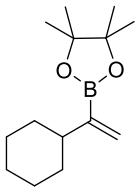


S1 **6d**

To a stirred solution of LiTMP in THF (4.5 mL) prepared from 2,2,6,6-tetramethylpiperidine (560 μL, 3.30 mmol) and *n*-BuLi (2.0 M in cyclohexane, 1.65 mL, 3.30 mmol) was added a solution of **S1** (1.01 g, 3.00 mmol) in THF (9.0 mL) dropwise at 0 ℃. After 5 min, a solution of CH_2I_2 (485 μL, 6.01 mmol) in THF (6.0 mL) was added. After being stirred at the same temperature for 10 min, the reaction mixture was warmed up to 60 ℃ and stirred for 2 h 40 min. The mixture was the cooled down to rt and the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain **6d** (30 mg, 1.38 mmol, 46%).

6d: colorless oil; IR (film) 2961, 2932, 2872, 1609, 1370, 1304, 1146, 970, 943, 855, 756, 669 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (d, *J* = 3.6 Hz, 1H), 5.53 (d, *J* = 3.6 Hz, 1H), 1.93 (pent, *J* = 7.2 Hz, 1H), 1.44 (app pent, *J* = 7.2 Hz, 1H), 1.25 (s, 12 H), 0.79 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 129.1, 83.1, 49.6, 26.9, 24.8, 12.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}BNaO_2$ $[M+Na]^+$ 247.1840, found 247.1840.

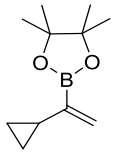
2-(1-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6f)



6f

6f was prepared according to a reported procedure.[12]

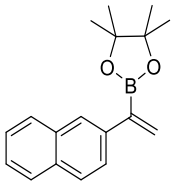
2-(1-cyclopropylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6h)



6h

6h was prepared according to a reported procedure.[13]

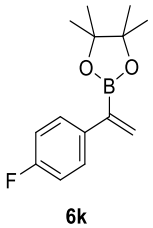
4,4,5,5-tetramethyl-2-(1-(naphthalen-2-yl)vinyl)-1,3,2-dioxaborolane (6i)



6i

6i was prepared according to a reported procedure.[10]

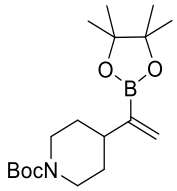
2-(1-(4-fluorophenyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6k)



6k

6k was prepared according to a reported procedure.[14]

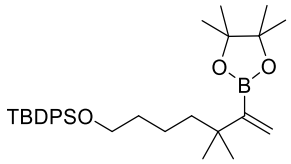
***tert*-butyl 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)piperidine-1-carboxylate (6l)**



6l

6l was prepared according to a reported procedure.[15]

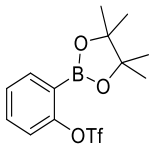
***tert*-butyl((5,5-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1 yl)oxy)diphenylsilane (6m)**



6m

6m was prepared according to a reported procedure.[16]

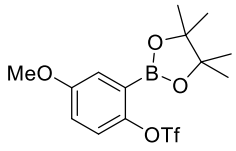
2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate (8a)



8a

8a was prepared according to a reported procedure.[3]

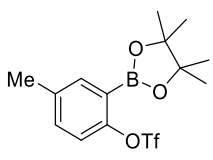
4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate (8n)



8n

8n was prepared according to a reported procedure.[17]

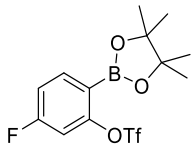
4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate (8o)



8o

8o was prepared according to a reported procedure.[17]

5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate (8p)

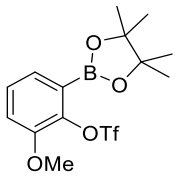


8p

8p was prepared from 4-fluoro-2-hydroxyphenylboronic acid following the reported procedure.[3]

8p: colorless oil; IR (film) 3525, 3433, 3358, 3327, 2980, 1622, 1485, 1423, 1203, 1053, 879, 705, 613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.50 (m, 1H), 7.20–7.16 (m, 2H), 1.36 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (d, J = 249 Hz), 149.8 (d, J = 3.0 Hz), 123.4 (d, J = 23 Hz), 123.1 (d, J = 8.0 Hz), 119.7 (d, J = 24 Hz), 119.0 (q, J = 319 Hz), 85.1, 24.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}BF_4NaO_5S$ $[M+Na]^+$ 393.0562, found 393.0558.

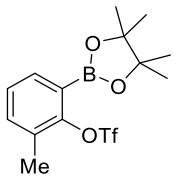
2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate (8q)



8q

8q was prepared according to a reported procedure.[3]

2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate (8r)



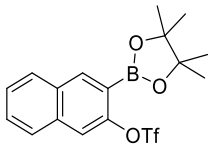
8r

8r was prepared from 2-hydroxy-3-methylphenylboronic acid following the reported procedure.[3]

8r: colorless oil; IR (film) 3502, 3464, 3365, 2982, 1614, 1458, 1359, 1070, 893, 611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.2, 1.7 Hz, 1H), 7.36 (dd, J = 7.6, 0.4 Hz, 1H), 7.26

(app t, *J* = 7.6 Hz, 1H), 2.37 (s, 3H), 1.37 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 135.2, 134.6, 130.3, 127.7, 118.9 (q, *J* = 318 Hz), 84.7, 25.0, 16.4 (q, *J* = 1.5 Hz); HRMS (ESI) *m/z* calcd for $C_{14}H_{18}BF_3NaO_5S$ $[M+Na]^+$ 389.0812, found 389.0777.

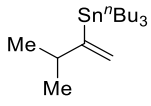
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl trifluoromethanesulfonate (8s)



8s

8s was prepared according to a reported procedure.[3]

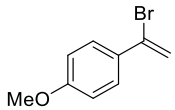
tributyl(3-methylbut-1-en-2-yl)stannane (12)



12

12 was prepared according to a reported procedure.[18]

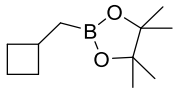
1-(1-bromovinyl)-4-methoxybenzene (13)



13

13 was prepared according to a reported procedure.[19]

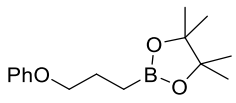
2-(cyclobutylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S2)



S2

S2 was prepared according to a reported procedure.[20]

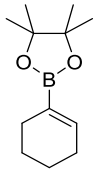
4,4,5,5-tetramethyl-2-(3-phenoxypropyl)-1,3,2-dioxaborolane (S3)



S3

S3 was prepared according to a reported procedure.[21,22]

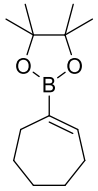
2-(cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S4)



S4

S4 was prepared according to a reported procedure.[23]

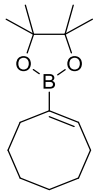
2-(cyclohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S5)



S5

S5 was prepared according to a reported procedure.[23]

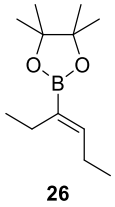
(*Z*)-2-(cyclooct-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S6)



S6

S6 was prepared according to a reported procedure.[23]

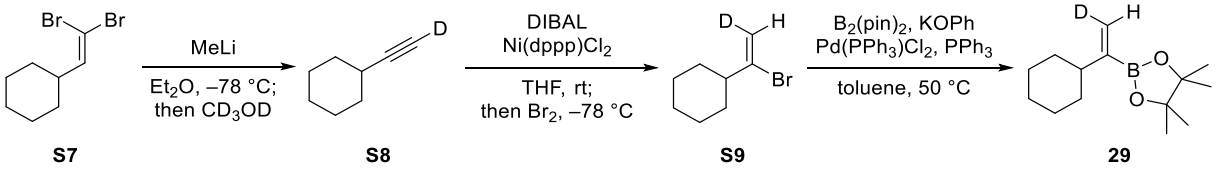
(*Z*)-2-(hex-3-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (26)



26

26 was prepared according to a reported procedure.[24]

(*Z*)-2-(1-cyclohexylvinyl-2-d)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (29)



S7 **S8** **S9** **29**

To a stirred solution of **S7** (2.55 g, 9.50 mmol) in Et_2O (30 mL) was added MeLi (1.5 M in Et_2O, 14.7 mL, 22.0 mmol) at –78 ℃. After being stirred for 40 min, the mixture was warmed up to rt and further stirred for 30 min. The reaction was quenched with CD_3OD and diluted with

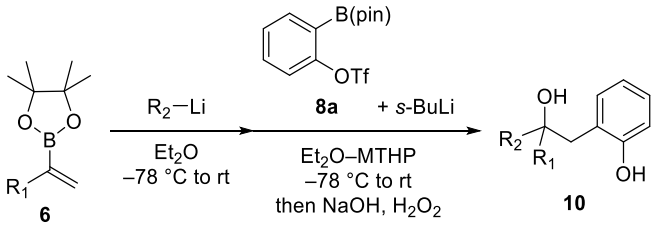
saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture of **S8** was used for next reaction without purification.

To a solution of Ni(dppp)Cl_2 (270 mg, 0.50 mmol) in THF (25 mL) was added DIBAL-H (1.0 M in hexane, 12 mL, 12 mmol) at room temperature. After 5 min, the mixture was cooled to 0 ℃ and a solution of **S8** (crude mixture, prepared above) was added. The mixture was warmed up to room temperature and stirred at room temperature for 4 h. After the period of time, the mixture was cooled to –78 ℃ and treated with bromide (0.665 mL, 12.9 mmol). After 30 min, the mixture was warmed up to rt and further stirred for 30 min. The reaction mixture was poured into 0 ℃ solution of saturated aqueous Rochelle salt and reslting clouded mixture was stirred for 30 min. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture of **S9** was roughly purified by column chromatography on silica gel and used for next reaction as a mixture (904 mg, < 4.75 mmol).

Half amount of the above mixture (450 mg, < 2.38 mmol), $B_2(pin)_2$ (665 mg, 2.62 mmol), $Pd(PPh_3)_2Cl_2$ (50.1 mg, 0.0714 mmol), PPh_3 (37.5 mg, 0.142 mmol), and KOPh (472 mg, 3.57 mmol) was mixed in toluene (15 mL) and the resulting suspension was stirred at 50 ℃ for 24 h. The mixture was cooled to room temperature and filtered through a pad of silica gel using hexane/Et_2O mixture (5:1) as an eluent. The eluate was concentrated under reduced preddure and purified by column chromatography on silica gel to obtain (200 mg, 0.843 mmol). By comparing the benzylic methylene proton signals with that of **29**, *E/Z* ratio was determined as 23:1.

29: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (s, 1H), 2.12–2.05 (m, 1H), 1.78–1.64 (m, 5H), 1.35–1.20 (m, 2H), 1.26 (s, 12H), 1.20–1.08 (m, 3H).

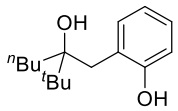
2-5-2. General procedure for the aryne triggered annulative coupling (oxidative workup)



To a solution of vinylboronic ester **6** (0.200 mmol, 1.0 eq.) in Et_2O (2.0 mL) was added *n*-BuLi (2.0 M in hexanes, 0.15 mL, 0.30 mmol, 1.5 eq.) at –78 ℃ and stirred for 5 min. A cooling bath was removed, and the mixture was further stirred for 30 min. The solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4-methyltetrahydropyran (4.0 mL). In the meantime, aryne precursor **8a** (0.6 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (4.0 mL).

The solution was treated with *s*-BuLi (1.2 M in hexanes, 0.5 mL, 0.6 mmol, 3.0 eq.) at –78 ℃ and stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 ℃. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanges to water bath which temperature was controlled to 20 ℃ with ice. The reaction mixture was stirred at the same temperature for 2 h. After this period of time, the reaction mixture was cooled to 0 ℃ and treated with saturated aqueous solution of NH_4Cl until the pH of the mixture became neutral. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to obtain hydroxyphenol **10**.

***rac*-2-(2-(*tert*-butyl)-2-hydroxyhexyl)phenol (10a)**



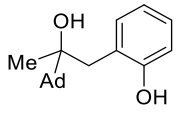
10a

Following the general procedure, vinylboronic ester **6a** (42.0 mg, 0.20 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10a** (33.8 mg, 0.135 mmol, 67%).

For the 1 mmol scale reaction , vinylboronic ester **X** (210 mg, 1.00 mmol) was converted to **10a** (205 mg, 0.820 mmol, 82%) followed the same procedure and purification method.

10a: yellow solid; IR (film) 3237, 2956, 2868, 1585, 1489, 1244, 1112, 1045, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.13 (app td, *J* = 7.6, 1.6 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.81 (app td, *J* = 7.6, 1.2 Hz, 1H), 3.13 (d, *J* = 14.4 Hz, 1H), 2.66 (d, *J* = 14.4 Hz, 1H), 2.08 (br s, 1H), 1.59–1.52 (m, 2H), 1.27–0.95 (m, 4H), 1.05 (s, 9 H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 132.4, 128.3, 125.7, 120.1, 117.3, 81.7, 39.3, 38.1, 35.8, 27.3, 25.8, 23.6, 14.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{26}NaO_2$ $[M+Na]^+$ 273.1830, found 273.1823.

***rac*-2-((*R*)-2-(adamantan-1-yl)-2-hydroxypropyl)phenol (10b)**

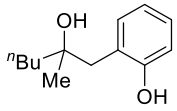


10b

Following the general procedure, vinylboronic ester **6b** (58.2 mg, 0.202 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10b** (45.6 mg, 0.159 mmol, 79%).

10b: yellow solid; IR (film) 3244, 2900, 2881, 1683, 1653, 1558, 1506, 1251, 1220, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.14 (app td, *J* = 7.6, 1.6 Hz, 1H), 6.96 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.82 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.16 (d, *J* = 14.4 Hz, 1H), 2.47 (d, *J* = 14.4 Hz, 1H), 2.07 (s, 3H), 2.00 (br s, 1H), 1.83–1.55 (m, 12H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 132.9, 128.3, 125.5, 120.0, 117.4, 80.3, 39.6, 37.6, 37.1, 36.2, 28.6, 20.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}NaO_2$ $[M+Na]^+$ 309.1830, found 309.1835.

***rac*-2-(2-hydroxy-2-methylhexyl)phenol (10c)**

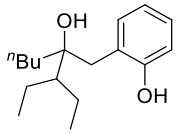


10c

Following the general procedure, vinylboronic ester **6c** (0.094 mL, 0.500 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10c** (29.0 mg, 0.14 mmol, 28%), along with [2+2]-adduct[x] (25.6 mg, 0.191 mmol, 38%).

10c: yellow oil; IR (film) 3223, 2931, 2858, 1585, 1489, 1456, 1247, 1126, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.16 (app td, *J* = 7.6, 1.6 Hz, 1H), 6.98 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.92 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.82 (app td, *J* = 7.4, 1.2 Hz, 1H), 2.91 (d, *J* = 14.8 Hz, 1H), 2.71 (d, *J* = 14.8 Hz, 1H), 2.07 (s, 3H), 2.12 (br s, 1H), 1.59–1.51 (m, 2H), 1.46–1.27 (m, 4H), 1.21 (s, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 132.6, 128.5, 124.7, 120.1, 117.5, 76.6, 44.0, 42.3, 26.9, 26.4, 23.2, 14.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{20}NaO_2$ $[M+Na]^+$ 231.1361, found 231.1357.

***rac*-2-(2-hydroxy-2-(pentan-3-yl)hexyl)phenol (10d)**



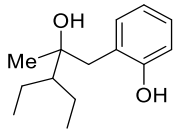
10d

Following the general procedure (1.3 eq. of butyllithium was used), vinylboronic ester **6d** (57.1 mg, 0.255 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10d** (53.3 mg, 0.202 mmol, 79%).

10d: colorless oil; IR (film) 3250, 2959, 2934, 2874, 1586, 1489, 1466, 1379, 1248, 1044, 1003, 851, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 7.15 (app td, *J* = 7.8, 1.8 Hz, 1H), 6.97 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.81 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.05 (d, *J* = 14.4 Hz, 1H), 2.64 (d, *J* = 14.4 Hz, 1H), 2.14 (br s, 1H), 1.76–1.68 (m, 1H), 1.64–

1.56 (m, 1H), 1.53–1.47 (m, 1H), 1.43–1.37 (m, 1H), 1.37–1.28 (m, 3H), 1.28–1.19 (m, 4H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 132.6, 128.3, 124.6, 120.0, 117.3, 81.4, 48.8, 39.8, 36.8, 25.5, 23.3, 22.9, 22.7, 14.2, 13.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{28}NaO_2$ $[M+Na]^+$ 287.1982, found 287.1983.

rac-2-(3-ethyl-2-hydroxy-2-methylpentyl)phenol (10e)

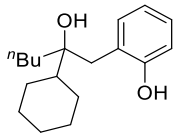


10e

Following the general procedure (1.3 eq. of methyllithium was used), vinylboronic ester **6e** (56.8 mg, 0.253 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10e** (33.0 mg, 0.148 mmol, 58%).

10e: colorless oil; IR (film) 3279, 3013, 2959, 2874, 1586, 1456, 1379, 1252, 1217, 1117, 851, 764, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 7.16 (app td, *J* = 7.8, 1.2 Hz, 1H), 6.98 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.92 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.83 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.04 (d, *J* = 14.4 Hz, 1H), 2.62 (d, *J* = 14.4 Hz, 1H), 2.22 (br s, 1H), 1.74–1.66 (m, 1H), 1.63–1.55 (m, 1H), 1.33 (app hept, *J* = 7.2 Hz, 1H), 1.30–1.22 (m, 2H), 1.12 (s, 3H), 1.01 (t, *J* = 7.8 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 132.7, 128.4, 124.7, 120.1, 117.5, 779.9, 52.3, 41.7, 24.5, 23.6, 23.0, 14.3, 13.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NaO_2$ $[M+Na]^+$ 245.1512, found 245.1512.

rac-2-(2-cyclohexyl-2-hydroxyhexyl)phenol (10f)

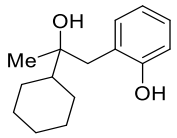


10f

Following the general procedure (1.3 eq. of butyllithium was used), vinylboronic ester **6f** (40.1 mg, 0.168 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10f** (25.7 mg, 0.0931 mmol, 55%).

X: yellow oil; IR (film) 3408, 3208, 2931, 2852, 1585, 1489, 1452, 1246, 1120, 1001, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (app td, *J* = 7.6, 1.6 Hz, 1H), 6.97 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.92 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.82 (app td, *J* = 7.6, 1.2 Hz, 1H), 3.02 (d, *J* = 14.4 Hz, 1H), 2.63 (d, *J* = 14.8 Hz, 1H), 1.93–1.54 (m, 5H), 1.52–1.03 (m, 12H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 132.6, 128.3, 124.7, 120.0, 117.3, 80.0, 45.1, 39.3, 36.2, 27.0, 26.8, 26.5, 25.4, 23.3, 14.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{28}NaO_2$ $[M+Na]^+$ 299.1987, found 299.1983.

***rac*-2-(2-cyclohexyl-2-hydroxypropyl)phenol (10g)**

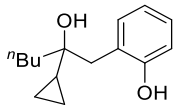


10g

Following the general procedure (1.3 eq. of methyllithium was used), vinylboronic ester **6g** (59.3 mg, 0.251 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10g** (34.2 mg, 0.146 mmol, 58%).

10g: yellow soild; IR (film) 3395, 3200, 2972, 2852, 1585, 1489, 1452, 1379, 1247, 1118, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (app td, *J* = 7.6, 1.6 Hz, 1H), 6.97 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.80 (app td, *J* = 7.4, 1.2 Hz, 1H), 2.98 (d, *J* = 14.4 Hz, 1H), 2.65 (d, *J* = 14.8 Hz, 1H), 1.94 (br d, *J* = 12.8 Hz, 1H), 1.99–1.62 (m, 3H), 1.69 (br d, *J* = 10.4 Hz, 1H), 1.42 (tt, *J* = 11.6, 2.8 Hz, 1H), 1.32–0.99 (m, 5H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 132.6, 128.4, 124.7, 120.0, 117.5, 78.7, 47.9, 41.5, 28.1, 27.0, 26.63, 26.59, 26.5, 24.0; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NaO_2$ $[M+Na]^+$ 257.1517, found 257.1524.

***rac*-2-(2-cyclopropyl-2-hydroxyhexyl)phenol (10h)**

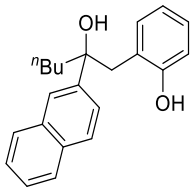


10h

Following the general procedure (1.3 eq. of butyllithium was used), vinylboronic ester **6h** (48.5 mg, 0.250 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10h** (36.2 mg, 0.155 mmol, 62%).

10h: yellow soild; IR (film) 3235, 3082, 2958, 2870, 1585, 1489, 1456, 1246, 1116, 1022, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.14 (app td, *J* = 7.6, 1.6 Hz, 1H), 7.02 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.82 (app td, *J* = 7.2, 1.2 Hz, 1H), 2.90 (d, *J* = 14.8 Hz, 1H), 2.82 (d, *J* = 14.8 Hz, 1H), 1.81 (br s, 1H), 1.57–1.22 (m, 6H), 0.99–0.91 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.46–0.37 (m, 2H), 0.37–0.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 132.6, 128.3, 124.7, 120.1, 117.3, 76.2, 42.7, 40.2, 26.0, 23.3, 19.5, 14.2, 0.48, 0.33; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NaO_2$ $[M+Na]^+$ 257.1517, found 257.1513.

***rac*-2-(2-hydroxy-2-(naphthalen-2-yl)hexyl)phenol (10i)**

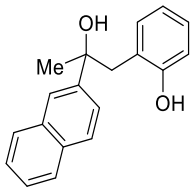


10i

Following the general procedure (1.3 eq. of butyllithium was used), vinylboronic ester **6i** (71.3 mg, 0.254 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10i** (47.1 mg, 0.147 mmol, 58%).

10i: yellow soild; IR (film) 3295, 3013, 2957, 2934, 2866, 1586, 1489, 1456, 1379, 1244, 1215, 1126, 1044, 945, 854, 752, 667 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.86 (d, *J* = 1.8 Hz, 1H), 7.85–7.79 (m, 3H), 7.51–7.45 (m, 3H), 7.10 (app td, *J* = 7.8, 1.8 Hz, 1H), 6.92 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.82 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.70 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.18 (ABq, *J* = 15.0 Hz, 2H), 2.91 (br s, 1H), 2.14 (ddd, *J* = 14.4, 12.6, 4.2 Hz, 1H), 1.92 (ddd, *J* = 13.8, 12.0, 4.2 Hz, 1H), 1.31–1.22 (m, 2H), 1.18–1.09 (m, 1H), 1.07–0.99 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 142.6, 133.3, 132.8, 132.4, 128.5, 128.3, 128.3, 127.6, 126.4, 126.1, 124.0, 123.9, 123.5, 120.3, 117.4, 80.8, 46.4, 40.2, 25.7, 23.0, 14.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}NaO_2$ $[M+Na]^+$ 343.1669, found 343.1665.

***rac*-2-(2-hydroxy-2-(naphthalen-2-yl)propyl)phenol (10j)**

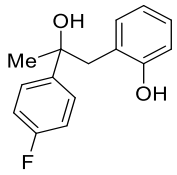


10j

Following the general procedure, vinylboronic ester **6j** (70.6 mg, 0.252 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10j** (49.4 mg, 0.177 mmol, 70%).

10j: yellow soild; IR (film) 3280, 3055, 2966, 1597, 1481, 1458, 1375, 1246, 1097, 1016, 856, 817, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 5.0 Hz, 1H), 7.90–7.78 (m, 3H), 7.60 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.53–7.44 (m, 2H), 7.14 (app td, *J* = 7.6, 1.6 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.88 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.76 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.29 (d, *J* = 14.8 Hz, 1H), 2.99 (d, *J* = 14.8 Hz), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 144.6, 133.2, 132.8, 132.6, 128.7, 128.3, 127.7, 126.4, 126.2, 124.3, 123.4, 123.1, 120.3, 117.6, 78.2, 46.8, 28.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}NaO_2$ $[M+Na]^+$ 301.1204, found 301.1198.

***rac*-2-(2-(4-fluorophenyl)-2-hydroxypropyl)phenol (10k)**

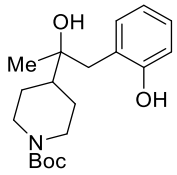


10k

Following the general procedure, vinylboronic ester **6k** (62.4 mg, 0.252 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10k** (43.0 mg, 0.175 mmol, 69%).

10k: colorless oil; IR (film) 3379, 3019, 1604, 1510, 1489, 1215, 1161, 930, 837, 768, 745, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.45–7.40 (m, 2H), 7.14 (ddd, *J* = 7.8, 7.2, 1.8 Hz, 1H), 7.04–7.00 (m, 2H), 6.92 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.81 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.77 (td, *J* = 7.2, 1.2 Hz, 1H), 3.12 (d, *J* = 14.4 Hz, 1H), 2.91 (d, *J* = 14.4 Hz, 1H), 2.81 (br s, 1H), 1.72 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0 (d, *J* = 244.2 Hz), 155.7, 142.9 (d, *J* = 2.4 Hz), 132.8, 128.7, 126.5 (d, *J* = 8.3 Hz), 124.2, 120.4, 117.5, 115.2 (d, *J* = 21.2 Hz), 77.7, 47.1, 28.6; HRMS (ESI) m/z calcd for $C_{15}H_{15}FNaO_2$ $[M+Na]^+$ 269.0954, found 269.0921.

tert-butyl _rac_-4-(2-hydroxy-1-(2-hydroxyphenyl)propan-2-yl)piperidine-1-carboxylate (10l)

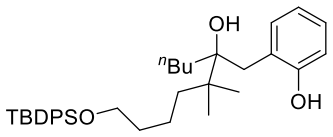


10l

Following the general procedure (1.3 eq. of methyllithium was used), vinylboronic ester **6l** (84.3 mg, 0.250 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10l** (44.2 mg, 0.113 mmol, 45%).

10l: White solid; IR (film) 3354, 3019, 2976, 1665, 1489, 1431, 1368, 1244, 1215, 1163, 1034, 928, 758, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.87 (br s, 1H), 7.14 (app td, *J* = 7.8, 1.2 Hz, 1H), 6.96 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.90 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.82 (app td, *J* = 7.2, 1.2 Hz, 1H), 4.18 (br s, 2H), 3.11 (br s, 1H), 2.99 (br d, *J* = 14.4 Hz, 1H), 2.71–2.51 (m, 2H), 2.60 (br d, *J* = 14.4 Hz, 1H), 1.84 (br dt, *J* = 13.2, 2.4 Hz, 1H), 1.77 (br dt, *J* = 13.2, 1.8 Hz, 1H), 1.56 (tt, *J* = 12.0, 3.0 Hz, 1H), 1.45 (s, 9H), 1.36–1.25 (m, 2H), 1.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 155.0, 132.6, 128.5, 124.4, 120.1, 117.4, 79.8, 77.4, 46.5. 44.6 (br), 43.8 (br), 41.6, 28.6, 27.1 (br), 26.3, 23.7; HRMS (ESI) m/z calcd for $C_{19}H_{29}NNaO_4$ $[M+Na]^+$ 358.1989, found 358.1988.

rac-2-(7-((_tert_-butyldiphenylsilyl)oxy)-2-hydroxy-2,3,3-trimethylheptyl)phenol (10m)

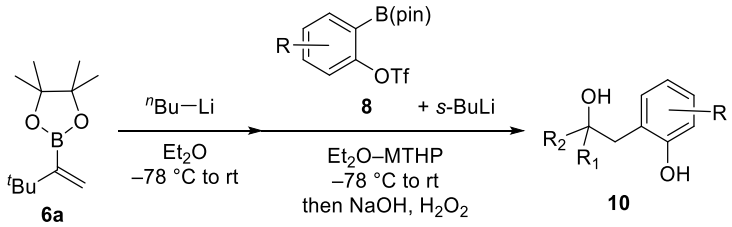


10m

Following the general procedure (1.3 eq. of methyllithium was used), vinylboronic ester **6m** (116 mg, 0.229 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10m** (64.6 mg, 0.128 mmol, 56%).

10m: White solid; IR (film) 3360, 3015, 2945, 2861, 1586, 1489, 1474, 1427, 1379, 1248, 1215, 1103, 754, 702, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 7.70–7.67 (m, 4H), 7.45–7.37 (m, 6H), 7.16 (td, *J* = 7.8, 1.2 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.95–6.91 (m, 1H), 6.85–6.82 (m, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.18 (d, *J* = 14.4 Hz, 1H), 2.50 (d, *J* = 14.4 Hz, 1H), 2.01 (br s, 1H), 1.62–1.55 (m, 2H), 1.49–1.37 (m, 3H), 1.36–1.30 (m, 1H), 1.07 (s, 9H), 1.03 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 135.7, 134.2, 132.8, 129.8, 129.7, 128.3, 127.8, 125.4, 120.1, 117.5, 115.4, 81.2, 63.9, 40.9, 38.5, 36.5, 33.7, 27.0, 21.8, 21.5, 21.3, 21.1, 19.4; HRMS (ESI) m/z calcd for $C_{32}H_{44}NaO_3Si$ $[M+Na]^+$ 527.2952, found 527.2953.

General procedure for the aryne triggered annulative coupling (oxidative workup) using substituted aryne precursors

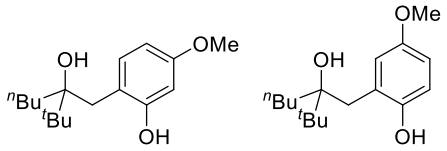


6a **10**

To a solution of vinylboronic ester **6a** (0.20 mmol, 1.0 eq.) in Et_2O (2.0 mL) was added *n*-BuLi (2.0 M in hexanes, 0.15 mL, 0.30 mmol, 1.5 eq.) at –78 °C and stirred for 5 min. A cooling bath was removed, and the mixture was further stirred for 30 min. The solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4-methyltetrahydropyran (4.0 mL). In the meantime, aryne precursor **8** (0.6 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (4.0 mL). The solution was treated with *s*-BuLi (1.2 M in hexanes, 0.5 mL, 0.6 mmol, 3.0 eq.) at –78 °C and stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. The reaction mixture was stirred at the same temperature for 2 h. After this period of time, the reaction mixture was cooled to 0 °C and treated with aqueous solution of NaOH (3 M, 5 mL) and aqueous solution of H_2O_2 (30%, 5 mL). This biphasic solution was warmed to rt and stirred

vigorously overnight. The flask was then cooled to 0 °C and treated with saturated aqueous solution of NH_4Cl until the pH of the mixture became neutral. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain hydroxyphenol **10**.

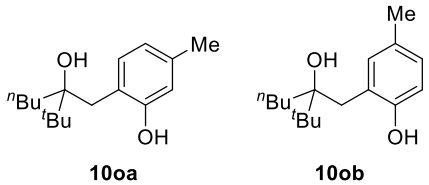
rac-2-(2-(_tert_-butyl)-2-hydroxyhexyl)-5-methoxyphenol (10na) and _rac_-2-(2-(_tert_-butyl)-2 hydroxyhexyl)-4-methoxyphenol (10nb)



Following the general procedure, vinylboronic ester **6a** (42.0 mg, 0.200 mmol) was coupled with aryne precursor **8n** to give corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10n** (23.6 mg, 0.0842 mmol, 42%, 1:1 mixture of inseparable regioisomers **10na** and **10nb**).

10na + **10nb**: colorless oil; IR (film) 3383, 2957, 2893, 1989, 1624, 1499, 1223 cm^{-1}; 1H NMR (600 MHz, $CDCl_3$) δ 6.88 (d, *J* = 8.4, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.70 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.59 (d, *J* = 3.0 Hz, 1H), 6.48 (d, *J* = 2.6 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.13 (d, *J* = 14.4 Hz, 1H), 3.05 (d, *J* = 14.4 Hz, 1H), 2.61 (d, *J* = 14.4 Hz, 1H), 2.60 (d, *J* = 14.4 Hz, 1H), 1.58–1.50 (m, 4H), 1.23–1.16 (m, 2H), 1.17–0.99 (m, 6H), 1.05 (s, 9H), 1.04 (s, 9H), 0.77 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.0, 157.2, 153.2, 150.3, 132.8, 126.6, 118.0, 117.72, 117.71, 113.2, 106.1, 102.7, 81.7(2C), 56.0, 55.4, 39.3, 39.2, 38.1, 37.4, 35.83, 35.80, 27.38, 27.35, 25.9, 25.8, 23.7(2C), 14.0(2C); HRMS (ESI) m/z calcd for $C_{17}H_{28}NaO_3$ $[M+Na]^+$ 303.1931, found 303.1922.

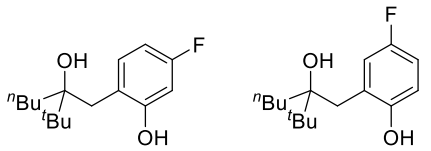
rac-2-(2-(_tert_-butyl)-2-hydroxyhexyl)-5-methylphenol (10oa) and _rac_-2-(2-(_tert_-butyl)-2-hydroxyhexyl) 4-methylphenol (10ob)



Following the general procedure, vinylboronic ester **6a** (42.4 mg, 0.202 mmol) was coupled with aryne precursor **8o** to give corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10o** (31.9 mg, 0.121 mmol, 60%, 5:4 mixture of inseparable regioisomers **10oa** and **10ob**).

10oa + **10ob**: colorless oil; IR (film) 3391, 3250, 2957, 2872, 1626, 1577, 1504, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 8.47 (br s, 1H), 6.93 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.72 (br s, 1H), 6.62 (dd, *J* = 7.5, 1.2 Hz, 1H), 3.11 (d, *J* = 14.4 Hz, 1H), 3.08 (d, *J* = 14.4 Hz, 1H), 2.63 (d, *J* = 14.4 Hz, 1H), 2.60 (d, *J* = 14.4 Hz, 1H), 2.28 (s, 3H), 2.24 (s, 3H), S24 2.01 (br s, 2H), 1.57–1.50 (m, 4H), 1.26–0.99 (m, 8H), 1.05 (s, 9H), 1.05 (s, 9H), 0.77 (t, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.1, 154.0, 138.2, 133.0, 132.2, 129.1, 128.7, 125.4, 122.5, 120.9, 117.9, 117.0, 81.69, 81.66, 39.31, 39.27, 38.0, 37.7, 35.9, 35.7, 27.4, 27.3, 25.9, 25.8, 23.7, 23.6, 21.2, 20.6, 14.0, 13.9; HRMS (ESI) m/z calcd for $C_{17}H_{28}NaO_2$ [M+Na]+ 287.1982, found 287.1977.

***rac*-2-(2-(*tert*-butyl)-2-hydroxyhexyl)-5-fluorophenol (10pa) and *rac*-2-(2-(*tert*-butyl)-2-hydroxyhexyl)-4 fluorophenol (10pb)**



10pa **10pb**

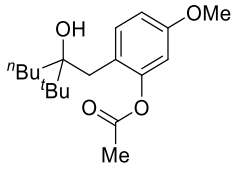
Following the general procedure, vinylboronic ester **6a** (53.5 mg, 0.255 mmol) was coupled with aryne precursor **8p** to give corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10p** (42.8 mg, 0.159 mmol, 63%, 3:1 mixture of regioisomers **10pa** and **10pb**). These regioisomers were able to separate to obtain pure **10pa** and **10pb** after multiple column chromatography.

10pa: pale yellow oil; IR (film) 3187, 2957, 2926, 2355, 1493, 1458, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (br, 1H), 6.93 (dd, *J* = 8.4, 6.8 Hz, 1H), 6.61 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.52 (app td, *J* = 8.4, 2.4 Hz, 1H), 3.07 (d, *J* = 14.8 Hz, 1H), 2.64 (d, *J* = 14.8 Hz, 1H), 2.06 (br s, 1H), 1.58–1.51 (m, 2H), 1.22–0.98 (m, 4H), 1.04 (s, 9H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, *J* = 243 Hz), 157.7 (d, *J* = 12 Hz), 132.8 (d, *J* = 9.0 Hz), 121.4 (d, *J* = 3.0 Hz), 106.7 (d, *J* = 21 Hz), 104.7 (d, *J* = 24 Hz), 81.8 (d, *J* = 1.0 Hz), 39.3, 37.7, 35.7, 27.3, 25.8, 23.6, 14.0; HRMS (ESI) m/z calcd for $C_{16}H_{25}FNaO_2$ $[M+Na]^+$ 291.1731, found 291.1729.

10pb: pale yellow oil; IR (film) 3129, 2961, 2903, 1603, 1506, 1468, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (br, 1H), 6.84–6.80 (m, 2H), 6.76–6.71 (m, 1H), 3.12 (d, *J* = 14.4 Hz, 1H), 2.60 (d, *J* = 14.4 Hz, 1H), 2.02 (br, 1H), 1.62–1.48 (m, 2H), 1.23–0.98 (m, 4H), 1.05 (s, 9H), 0.77 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6 (d, *J* = 236 Hz), 152.4 (d, *J* = 2.0 Hz), 127.1 (d, *J* = 7.0 Hz), 118.3 (d, *J* = 22 Hz), 118.0 (d, *J* = 9.0 Hz), 114.4 (d, *J* = 22 Hz),

81.9, 39.4, 38.2, 35.7, 27.3, 25.8, 23.6, 13.9; HRMS (ESI) m/z calcd for $C_{16}H_{25}FNaO_2$ $[M+Na]^+$ 291.1731, found 291.1723.

***rac*-2-(2-(*tert*-butyl)-2-hydroxyhexyl)-6-methoxyphenyl acetate (S10)**

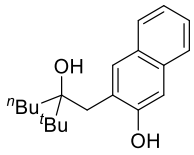


S10 (acetylated **10q**)

Following the general procedure, vinylboronic ester **6a** (42.0 mg, 0.192 mmol) was coupled with aryne precursor **8q** to give corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10q**. Because **10q** was not able to separate from unknown byproducts, it was converted to acetate derivative (Ac_2O, DMAP, pyridine). Purification of the crude mixture by flash chromatography gave **S10** (11.3 mg, 0.035 mmol, 18% in 2 steps).

S10: white solid; IR (film) 3568, 2957, 2872, 1773, 1734, 1478, 1437 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.13 (app t, *J* = 8.4 Hz, 1H), 6.87–6.84 (m, 2H), 3.81 (s, 3H), 2.91 (d, *J* = 13.2 Hz, 1H), 2.67 (d, *J* = 13.2 Hz, 1H), 2.32 (s, 3H), 1.53–1.48 (m, 2H), 1.29–1.12 (m, 3H), 1.04–0.96 (m, 1H), 1.02 (s, 9H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.0, 151.4, 139.4, 132.3, 126.1, 124.3, 110.5, 77.7, 56.1, 39.1, 29.9, 27.8, 25.9, 23.8, 20.7, 14.2; HRMS (ESI) m/z calcd for $C_{19}H_{30}NaO_4$ $[M+Na]^+$ 345.2036, found 345.1970.

***rac*-3-(2-(*tert*-butyl)-2-hydroxyhexyl)naphthalen-2-ol (10s)**



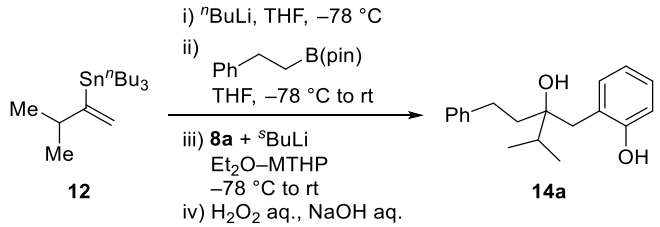
10s

Following the general procedure, vinylboronic ester **6a** (45.2 mg, 0.215 mmol) was coupled with aryne precursor **8s** to give corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **10s** (12.8 mg, 0.039 mmol, 18%).

10s: colorless oil; IR (film) 3471, 2959, 2872, 2490, 1956, 1458, 1260 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 7.68 (app d, *J* = 9.0 Hz, 2H), 7.51 (s, 1H), 7.37 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1H), 7.29–7.26 (m, 2H), 3.29 (d, *J* = 14.4 Hz, 1H), 2.89 (d, *J* = 14.4 Hz, 1H), 2.14 (br s, 1H), 1.64–1.54 (m, 2H), 1.37–1.20 (m, 2H), 1.09 (s, 9H), 1.07–1.00 (m, 2H), 0.68 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.7, 134.4, 131.3, 128.8, 128.6, 127.1, 126.3, 125.8, 123.3, 111.8, 81.5, 39.5, 38.6, 35.8, 27.2, 25.9, 23.5, 13.9; HRMS (ESI) m/z calcd for $C_{20}H_{28}NaO_2$ $[M+Na]^+$ 323.1982, found 323.1939.

Procedure for the aryne triggered annulative coupling using vinyltin as a substrate (oxidative workup)

***rac*-2-(2-hydroxy-2-isopropyl-4-phenylbutyl)phenol (14a)**

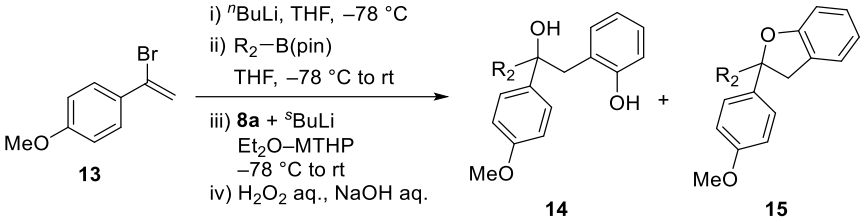


To a solution of vinyltin **12** (0.208 mmol, 1.0 eq.) in THF (1.0 mL) was added *n*-BuLi (2.5 M in hexanes, 0.10 mL, 0.24 mmol, 1.2 eq.) at –78 °C and stirred for 30 min. A cooling bath was then removed, and the mixture was further stirred at 0 °C for 10 min. Resulting vinyllithium solution was cooled again to –78 °C and a THF solution (1.5 mL) of boronic ester (60.4 mg, 0.26 mmol, 1.3 eq.) was added dropwise. After being stirred at the same temperature for 5 min, the cooling bath was removed, and the mixture was stirred at rt for 45 min. Then, the solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4 methyltetrahydropyran (2.0 mL). In the meantime, aryne precursor **8a** (0.60 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (4.0 mL). The solution was treated with *s*-BuLi (1.06 M in hexanes, 0.57 mL, 0.60 mmol, 3.0 eq.) at –78 °C and being stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. The reaction mixture was stirred at the same temperature for 2 h. After this period of time, the reaction mixture was cooled to 0 °C and treated with aqueous solution of NaOH (3 M, 10.0 mL) and aqueous solution of H_2O_2 (30%, 5.0 mL). This biphasic solution was warmed to rt and stirred vigorously overnight. The flask was then cooled to 0 °C and treated with aqueous solution of HCl (1 M) until the pH of the mixture became slightly acidic. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain hydroxyphenol **14a** (37.2 mg, 0.126 mmol, 61%).

14a: Yellow solid; IR (film) 3414, 2922, 1585, 1489, 1456, 1250, 1217, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 7.25 (app t, *J* = 7.8 Hz, 2H), 7.17 (app tt, *J* = 7.8, 1.8 Hz, 2H), 7.09–7.07 (m, 2H), 7.06 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.93 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.84 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.07 (d, *J* = 15.0 Hz, 1H), 2.78 (d, *J* = 15.0 Hz, 1H), 2.73 (ddd, *J* = 13.8, 12.6, 5.4 Hz, 1H), 2.60 (ddd, *J* = 12.6, 12.0, 6.0 Hz, 1H), 2.06 (br s, 1H), 1.98 (septet, *J* = 7.2 Hz, 1H), 1.77 (ddd, *J* = 13.8, 12.0, 4.8 Hz, 1H), 1.75 (ddd, *J* = 13.8, 12.0, 6.0 Hz, 1H), 1.04 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ156.0, 141.7, 132.5, 128.5, 128.4, 128.3,

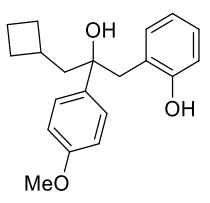
126.1, 124.0, 119.9, 117.3, 79.9, 39.1, 38.2, 34.7, 29.7, 16.9, 16.7; HRMS (ESI) m/z calcd for $C_{22}H_{30}NaO_2$ $[M+Na]^+$ 307.1669, found 307.1663.

General procedure for the aryne triggered annulative coupling using vinylbromide as a substrate (oxidative workup)

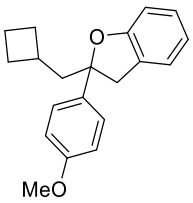


A solution of vinylbromide **13** (0.30 mmol, 1.0 eq.) in THF–Et_2O (1:1, 2.0 mL) was cooled to –78 °C and treated with *n*-BuLi (1.5 M in hexanes, 0.22 mL, 0.33 mmol, 1.1 eq.). After being stirred for 30 min at same temperature, resulting vinyllithium solution was added a THF solution (1.5 mL) of boronic ester (0.39 mmol, 1.3 eq.) dropwise. After being stirred at the same temperature for 5 min, the cooling bath was removed, and the mixture was stirred at rt for 1 h. Then, the solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4-methyltetrahydropyran (3.0 mL). In the meantime, aryne precursor **X** (0.90 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (6.0 mL). The solution was treated with *s*-BuLi (1.23 M in hexanes, 0.73 mL, 0.90 mmol, 3.0 eq.) at –78 °C and being stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. The reaction mixture was stirred at the same temperature for 2 h. After this period of time, the reaction mixture was cooled to 0 °C and treated with aqueous solution of NaOH (3 M, 10.0 mL) and aqueous solution of H_2O_2 (30%, 5.0 mL). This biphasic solution was warmed to rt and stirred vigorously overnight. The flask was then cooled to 0 °C and treated with saturate aqueous solution of NH_4Cl until the pH of the mixture became slightly acidic. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain hydroxyphenol **14** and dihydrobenzofuran **15**.

***rac*-2-(3-cyclobutyl-2-hydroxy-2-(4-methoxyphenyl)propyl)phenol (14b) and *rac*-2 (cyclobutylmethyl)-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (15a)**



14b



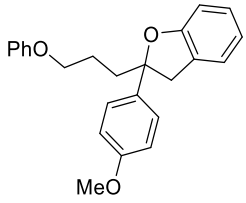
15a

Following the general procedure, vinylbromide **13** (63.9 mg, 0.300 mmol) and boronic ester **S2** (76.5 mg, 0.39 mmol) was converted to corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **14b** (8.4 mg, 0.0342 mmol, 11%) and dihiydrobenzofuran **15a** (36.7 mg, 0.124 mmol, 41%).

14b: Yellow solid; IR (film) 3292, 2959, 2930, 2859, 1584, 1489, 1248, 1035, 760 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.27–7.24 (m, 2H), 7.11 (app td, *J* = 8.4, 1.2 Hz, 1H), 6.91 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.86–6.83 (m, 2H), 6.77 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.72 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.80 (s, 3H), 3.01 (ABq, *J* = 14.4 Hz, 2H), 2.54 (br s, 1H), 2.26–2.18 (m, 1H), 2.10 (dd, *J* = 14.4, 5.4 Hz, 1H), 1.95 (dd, *J* = 14.4, 8.4 Hz, 1H), 1.96–1.88 (m, 1H), 1.79–1.57 (m, 4H), 1.60–1.50 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.5, 155.9, 137.2, 132.9, 128.4, 126.2, 124.1, 120.1, 117.4, 113.6, 81.2, 55.4, 47.4, 46.9, 31.7, 29.9, 29.7, 19.9; HRMS (ESI) m/z calcd for $C_{20}H_{24}NaO_3$ $[M+Na]^+$ 335.1618, found 335.1618.

15a: Yellow solid; IR (film) 2955, 2930, 2857, 1584, 1481, 1248, 1034, 752 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.31 (m, 2H), 7.13–7.08 (m, 2H), 6.87–6.84 (m, 2H), 6.81 (app td, *J* = 7.8, 1.2 Hz, 1H), 3.79 (s, 3H), 3.35 (ABq, *J* = 15.6 Hz, 2H), 2.40–2.32 (m, 1H), 2.13 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.06 (dd, *J* = 14.4, 6.6 Hz, 1H), 1.99–1.90 (m, 1H), 1.76–1.60 (m, 4H), 1.54–1.46 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 158.5, 138.2, 128.1, 126.8, 126.3, 125.0, 120.3, 113.6, 109.5, 91.7, 55.4, 49.6, 43.5, 32.4, 30.0, 29.7, 19.4; HRMS (ESI) m/z calcd for $C_{20}H_{22}NaO_2$ $[M+Na]^+$ 317.1512, found 317.1512.

rac-2-(4-methoxyphenyl)-2-(3-phenoxypropyl)-2,3-dihydrobenzofuran (15b)

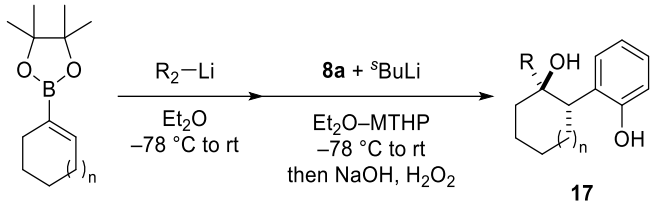


15b

Following the general procedure, vinylbromide **13** (63.9 mg, 0.30 mmol) and boronic ester **S3** (102 mg, 0.33 mmol) was converted to corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave dihydrobenzofuran **15b** (48.4 mg, 0.134 mmol, 45%).

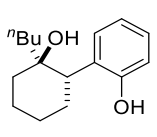
15b: Yellow solid; IR (film) 2924, 2899, 1586, 1479, 1246, 1034, 750 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2H), 7.26–7.22 (m, 2H), 7.15–7.10 (m, 2H), 6.91 (tt, *J* = 7.8, 1.2 Hz, 1H), 6.89–6.86 (m, 3H), 6.84–6.82 (m, 3H), 3.89 (app td, *J* = 6.6, 1.2 Hz, 2H), 3.79 (s, 3H), 3.41 (ABq, *J* = 15.6 Hz, 2H), 2.26–2.14 (m, 2H), 1.94–1.86 (m, 1H), 1.73–1.65 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 158.6, 137.7, 129.5, 128.2, 126.6, 126.3, 125.1, 120.7, 120.5, 114.6, 113.8, 109.6, 91.2, 67.8, 55.4, 43.9, 39.0, 24.3; HRMS (ESI) m/z calcd for $C_{24}H_{24}NaO_3$ [M+Na]+ 383.1618, found 383.1616.

Procedure for the aryne triggered annulative coupling of a vinylboronic ester with internal alkene (oxidative workup)

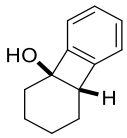


To a solution of vinylboronic ester **16** (0.25 mmol, 1.0 eq.) in Et_2O (2.0 mL) was added MeLi (3.1 M in hexanes, 0.115 mL, 0.357 mmol, 1.4 eq.) at –78 °C and stirred for 5 min. A cooling bath was removed, and the mixture was further stirred for 30 min. The solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4-methyltetrahdyropyran (4.0 mL). In the meantime, aryne precursor **8a** (0.75 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (4.0 mL). The solution was treated with *s*-BuLi (1.2 M in hexanes, 0.625 mL, 0.75 mmol, 3.0 eq.) at –78 °C and stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. The reaction mixture was stirred at the same temperature for 2 h. After this period of time, the reaction mixture was cooled to 0 °C and treated with aqueous solution of NaOH (3 M, 5 mL) and aqueous solution of H_2O_2 (30%, 5 mL). This biphasic solution was warmed to rt and stirred vigorously overnight. The flask was then cooled to 0 °C and treated with saturated aqueous solution of NH_4Cl until the pH of the mixture became neutral. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain hydroxyphenol **17** and [2+2] adduct **18.**

***rac*-2-((1*S*,2*R*)-2-butyl-2-hydroxycyclohexyl)phenol (17a)**



17a

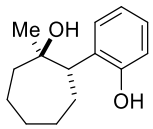


18

Following the procedure described above (1.3 eq. of 2 M solution of *n*-butyllithium was used), vinylboronic ester **16a** (54.0 mg, 0.259 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **17a** (8.2 mg, 0.0330 mmol, 13%) and [2+2] adduct **18**[25] (24.2 mg, 0.139 mmol, 54%).

17a: colorless oil; IR (film) 3300, 3019, 2936, 2862, 1582, 1487, 1456, 1217, 1044, 773, 760, 743, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.42 (app td, *J* = 7.8, 1.2 Hz, 1H), 7.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.95 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.91 (td, *J* = 7.2, 1.2 Hz, 1H), 3.10 (dd, *J* = 12.6, 3.0 Hz, 1H), 2.24 (br s, 1H), 2.07–2.01 (m, 1H), 1.95–1.84 (m, 2H), 1.78–1.69 (m, 3H), 1.58–1.52 (m, 1H), 1.39 (app qt, *J* = 13.2, 3.62 Hz, 1H), 1.31 (tt, *J* = 13.8, 3.6 Hz, 1H), 1.28–1.05 (m, 5H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.4, 129.4, 128.7, 127.7, 120.4, 117.7, 78.8, 47.2, 37.7, 30.6, 29.0, 26.4, 24.6, 23.8, 23.2, 14.3; HRMS (ESI) m/z calcd for $C_{16}H_{24}NaO_2$ $[M+Na]^+$ 271.1674, found 271.1659.

***rac*-(1*R*,2*S*)-1-butyl-2-(2-hydroxyphenyl)cycloheptan-1-ol (17b)**

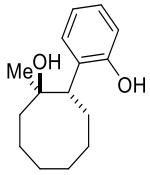


17b

Following the procedure described above (1.3 eq. of 3.1 M solution of methyllithium was used), vinylboronic ester **16b** (56.1 mg, 0.253 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **17b** (41.7 mg, 0.189 mmol, 75%).

17b: colorless solid; IR (film) 3603, 3277, 3019, 2932, 2859, 2400, 1582, 1487, 1456, 1215, 763, 746, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.11 (ddd, *J* = 7.8, 7.2, 1.8 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.92 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.89 (app td, *J* = 7.2, 1.2 Hz, 1H), 3.26 (d, *J* = 10.2 Hz, 1H), 1.99–1.93 (m, 1H), 1.93–1.87 (m, 3H), 1.87–1.79 (m, 2H), 1.76 (dd, *J* = 14.4, 10.2 Hz, 1H), 1.73–1.63 (m, 2H), 1.51 (dddd, *J* = 26.4, 12.6, 4.8, 2.4 Hz, 1H), 1.38–1.29 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.7, 132.0, 129.1, 127.4, 120.4, 117.5, 80.1, 48.1, 45.0, 30.9, 30.8, 30.3, 26.7, 21.8; HRMS (ESI) m/z calcd for $C_{14}H_{20}NaO_2$ $[M+Na]^+$ 243.1356, found 243.1350.

***rac*-(1*R*,2*S*)-2-(2-hydroxyphenyl)-1-methylcyclooctan-1-ol (17c)**

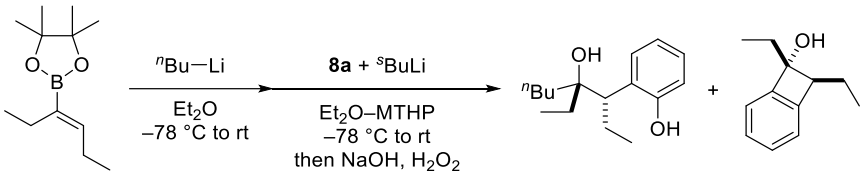


17c

Following the procedure described above (1.3 eq. of 3.1 M solution of methyllithium was used), vinylboronic ester **16c** (59.4 mg, 0.251 mmol) was converted to the corresponding hydroxyphenol. Purification of the crude mixture by flash chromatography gave **17c** (30.6 mg, 0.131 mmol, 52%).

17c: colorless oil; IR (film) 3449, 3019, 2924, 1487, 1379, 1215, 1044, 932, 775, 669 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.15 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.12 (ddd, *J* = 7.8, 7.2, 1.8 Hz, 1H), 6.95–6.90 (m, 2H), 3.57 (t, *J* = 6.0 Hz, 1H), 2.00 (ddd, *J* = 15.0, 10.2, 1.8 Hz, 1H), 1.97–1.89 (m, 1H), 1.86 (app br q, *J* = 6.0 Hz, 2H), 1.84–1.77 (m, 2H), 1.74–1.64 (m, 4H), 1.54–1.45 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.4, 132.0, 129.6, 127.4, 120.6, 117.7, 79.3, 41.1, 40.8, 30.5, 28.8, 27.9, 25.5, 24.9, 21.9; HRMS (ESI) m/z calcd for $C_{15}H_{22}NaO_2$ $[M+Na]^+$ 257.1517, found 257.1510.

rac-2-((3*S*,4*S*)-4-ethyl-4-hydroxyoctan-3-yl)phenol (20) and *rac*-(7*R*,8*S*)-7,8-diethylbicyclo[4.2.0]octa-1(6),2,4-trien-7-ol (21)



19 **20** **21**

To a solution of vinylboronic ester **19** (63.0 mg, 0.250 mmol, 1.0 eq.) in Et_2O (3.0 mL) was added *n*-BuLi (1.28 M in hexanes, 0.260 mL, 0.330 mmol, 1.3 eq.) at –78 °C and stirred for 5 min. A cooling bath was removed, and the mixture was further stirred for 30 min. The solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4-methyltetrahydropyran (5.0 mL). In the meantime, aryne precursor **8a** (264 mg, 0.75 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (5.0 mL). The solution was treated with *s*-BuLi (1.23 M in hexanes, 0.610 mL, 0.75 mmol, 3.0 eq.) at –78 °C and stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. The reaction mixture was stirred at the same temperature for 2 h. After this period of time, the reaction mixture was cooled to 0 °C and treated with aqueous solution of NaOH (3 M, 5 mL) and aqueous solution of H_2O_2 (30%, 5 mL). This biphasic

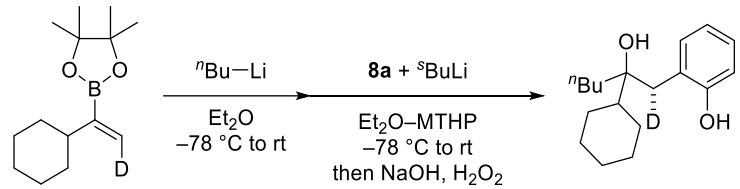
solution was warmed to rt and stirred vigorously overnight. The flask was then cooled to 0 °C and treated with saturated aqueous solution of NH_4Cl until the pH of the mixture became neutral. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain hydroxyphenol **20** (10.4 mg, 0.0415 mmol, 17%) and benzocyclobutene **21** (21.4 mg, 0.121 mmol, 49%).

20: colorless solid; IR (film) 3395, 3021, 2955, 2874, 1489, 1217, 776, 754, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.25 (br s, 1H), 7.14 (td, *J* = 7.8, 7.2 Hz, 1H), 6.91 (br d, *J* = 7.2 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.77 (t, *J* = 7.2 Hz, 1H), 2.49 (br s, 1H), 2.22 (br s, 1H), 1.91–1.82 (m, 1H), 1.82–1.74 (m, 1H), 1.72 1.63 (m, 2H), 1.45–1.32 (m, 4H), 1.32–1.18 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.79 (br t, *J* = 7.2 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 133.5, 128.2, 126.7, 119.4, 117.8, 79.4, 55.5, 35.8, 30.4, 26.4, 23.3, 19.5, 14.2, 13.4, 7.9; HRMS (ESI) m/z calcd for $C_{16}H_{26}NaO_2$ $[M+Na]^+$ 273.1830, found 273.1811.

21: colorless solid; IR (film) 3385, 3019, 2961, 2920, 2874, 1458, 1375, 1217, 1132, 995, 970, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33–7.29 (m, 1H), 7.27–7.23 (m, 3H), 3.32 (dd, *J* = 10.2, 6.0 Hz, 1H), 2.26 (br s, 1H), 1.93 (dq, *J* = 14.4, 7.8 Hz, 1H), 1.91–1.84 (m, 1H), 1.77 (dq, *J* = 14.4, 7.8 Hz, 1H), 1.66–1.58 (m, 1H), 1.21 (t, *J* = 7.8 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 146.5, 129.3, 127.5, S34 123.6, 121.8, 82.9, 61.3, 27.9, 22.8, 13.2, 8.8; HRMS (ESI) m/z calcd for $C_{12}H_{16}NaO$ $[M+Na]^+$ 199.1099, found 199.1117.

Procedure for the aryne triggered annulative coupling of deuterated substrate and their derivatization

rac-2-((1*S*)-2-cyclohexyl-2-hydroxyhexyl-1-d)phenol (23)



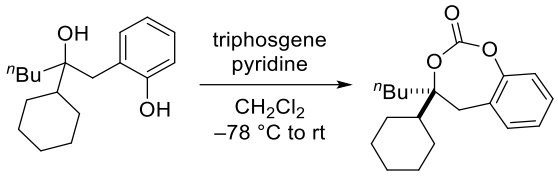
22 (*E*/*Z* = 23:1) **23** 43% (dr = 15:1)

To a solution of vinylboronic ester **22** (45.9 mg, 0.194 mmol, *E*/*Z* = 23:1, 1.0 eq.) in Et_2O (2.0 mL) was added *n*-BuLi (1.79 M in cyclohexane, 0.145 mL, 0.26 mmol, 1.3 eq.) at –78 °C and stirred for 5 min. A cooling bath was removed, and the mixture was further stirred for 30 min. The solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate complex was then dissolved in 4-methyltetrahydropyran (4.0 mL). In the meantime, aryne precursor **8a** (211 mg, 0.60 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (4.0 mL). The solution was treated with *s*-BuLi (1.23 M in hexanes, 0.490 mL, 0.75 mmol, 3.0 eq.) at –78 °C and stirred for 10

min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. The reaction mixture was stirred at the same temperature for 2 h. After this period of time, the reaction mixture was cooled to 0 °C and treated with aqueous solution of NaOH (3 M, 5 mL) and aqueous solution of H_2O_2 (30%, 5 mL). This biphasic solution was warmed to rt and stirred vigorously overnight. The flask was then cooled to 0 °C and treated with saturated aqueous solution of NH_4Cl until the pH of the mixture became neutral. The mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain hydroxyphenol **23** (23.1 mg, 0.0833 mmol, 43%, dr 15:1).

23: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (app td, *J* = 7.6, 1.6 Hz, 1H), 6.97 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.81 (app td, *J* = 7.4, 1.2 Hz, 1H), 3.01 (s, 1H), 1.91–1.80 (m, 2H), 1.75 (br d, *J* = 12.0 Hz, 1H), 1.69 (br d, *J* = 10.8 Hz, 1H), 1.50–1.41 (m, 2H), 1.40–1.29 (m, 2H), 1.27–1.07 (m, 8H), 0.86 (t, *J* = 7.2 Hz, 3H);

***rac*-(4*S*,5*S*)-4-butyl-4-cyclohexyl-4,5-dihydrobenzo[d][1,3]dioxepin-2-one (S11)**

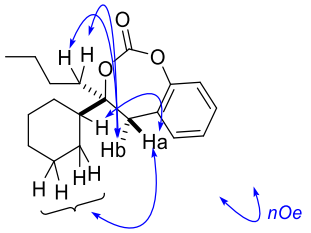


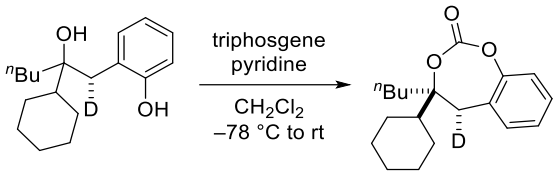
10f **S11**

To a stirred solution of **10f** (9.5 mg, 0.0344 mmol) and pyridine (30 μL, 0.372 mmol) in CH_2Cl_2 (1.0 mL) was added triphosgene (12.5 mg, 0.0421 mmol) at –78 °C. After being stirred at same temperature for 10 min, the reaction mixture was warmed to rt. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The mixture was extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain carbonate **S11** (10.5 mg, 0.0347 mmol, quant.).

S11: white powder; IR (film) 2928, 2855, 1759, 1489, 1456, 1233, 1211, 1173, 1146, 1001, 764 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.26 (m, 1H), 7.19–7.16 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 3.26 (d, *J* = 15.0, 1H), 2.89 (d, *J* = 15.0, 1H), 1.89 (br dd, *J* = 10.8, 1.8 Hz, 1H), 1.84–1.78 (m, 3H), 1.74 (app tt, *J* = 11.4, 2.4 Hz, 1H), 1.68 (br d, *J* = 10.8 Hz, 1H), 1.61 (dd, *J* = 9.0, 7.2 Hz, 2H), 1.42–1.28 (m, 2H), 1.28–1.11 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.7, 150.1, 130.5, 128.7, 128.0, 125.9, 119.7, 98.6, 46.0, 36.7, 35.8,

27.6, 27.4, 26.8, 26.6, 26.4, 25.7, 23.2, 14.1; HRMS (ESI) m/z calcd for $C_{19}H_{26}NaO_3$ $[M+Na]^+$ 325.1774, found 325.1771.





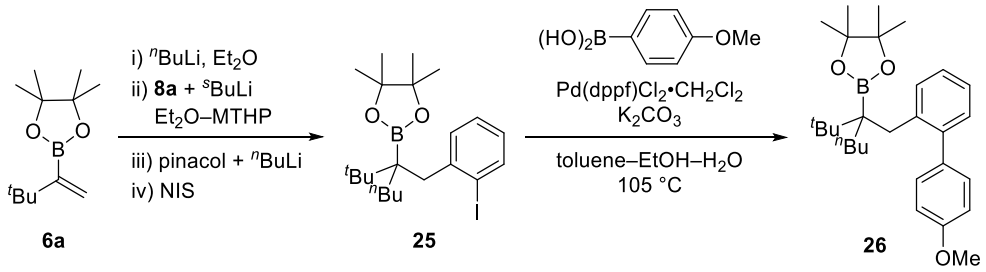
23 **24**

Following the same procedure, deuterated hydroxyphenol **23** (9.9 mg, 0.0357 mmol) was converted to corresponding carbonate **24** (9.7 mg, 0.0320 mmol, 90%).

By comparing the ^{1}H-NMR of **S11** and **24**, deuterated proton was assigned as H_b.

Procedure for the aryne triggered annulative coupling (iodination of the borinic ester), and Suzuki-Miyaura coupling of aryl iodide

***rac*-2-(3-(2-iodobenzyl)-2,2-dimethylheptan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (X)**



6a **25** **26**

To a solution of vinylboronic ester **6a** (42.3 mg, 0.201 mmol, 1.0 eq.) in Et_2O (2.0 mL) was added *n*-BuLi (2.0 M in cyclohexanes, 1.5 mL, 0.3 mmol, 1.5 eq.) at –78 °C and stirred for 5 min. A cooling bath was removed, and the mixture was further stirred for 45 min. The solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4-methyltetrahydropyran (4.0 mL). In the meantime, aryne precursor **8a** (0.600 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (4.0 mL). The solution was treated with *s*-BuLi (1.23 M in hexanes, 0.49 mL, 0.6 mmol, 3.0 eq.) at –78 °C and stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a

dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. The reaction mixture was stirred at the same temperature for 2 h before being cooled to 0 °C. In a mean time, pinacol (47.6 mg, 0.4 mmol, 2.0 eq.) placed in a separate flask was dissolved in THF (2.0 mL). This solution was treated with *n*-BuLi (2.0 M in cyclohexanes, 0.41 mL, 0.82 mmol, 4.1 eq.) at 0 °C and stirred at the same temperature for 10 min. Then, 1.2 mL (0.2 mmol) of this alkoxide solution was added dropwise to an above reaction mixture via syringe. The resulting mixture was warmed to rt and being stirred for 30 min before it was placed into a –78 °C cooling bath. To the reaction mixture was then added a THF solution (4.0 mL) of *N*-iodosuccinimide (181 mg, 0.8 mmol, 4.0 eq.) and being stirred at same temperature for 1 h. After this period of time, the reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain boronic ester **25** (46.1 mg, 0.098 mmol, 49%).

25: colorless oil; IR (film) 2959, 2870, 1466, 1371, 1294, 1144, 1009, 856 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.72 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.16 (app td, *J* = 7.2, 1.2 Hz, 1H), 6.81 (app dt, *J* = 7.8, 1.8 Hz, 1H), 3.26 (d, *J* = 13.8 Hz, 1H), 2.88 (d, *J* = 13.8 Hz, 1H), 1.56–1.47 (m, 2H), 1.31 (s, 6H), 1.26 (s, 6H), 1.06 (s, 9H), 1.06–0.98 (m, 2H), 0.97–0.92 (m, 1H), 0.60 (t, *J* = 7.2 Hz, 3H), 0.14–0.06 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.0, 139.8, 131.0, 127.5, 127.4, 103.8, 83.5, 42.2, 37.1, 31.5, 29.9, 27.8, 25.9, 24.9, 24.4, 14.1; HRMS (ESI) m/z calcd for $C_{22}H_{36}BINaO_2$ $[M+Na]^+$ 493.1745, found 493.1746.

rac-2-(3-((4'-methoxy-[1,1'-biphenyl]-2-yl)methyl)-2,2-dimethylheptan-3-yl)-4,4,5,5-tetramethyl-1,3,2 dioxaborolane (26)

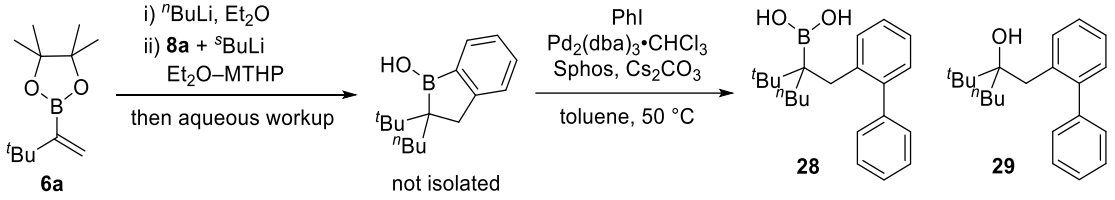
Aryliodide **25** (37.4 mg, 0.0795 mmol, 1.0 eq.), 4-methoxyphenylboronic acid (18.1 mg, 0.119 mmol, 1.5 eq.), $Pd(dppf)Cl_2$ (3.2 mg, 3.98 μmol, 5 mol%), and K_2CO_3 (55 mg, 0.400 mmol, 5.0 eq.) were dissolved in toluene–EtOH (5:2, 1.4 mL) and stirred at 105 °C for 2 h. After being cooled to rt, the mixture was diluted with AcOEt and water. The mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain boronic ester **26** (32.1 mg, 0.0713 mmol, 90%).

26: white powder; IR (film) 3061, 2953, 2870, 2837, 1611, 1514, 1371, 1296, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 1H), 7.25–7.21 (m, 2H), 7.19–7.11 (m, 3H), 6.96–6.91 (m, 2H), 3.85 (s, 3H), 2.98 (ABq, *J* = 13.6 Hz, 2H), 1.30 (s, 6H), 1.26 (s, 6H), 1.24–1.16 (m, 1H), 1.00–0.87 (m, 4H), 0.75 (s, 9H), 0.64 (t, *J* = 7.2 Hz, 3H), 0.35–0.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 142.9, 140.6, 135.5, 131.3, 130.8, 130.4, 129.2, 128.4, 126.4, 125.5,

125.3, 113.4, 83.2, 55.4, 36.7, 33.5, 31.8, 29.7, 27.5, 25.9, 25.0, 24.6, 14.2; HRMS (ESI) m/z calcd for $C_{29}H_{43}BNaO_3$ $[M+Na]^+$ 473.3197, found 473.3194.

Procedure for the aryne triggered annulative coupling/Suzuki-Miyaura coupling sequence

***rac*-(3-([1,1'-biphenyl]-2-ylmethyl)-2,2-dimethylheptan-3-yl)boronic acid (28) and *rac*-3-([1,1'-biphenyl]-2-ylmethyl)-2,2-dimethylheptan-3-ol (29)**



To a solution of vinylboronic ester **6a** (42 mg, 0.20 mmol, 1.0 eq.) in Et_2O (2.0 mL) was added *n*-BuLi (1.28 M in hexanes, 0.23 mL, 0.294 mmol, 1.5 eq.) at –78 °C and stirred for 5 min. A cooling bath was removed, and the mixture was further stirred for 30 min. The solvent was removed in vacuo and the flask was back filled with nitrogen. The obtained mixture of vinylboronic ester ate-complex was then dissolved in 4-methyltetrahyrdopyran (4.0 mL). In the meantime, aryne precursor **8a** (211 mg, 0.60 mmol, 3.0 eq.) was added to a separate flask and dissolved in Et_2O (4.0 mL). The solution was treated with *s*-BuLi (1.0 M in hexanes, 0.6 mL, 0.60 mmol, 3.0 eq.) at –78 °C and being stirred for 10 min at this temperature. To this activated aryne precursor solution was then added the solution of vinylboronic ester ate-complex prepared above dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and a dry ice/acetone bath was exchanged to water bath which temperature was controlled to 20 °C with ice. After being stirred at same temperature for 2 h, the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl. The mixture was quickly extracted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in degassed toluene (1.0 mL) and added to a separate flask containing a degassed toluene solution (4.0 mL) of $Pd_2(dba)_3{\cdot}CHCl_3$ (10.3 mg, 0.010 mmol, 5 mol%), SPhos (9.9 mg, 0.024 mmol, 12 mol%) and Cs_2CO_3 (215 mg, 0.66 mmol, 3.3 eq.). The mixture was stirred at 50 °C for 6 h. The reaction was quenched by the addition of EtOAc, filtered through a pad of celite and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain boronic ester **28** (25.8 mg, 0.0763 mmol, 38%), along with overoxidized alcohol **29** (24.2 mg, 0.0779 mmol, 39%).

28: pale yellow oil; IR (film) 3464, 2951, 2872, 1558, 1473, 1375, 1338, 1219, 1010, 767, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.10 (m, 9H), 2.98 (d, *J* = 14.0 Hz, 1H), 2.86 (d, *J* = 14.0 Hz, 1H), 1.27–1.07 (m, 2H), 1.05–0.90 (m, 4H), 0.79 (s, 9H), 0.71 (t, *J* = 7.2 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 143.2, 142.5, 139.2, 130.4, 130.1, 129.9, 128.1, 127.3, 126.8, 125.7, 35.9, 34.2, 32.3, 30.0, 27.8, 24.7, 14.1; HRMS (ESI) m/z calcd for $C_{22}H_{31}BNaO_2$ $[M+Na]^+$ 361.2315, found 361.2308.

29: colorless oil; IR (film) 3676, 2960, 1598, 1396, 1261, 1093, 1020, 866, 775, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43–7.38 (m, 3H), 7.34–7.31 (m, 3H), 7.30–7.27 (m, 2H), 7.24–7.22 (m, 1H), 3.03 (d, *J* = 13.8 Hz, 1H), 2.95 (d, *J* = 13.8 Hz, 1H), 1.30 (ddd, *J* = 13.8, 12.6, 4.2 Hz, 1H), 1.25 (br s, 1H), 1.24–1.17 (m, 1H), 1.11–1.03 (m, 2H), 0.99–0.92 (m, 1H), 0.82–0.75 (m, 1H), 0.77 (s, 9H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.5, 136.3, 131.8, 130.5, 130.0, 128.4, 127.1, 126.9, 126.4, 78.2, 39.0, 36.5, 35.7, 27.5, 25.6, 23.9, 14.2; HRMS (ESI) m/z calcd for $C_{22}H_{30}NaO$ $[M+Na]^+$ 333.2194, found 333.2200.

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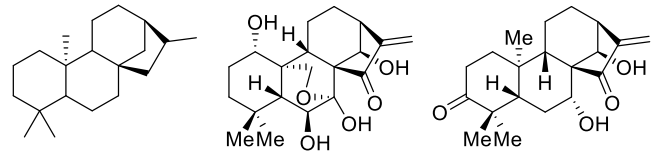
Chapter 3. Rapid construction of a diterpene-inspired tetracyclic skeleton bearing bicyclo[3.2.1]octane rings based on desymmetrization of 1,3-diketones

3-1. Abstract

Rapid construction of A-ring aromatic *ent*-kaurane-like tetracyclic skeleton including bicyclo[3.2.1]octane ring has been developed. Using a symmetric diketone as a key intermediate, the sequence of desymmetric Friedel–Crafts cyclization and Pd-catalyzed intramolecular α-vinylation of ketone constructed the *ent*-kaurane-like tetracyclic skeleton from 1,3-cyclohexanedione in only four steps.

3-2. Introduction

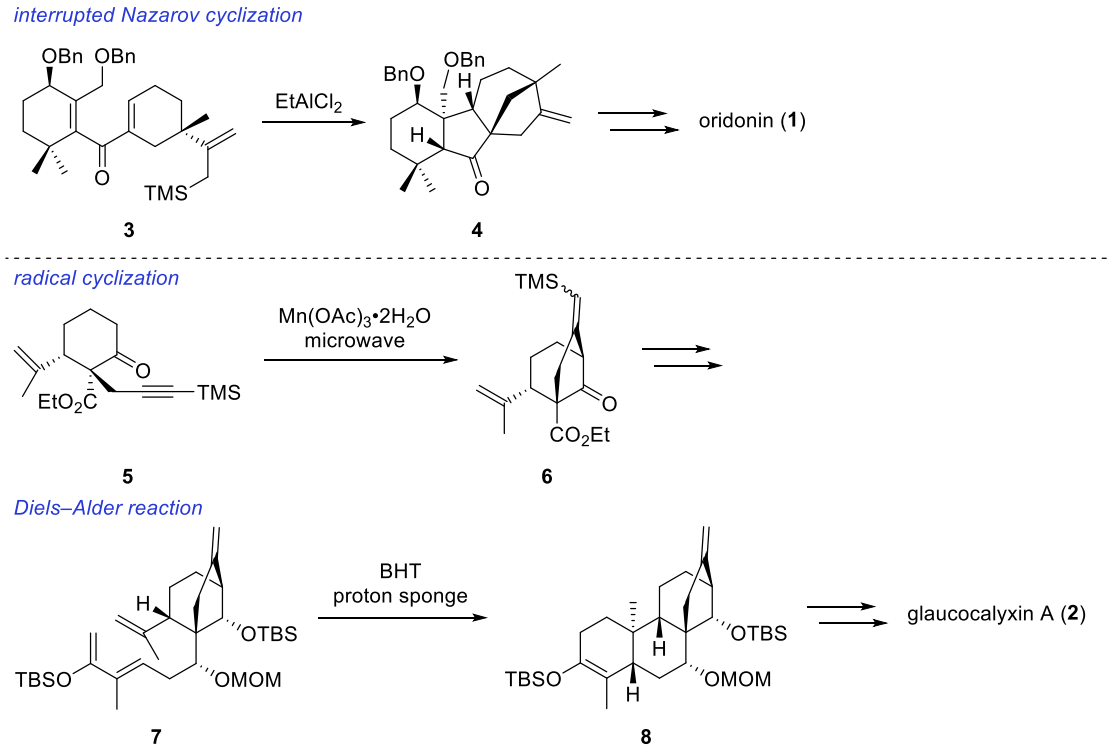
ent-Kaurane diterpenoids are a family of tetracyclic diterpenoids with a [6.6.6.5] tetracyclic skeleton including bicyclo[3.2.1]octane ring (Figure 1).[1] This family has many members exhibiting multiple oxygen functional groups and many structural diversities. Therefore, *ent*-kaurane diterpenoids are known for their various biological activities and are expected to lead to drug compounds. For example, oridonin (**1**)[2] and glaucocalyxin A (**2**)[3], a representative of these diterpenoids, is primarily known to possess *anti*-tumor activity.



ent-kaurane skeleton | oridonin (**1**) *anti*-tumor *anti*-inflammatory | glaucocalyxin A (**2**) *anti*-tumor

Figure 1. *ent*-kaurane diterpenoids

Thus, this family is very attractive to chemists because of its biological activity and complex tetracyclic skeleton. Since total synthesis of kaurene was reported by Partyka in 1962,[4] various synthetic methods have been developed over half a century.[5] For examples, the total synthesis of oridonin (**1**) was described by Luo and co-workers utilizing an interrupted Nazarov reaction approach as a key strategy.[6] Synthesis of glaucocalyxin A (**2**) was achieved by Jia and co-workers featuring a radical cyclization and a Diels–Alder reaction.[7]



Scheme 1. Previous synthetic report of *ent*-kaurane diterpenoids

Other methods for constructing the *ent*-kaurane skeleton employed a strain-release Diels–Alder reaction[8] and a method utilizing [5+2]cycloaddition/pinacol rearrangement.[9] The *ent*-kaurane skeleton, featuring a [6.6.6.5] tetracyclic framework with a bicyclo[3.2.1]octane ring fused at a quaternary carbon and multiple oxygen functional groups, is extremely challenging to construct. Therefore, the development of efficient and facile methods to construct the *ent*-kaurane skeleton remains important.

As stated in Chapter 1, the author aimed to construct the grayanane skeleton through biomimetic strategy and planned to synthesize the *ent*-kaurane framework. In order to develop the construction of grayanane skeleton via skeletal rearrangement, it is important to establish an effective and a facile synthesis for *ent*-kaurane-like tetracyclic framework, the author considered a rapid construction of a simplified *ent*-kaurane skeleton.

Simplification of natural product structures is a useful strategy for exploring biologically active synthetic ligands. Simplification enables short-step access to natural product skeletons, facilitating divergent-oriented synthesis.[10] The author considered that converting the A-ring of the *ent*-kaurane skeleton into an aromatic ring would enable the rapid construction of the *ent*-kaurane framework. This approach allows for the utilization of aromatic ring-based skeleton construction methods and diverse transformations based on dearomatization. As the A-ring of *ent*-kaurane diterpenoids contains critical and diverse functional groups, such as dimethyl groups and quaternary carbons, employing well-developed aromatic chemistry is a logical choice.[11]

3-3. Results and discussions

Figure 2 shows the author's plan for the construction of A-ring aromatic *ent*-kaurane-like tetracyclic skeleton including bicyclo[3.2.1]octane unit. Tetracyclic compound **9** was planned to be constructed by a site-selective Friedel–Crafts cyclization of **10** possessing a bicyclo[3.2.1]octane structure with two ketones. The construction of bicyclo[3.2.1]octane ring could be achieved to palladium-catalyzed desymmetric α-vinylation of symmetric diketone **11**. Symmetric diketone **11** would be synthesized by sequential assembly of 1,3-cyclohexanedione **12**,[12] 2,3-dibromopropene **13** and aldehyde **14**.

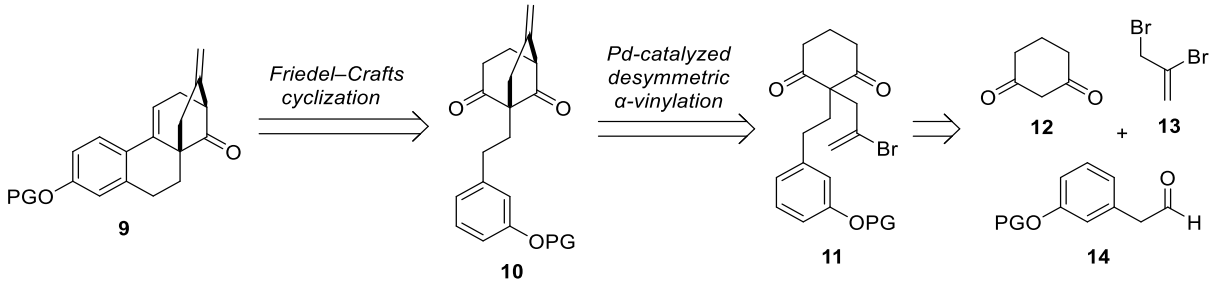
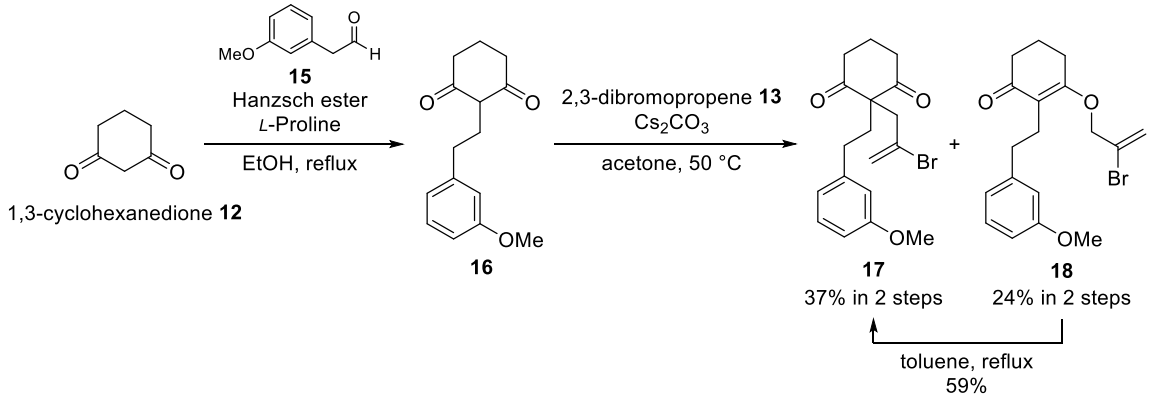


Figure 2. Synthetic plan for the construction of an *ent*-kaurane-like tetracyclic skeleton.

The author commenced with reductive Knoevenagel condensation to obtain diketone **16** from commercially available 1,3-cyclohexanedione **12** and aldehyde **15**, which was prepared in two steps from *m*-anisaldehyde (Scheme 1).[13] Symmetrc diketone **17** was then synthesized **15** from 2,3-dibromopropene **13**. Although *O*-allylation product **18** was also obtained in the reaction, it could be converted to the *C*-allylated **17** through a Claisen rearrangement in boiling toluene.

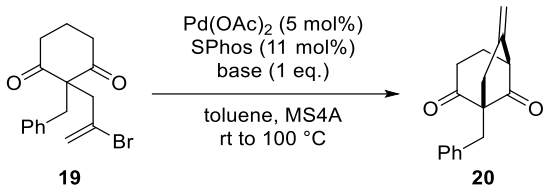


Scheme 1. Synthesis of symmetric diketone **17**

With symmetric diketone **17** in hand, the author investigated the construction of a bicyclo[3.2.1]octane ring via desymmetric α-vinylation using symmetric diketone **19** as a model substrate. Based on the report by Shi and co-workers,[14] with $Pd(OAc)_2$, SPhos fixed, the screening of bases for α-vinylation was conducted (Table 1). the use of Cs_2CO_3 as the base resulted in the formation of a diketone **20** bearing a bicyclo[3.2.1]octane framework in 97% yield (entry 1). However, due to the hygroscopic of Cs_2CO_3, the reaction showed poor reproducibility, prompting further investigation into alternative bases. the use of K_2CO_3

afforded **20** in 99% yield with good reproducibility (entry 2). On the other hand, when Li_2CO_3 or Na_2CO_3 was employed, no reaction was observed (entries 3,4). Since it was found that the countercation plays a crucial role in this reaction, other potassium bases were explored. When K_3PO_4 was used, **20** was obtained in high yield (entry 5). On the other hand, the use of KO^{t}Bu or KOPh resulted in poor conversion, likely due to its low reactivities (entries 6,7). Finally, Et_3N as an organic base was employed, **19** was completely recovered (entry 8).

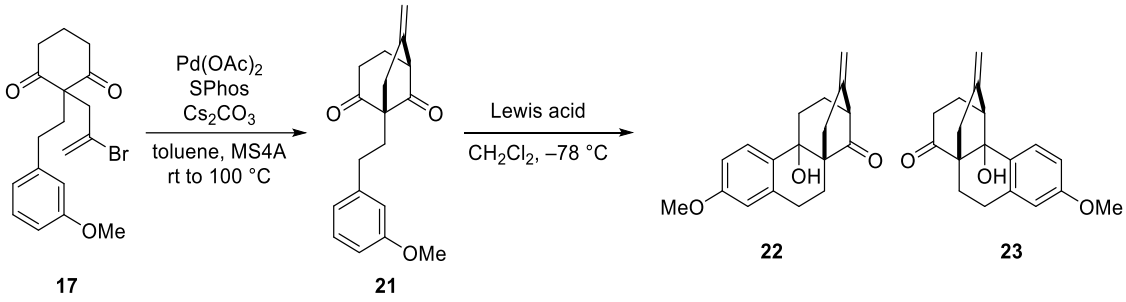
Table 1. Screening of bases for the desymmetric α-vinylation



entry	base	crude NMR
1	Cs_2CO_3	**20** 97%
2	K_2CO_3	**20** 99%
3	Li_2CO_3	N.R.
4	Na_2CO_3	N.R.
5	K_3PO_4	**20** 82%
6	KO^{t}Bu	**19** 10%, **20** 21%
7	KOPh	**19** 56%, **20** 28%
8	Et_3N	N.R.

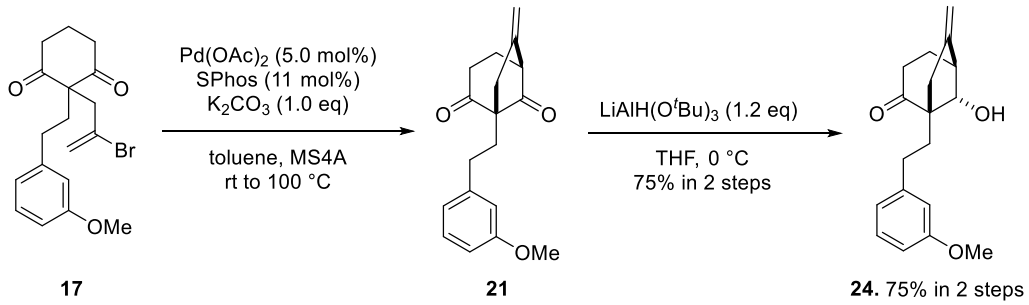
Based on the established method for constructing the bicyclic framework, desymmetric α-vinylation was performed using symmetric diketone **17**. As a result, diketone **21** including bicyclo[3.2.1]octane unit was obtained, but **21** was found to be unstable on silica gel (Table 2). The site-selective Friedel–Crafts cyclization reaction was performed with the crude product of **21**. With $EtAlCl_2$ as a Lewis acid, the Friedel–Crafts cyclization of **21** proceeded smoothly at –78 °C to afford tetracyclic skeleton (entry 1). However, the obtained tetracyclic skeleton did not form the desired kaurane-like tetracyclic framework, but cyclization of the aromatic ring with right-side ketone was conducted, a pseudo-symmetric structure of the desired *ent*-kaurane-type skeleton **23** was obtained in 51% yield as a 2.5:1 mixture of diastereomers. Various other Lewis acids, using TMSOTf, $SnCl_4$, and their BINOL complexes, were also examined in an attempt to construct a *ent*-kaurane like skeleton (entries 2–4). However, as observed with $EtAlCl_2$, these attempts resulted in the formation of a pseudo-symmetric tetracyclic skeleton **23**. The use of $B(C_6F_5)_3$, MABR, and BF_3·OEt_2 did not result in cyclization but instead led to complex product mixtures or complete recovery of the starting material **21** (entries 5–7).

Table 2. Screening of Lewis acid for the site-selective Friedel–Crafts cyclization



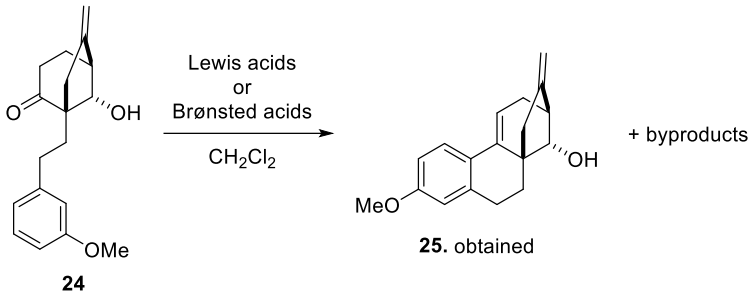
entry	Lewis Acid	yields (in 2 steps)		
		21	**22**	**23**
1	$EtAlCl_2$	22%	0%	51%
2	TMSOTf	0%	0%	24%
3	$SnCl_4$	10%	0%	40%
4	$SnCl_4$(BINOL)	0%	0%	28%
5	$B(C_6F_5)_3$	17%	0%	0%
6	MABR	quant.	0%	0%
7	BF_3·OEt_2	quant.	0%	0%

Due to the higher reactivity of the right-side ketone of diketone **21** bearing bicyclo[3.2.1]ring, the author considered that regioselective functionalization of this ketone could be performed, followed by the Friedel–Crafts cyclization of remaining ketone to construct *ent*-kaurane-like tetracyclic framework. After constructing the bicyclo[3.2.1]octane unit through desymmetric α-vinylation, the regioselective reduction of ketone **21** was attempted using $LiAlH(O^tBu)_3$, resulting in the synthesis of the desired β-hydroxyketone **24** as a single diastereomer (Scheme 2).



Scheme 2. Regio- and diastereoselective reduction of diketone **21** bearing bicyclo[3.2.1]octane ring

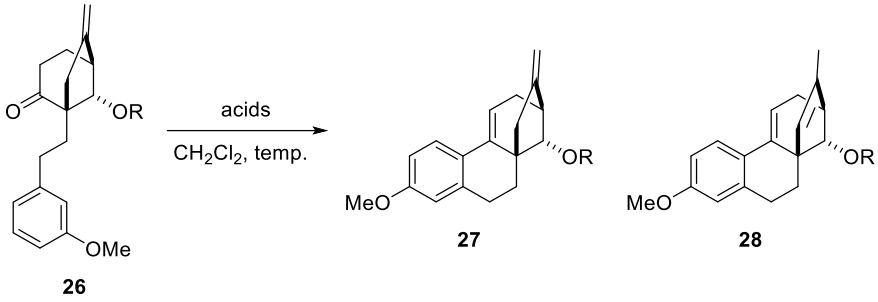
The Friedel–Crafts cyclization of **24** was attempted (Scheme 3). However, when using various Lewis acids or Brønsted acids, the desired *ent*-kaurane-like tetracyclic skeleton **25** was obtained in each case, but inseparable byproducts were also produced.



Scheme 3. Friedel–Crafts cyclization of **24**

Therefore, the author subsequently protected the hydroxy group of **24** with an acyl group, followed by performing the Friedel–Crafts cyclization, aiming to obtain the corresponding tetracyclic skeleton without byproduct (Table 3). Utilizing the ketone **26** protected by an acetyl group of a hydroxy group, the Friedel–Crafts cyclization was conducted using TMSOTf, but the reaction did not proceed (entry 1). A combination of TMSOTf and TfOH was used, which proceeded cyclization, yielding the corresponding *ent*-kaurane-like tetracyclic skeleton **27** (entry 2). However, inseparable byproduct was also obtained. The protecting group of a hydroxy group was changed an acetyl group to a methyl carbonate group, but the result was similar to those ratio with acetyl group (entry 3). Fortunately, the use of TfOH as a Brønsted acid prevented the formation of byproduct (entry 4). However, isomerization of the *exo*-methylene group was observed, resulting in a mixture of **27** and **28**. To facilitate analysis, the protecting group of hydroxy group was changed to an ethyl carbonate, and a temperature was raised to –20 °C, resulting in **28**, in which the *exo*-methylene was completely isomerized, was obtained as a single product (entry 5).

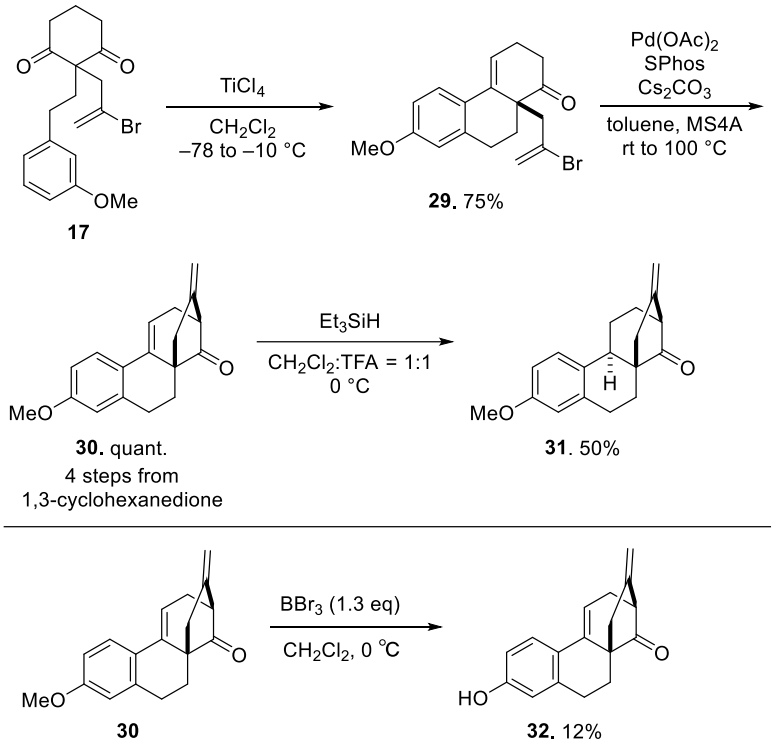
Table 3. Investigation of Friedel–Crafts cyclization with **26**



26 **27** **28**

entry	R	acids	temp.	results
1	Ac	TMSOTf (2.0 eq.)	–78 to –55 °C	N.R.
2	Ac	TMSOTf (2.0 eq.) TfOH (1.0 eq.)	–78 °C	**27**:byproduct = 6:1
3	CO_2Me	TMSOTf (2.0 eq.) TfOH (1.0 eq.)	–78 °C	**27**:byproduct = 5:1
4	CO_2Me	TfOH (12 eq.)	–78 to –50 °C	**27**:**28** = 10:3
5	CO_2Et	TfOH (20 eq.)	–78 to –20 °C	**28** 80%

The *ent*-kaurane-like tetracyclic framework was successfully constructed. However, prior to performing the Friedel–Crafts cyclization, the reduction of the ketone and the protection of the hydroxyl group were required. The author aimed to develop a more facile route to construct the desired tetracyclic skeleton by reversing the sequence of the cyclization reactions (Scheme 4). A desymmetric Friedel–Crafts cyclization reaction using $TiCl_4$ on a symmetric diketone **17** resulted in the formation of styrene **29**. Afterwards, intramolecular α-vinylation of styrene **29** was performed, resulting in desired kaurane-like tetracyclic skeleton **30**. Consequently, starting from 1,3-cyclohexanedione, the *ent*-kaurane-like tetracyclic skeleton could be constructed in only four steps, achieving a highly efficient synthetic route. This terpenoid-inspired scaffold possesses various useful functional groups such as protected phenol, benzylic alkene, *gem*-disubstituted alkene, and highly reactive ketone. For example, styrene was diastereoselectively reduced using Et_3SiH and TFA, the corresponding reductant **31**. On the other hand, attempts to remove a methyl protecting group from phenol using BBr_3 resulted in a complex reaction mixture, possibly due to the presence of a highly reactive ketone, yielding only a small amount of the desired phenol **32**.



Scheme 4. Construction of A-ring aromatic *ent*-kaurane-like tetracyclic skeleton

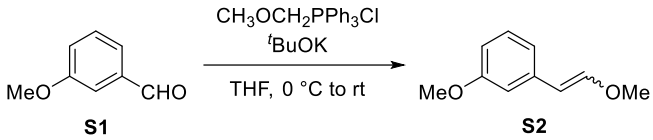
3-4. Conclusion

The author has developed rapid construction of A-ring aromatic *ent*-kaurane-like tetracyclic skeleton based on desymmetrization of 1,3-diketones. By chance, reversing the two cyclization reactions, α-vinylation and Friedel–Crafts cyclization discovered to construct two pseudo-synnteric tetracyclic skeleton.

3-5. Experimental section General Experimental Information

IR spectra were recorded on a SHIMADZU FTIR-8400 spectrometer. ^{1}H NMR spectra were measured on JEOL JNMECZ600R spectrometer (600 MHz), Varian NMR System 600 PS600 spectrometer (600 MHz), Varian 400-MR ASW spectrometer (400 MHz), and Varian Mercury-300 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from the solvent resonance employed as the internal standard ($CHCl_3$ at 7.26 ppm) on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on JEOL JNMECZ600R spectrometer (150* MHz), Varian NMR System 600 PS600 spectrometer (150 MHz) and Varian 400-MR ASW spectrometer (100 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.16 ppm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F254 0.25 mm), and Wako precoated TLC plates (silica gel 60 F254 0.25 mm) was used. Kanto Chemical Co., Inc. silica gel 60 N (spherical, neutral) and Fuji Silysia Chemical PSQ100B and PSQ60B were used for preparative column chromatography. High- and low-resolution mass spectral analysis (HRMS) was measured on a Bruker micrOTOF II (ESI) at the Chemical Instrument Facility, Okayama University. Dry toluene, tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene, dimethyl sulfoxide (DMSO), methanol (MeOH), diethyl ether (Et_2O), ethyl acetate (EtOAc) and chloroform ($CHCl_3$) were purchased from Kanto Chemical Co., Inc. or Wako Pure Chemical Industries Ltd. as the “anhydrous” and stored under nitrogen. Other materials were obtained from commercial supplies and used without further purification. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere, otherwise noted.

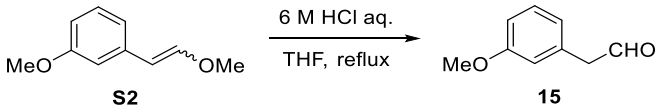
1-methoxy-3-(2-methoxyvinyl)benzene (S2)



To a stirred solution of triphenyl(methoxymethyl)phosphonium chloride (4.12 g, 17.0 mmol, 1.4 eq) in THF (76 mL) was added KO^{t}Bu (1.92 g, 17.1 mmol, 1.4 eq) at 0 °C. After being stirred for 30 min at same temperature, *m*-anisaldehyde **S1** (1.5 mL, 12.3 mmol, 1.0 eq) in THF (24 mL) was added to the flask. The reaction mixture was stirred for 19 h at room temperature. After a period of time, the reaction was quenched with a saturated aqueous solution of NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give enol ether **S2** (1.59 g, 79%, E/Z = 1/1) as a colorless oil.

The characterization data are consistent with those reported in the literature.[15]

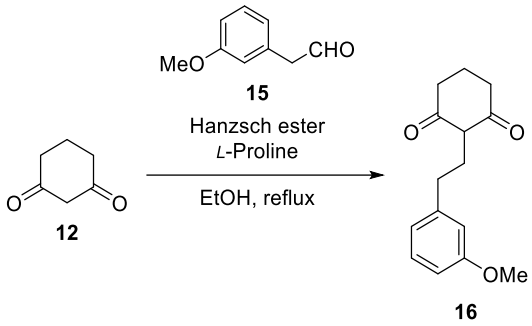
2-(3-methoxyphenyl)acetaldehyde (15)



To a stirred solution of enol ether **S2** (1.74 g, 10.6 mmol) in THF (60 mL) was added 6 M HCl aq. (6 mL) at room temperature. The reaction mixture was heated to reflux for 30 minutes before allowing it to cool to room temperature. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ at 0 °C, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give aldehyde **15** (1.36 g, 85%) as a yellow oil.

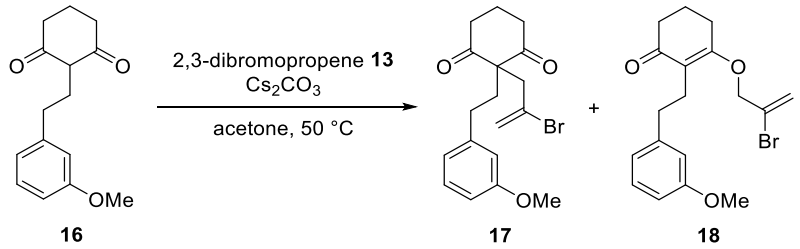
The characterization data are consistent with those reported in the literature.[15]

2-(3-methoxyphenethyl)cyclohexane-1,3-dione (16)



To a stirred solution of aldehyde **15** (1.27 g, 8.51 mmol, 1.0 eq) in EtOH (17 mL) was added 1,3 cyclohexanedione **12** (954 mg, 8.51 mmol, 1.0 eq), Hantzsch ester (2.15 g, 8.51 mmol, 1.0 eq) and *L*-proline (196 mg, 1.70 mmol, 0.2 eq) sequentially at room temperature. The reaction mixture was heated to reflux for 15 h before allowing it to cool to room temperature. EtOH was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) to give diketone **16** (1.45 g). Since the impurities could not be separated, the mixture was used in the next reaction without further purification.

2-(2-bromoallyl)-2-(3-methoxyphenethyl)cyclohexane-1,3-dione (17) and 3-((2-bromoallyl)oxy)-2-(3 methoxyphenethyl)cyclohex-2-en-1-one (18)



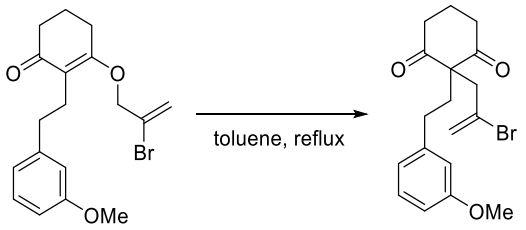
To a stirred solution of diketone **16** (1.45 g, <5.86 mmol, 1.0 eq) in acetone (53 mL) was added cesium carbonate (1.91 g, 7.03 mmol, 1.2 eq) at room temperature. The mixture was heated at 50 °C for 50 min before allowing it to cool to room temperature. 2,3-Dibromopropene (0.70 mL, 7.03 mmol, 1.2 eq) was then added to the flask, and the reaction mixture was stirred for 3 h at 50 °C. The reaction mixture was cooled to room temperature, and acetone was removed under reduced pressure. EtOAc and water were added to the residue and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 7/1) to give symmetric diketone **17** (1.14 g, 37% in 2 steps) and *O*-allylated product **18** (760 mg, 24% in 2 steps).

17: colorless oil; IR (film) 2933, 2833, 1722, 1694, 1601, 1489, 1456, 1261, 1151, 779 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.73 (dd, *J* = 7.8, 2.4 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.64 (dd, *J* = 2.4, 1.8 Hz, 1H), 5.57–5.56 (m, 1H), 5.48 (d, *J* = 1.8 Hz,

1H), 3.78 (s, 3H), 3.07 (s, 2H), 2.78 (app ddd, *J* = 17.4, 7.8, 5.4 Hz, 2H), 2.65 (app ddd, *J* = 17.4, 8.4, 5.4 Hz, 2H), 2.38–2.36 (m, 2H), 2.17–2.10 (m, 1H), 2.07–2.03 (m, 2H), 2.07–1.98 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.4, 159.9, 142.3, 129.7, 127.9, 121.9, 120.8, 114.0, 112.0, 67.3, 55.3, 47.9, 40.7, 40.3, 31.4, 16.9; HRMS (ESI) m/z calcd for $C_{18}H_{21}BrNaO_3$ $[M+Na]^+$ 387.0566, found 387.0508.

18: colorless oil; IR (film) 2903, 2359, 1684, 1601, 1489, 1277, 1161, 1042 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.77 (s, 1H), 6.70 (dd, *J* = 7.8, 2.4 Hz, 1H), 5.85–5.83 (m, 1H), 5.66–5.64 (m, 1H), 4.50–4.49 (m, 2H), 3.78 (s, 3H), 2.65–2.58 (m, 4H), 2.49 (t, *J* = 6.0 Hz, 2H), 2.36 (d, *J* = 6.0 Hz, 2H), 1.97 (dtd, *J* = 12.6, 6.0, 1.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 170.0, 159.6, 144.4, 129.1, 126.7, 121.2, 120.2, 118.0, 114.2, 111.2, 70.5, 55.3, 36.6, 34.9, 25.2, 24.5, 21.1; HRMS (ESI) m/z calcd for $C_{18}H_{21}BrNaO_3$ $[M+Na]^+$ 387.0566, found 387.0557.

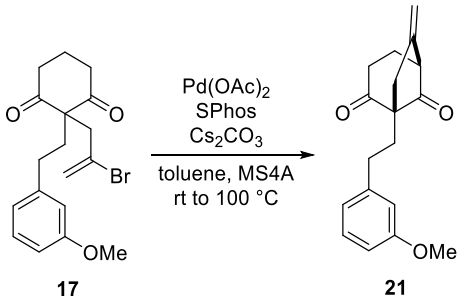
2-(2-bromoallyl)-2-(3-methoxyphenethyl)cyclohexane-1,3-dione (17)



18 **17**

A stirred solution of *O*-allylated product **18** (85.8 mg, 0.217 mmol) in toluene (2.0 mL) was heated at 130 °C for 24 h before allowing it to cool to room temperature. Toluene was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) to give symmetric diketone **17** (50.7 mg, 59%).

***rac*-(1S,5S)-1-(3-methoxyphenethyl)-6-methylenebicyclo[3.2.1]octane-2,8-dione (21)**

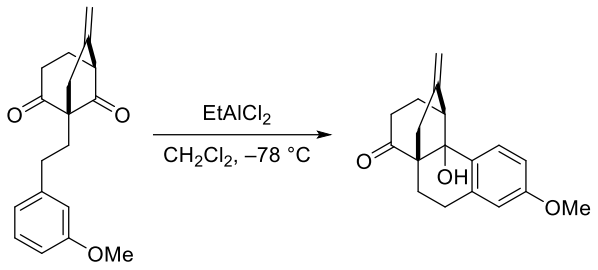


17 **21**

A mixture of symmetric diketone **17** (248 mg, 0.678 mmol, 1.0 eq), $Pd(OAc)_2$ (7.1 mg, 0.031 mmol, 0.05 eq), SPhos (29.2 mg, 0.071 mmol, 0.11 eq), Cs_2CO_3 (205 mg, 0.629 mmol, 1.0 eq) and MS4A (627 mg) in toluene (6.3 mL) was stirred for 1 h at room temperature. The mixture was then heated to 100 °C and stirred for an additional 3 h. After cooling to room temperature, the solution was filtrated through a short pad of silica gel (EtOAc) to give crude **21** (229 mg).

A portion of the crude mixture (82.8 mg) was used for the next reaction without further purification.

rac-(4S,10aR)-4a-hydroxy-7-methoxy-12-methylene-2,3,4,4a,9,10-hexahydro-1H-4,10a ethanophenanthren-1-one (23)



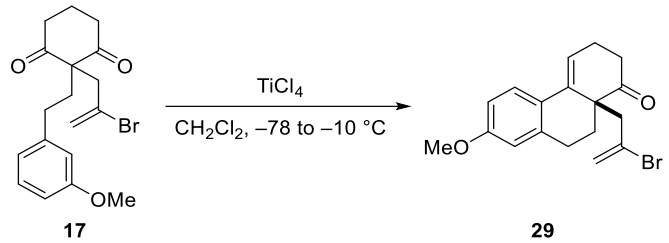
21 **23**

To a stirred solution of cyclized product **21** (82.8 mg, <0.245 mmol, 1.0 eq) in dichloromethane (1.9 mL) was added $EtAlCl_2$ (1.0 M in dichloromethane, 0.3 mL, 0.300 mmol, 1.1 eq) at –78 °C. The reaction mixture was stirred for 2 h at the same temperature, and additional $EtAlCl_2$ (1.0 M in dichloromethane, 0.15 mL, 0.150 mmol, 0.55 eq) was added. The mixture was stirred for 1 h at the same temperature before the reaction was quenched by the addition of Et_3N and $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 15/1) to give benzyl alcohol **23** (35.2mg, 51% in 2 steps, dr = 2.5:1).

23a: colorless oil; IR (film) 3019, 2936, 1701, 1609, 1503, 1452, 1215, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 5.29 (s, 1H), 5.17 (s, 1H), 3.76 (s, 3H), 3.34 (s, 1H), 3.25–3.17 (m, 1H), 2.81 (dd, *J* = 18.0, 8.4 Hz, 1H), 2.69 (dtd, *J* = 16.8, 2.4, 1.2 Hz, 1H), 2.38–2.34 (m, 3H), 2.04–1.91 (m, 3H), 1.81 (br s, 1H), 1.80–1.74 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.3, 159.7, 151.2, 140.1, 128.7, 127.9, 114.2, 112.9, 109.7, 80.0, 61.1, 55.3, 49.2, 40.5, 33.4, 26.6, 26.3, 21.0; HRMS (ESI) m/z calcd for $C_{18}H_{20}NaO_3$ $[M+Na]^+$ 307.1310, found 307.1300.

23b: colorless oil; IR (film) 3019, 2936, 1707, 1609, 1501, 1443, 1323, 1215, 1036, 758, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 9.0 Hz, 1H), 6.81 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 5.03 (t, *J* = 2.4 Hz, 1H), 4.81 (t, *J* = 1.8 Hz, 1H), 3.78 (s, 3H), 3.31 (s, 1H), 2.92–2.77 (m, 2H), 2.60–2.51 (m, 2H), 2.45 (dt, *J* = 18.6, 2.4 Hz, 1H), 2.44–2.37 (m, 1H), 2.25 (dt, *J* = 18.6, 2.4 Hz, 1H), 2.01 (ddd, *J* = 15.0, 12.6, 6.6 Hz, 1H), 1.93 (dd, *J* = 15.0, 1.8 Hz, 1H), 1.90–1.84 (m, 1H), 1.72 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.3, 159.3, 148.7, 137.3, 130.6, 128.6, 114.0, 113.4, 109.0, 80.1, 57.4, 55.3, 50.5, 35.0, 34.7, 27.6, 25.3, 18.5 ; HRMS (ESI) m/z calcd for $C_{18}H_{20}NaO_3$ $[M+Na]^+$ 307.1310, found 307.1296.

rac-(_S_)-10a-(2-bromoallyl)-7-methoxy-3,9,10,10a-tetrahydrophenanthren-1(2H)-one (29)

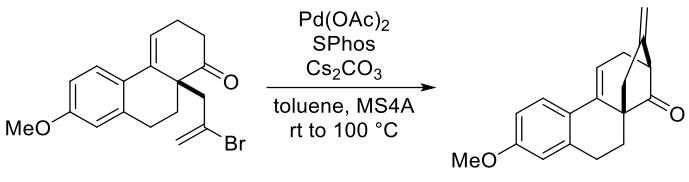


17 **29**

To a stirred solution of symmetric diketone **17** in dichloromethane (1.2 mL) was added $TiCl_4$ (1.0 M in dichloromethane, 0.17 mL, 0.170 mmol, 1.1 eq) at –78 °C. The mixture was stirred for 4.5 h while gradually warming up the temperature to –10 °C. The reaction was then quenched by adding ice-cooled water at 10°C. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 20/1) to give cyclized product **29** (34.1 mg, 75%).

29: yellow solid; IR (film) 3018, 2926, 2400, 1707, 1608, 1497, 1215, 1045, 758, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 9.0 Hz, 1H), 6.76 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.24 (dd, *J* = 4.8, 4.2 Hz, 1H), 5.41 (d, *J* = 1.8 Hz, 1H), 5.35–5.33 (m, 1H), 3.80 (s, 3H), 3.03 (d, *J* = 14.4 Hz, 1H), 2.94 (ddd, *J* = 18.0, 12.0, 6.0 Hz, 1H), 2.86 (ddd, *J* = 18.0, 7.2, 1.8 Hz, 1H), 2.81–2.68 (m, 2H), 2.74 (d, *J* = 14.4 Hz, 1H), 2.61–2.52 (m, 2H), 2.17 (ddd, *J* = 13.8, 6.6, 1.8 Hz, 1H), 1.86 (ddd, *J* = 13.8, 12.0, 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.7, 159.1, 138.0, 135.5, 128.9, 127.1, 126.9, 120.9, 120.8, 113.3, 113.0, 55.4, 50.6, 44.7, 36.9, 30.4, 25.6, 24.7; HRMS (ESI) m/z calcd for $C_{18}H_{19}BrNaO_2$ $[M+Na]^+$ 369.0466, found. 369.0425.

rac-(6a_S_,9_S_)-3-methoxy-8-methylene-5,6,7,8,9,10-hexahydro-6a,9-methanocyclohepta[a]naphthalen 12-one (30)



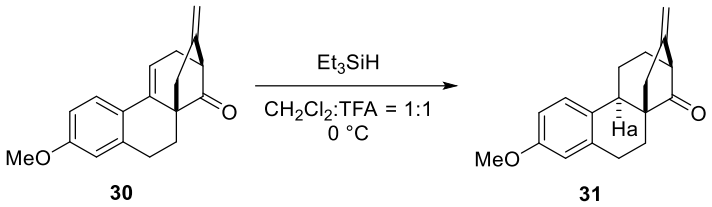
29 **30**

A mixture of **29** (28.2 mg, 0.081 mmol, 1.0 eq), $Pd(OAc)_2$ (1.1 mg, 4.90 μmol, 0.05 eq), SPhos (4.5 mg, 11.0 μmol, 0.11 eq), Cs_2CO_3 (32.4 mg, 0.089 mmol, 1.1 eq) and MS4A (100 mg) in toluene (1.0 mL) was stirred for 3 h at 100 °C. After cooling to room temperature, the solution was filtrated through a short pad of silica gel (EtOAc) to give the crude mixture. The

crude product was purified by column chromatography on silica gel (hexane/EtOAc = 8/1) to give ketone **30** (21.8 mg, quant.).

30: yellow oil; IR (film) 2931, 2830, 2359, 1751, 1605, 1491, 1326, 1040, 752 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 9.0 Hz, 1H), 6.74 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.64 (d, *J* = 3.0 Hz, 1H), 6.03 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.13 (s, 1H), 5.01–4.99 (m, 1H), 3.80 (s, 3H), 3.12 (ddd, *J* = 16.8, 4.2, 3.0 Hz, 1H), 3.10–3.07 (m, 1H), 3.04 (ddd, *J* = 16.2, 3.0, 1.8 Hz, 1H), 2.80–2.68 (m, 3H), 2.52 (dt, *J* = 16.2, 3.0 Hz, 1H), 2.13 (ddd, *J* = 13.2, 10.8, 4.8 Hz, 1H), 1.65 (dt, *J* = 13.2, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.0, 158.9, 146.7, 140.5, 138.2, 125.8, 124.8, 115.4, 113.3, 113.1, 109.7, 55.4, 52.0, 50.6, 45.5, 43.3, 27.5, 25.4; HRMS (ESI) m/z calcd for $C_{18}H_{18}NaO_2$ $[M+Na]^+$ 289.1199, found 289.1170.

rac-(6a*S*,9*S*,11a*R*)-3-methoxy-8-methylene-5,6,7,8,9,10,11,11a-octahydro-6a,9 methanocyclohepta[a]naphthalen-12-one (31)

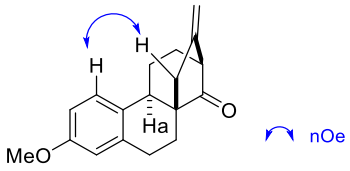


30 **31**

To a stirred solution of ketone **30** (23.1 mg, 0.087 mmol, 1.0 eq) in dichloromethane (1.7 mL) was added Et_3SiH (15 μL, 0.094 mmol, 1.2 eq) and TFA (1.7 mL) at 0 °C, and the reaction mixture was stirred for 3 h at the same temperature. The solution was diluted with ethyl acetate, and the reaction was quenched by the addition of water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give ketone **31** (11.7 mg, 50%).

31: white solid; IR (film) 3019, 2936, 2400, 1746, 1611, 1501, 1215, 1044, 750, 669 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 4.99 (t, *J* = 2.4 Hz, 1H), 4.91 (t, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 3.04 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.99–2.97 (m, 1H), 2.81 (ddd, *J* = 17.4, 6.6, 3.6 Hz, 1H), 2.72 (ddd, *J* = 16.2, 11.4, 6.0 Hz, 1H), 2.62 (ddd, *J* = 17.4, 3.0, 4.0 Hz, 1H), 2.31 2.25 (m, 2H), 2.18 (tdd, *J* = 13.2, 4.8, 2.4 Hz, 1H), 2.14–2.04 (m, 2H), 1.74 (ddd, *J* = 26.4, 12.6, 6.0 Hz, 1H), 1.62 (ddd, *J* = 13.8, 6.0, 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 219.8, 158.0, 144.5, 137.2, 130.1, 128.0, 113.6, 112.4, 107.9, 55.4, 54.8, 51.4, 49.2, 37.8, 35.3, 26.8, 26.2, 23.9; HRMS (ESI) m/z calcd for $C_{18}H_{20}NaO_2$ $[M+Na]^+$ 291.1361, found 291.1329.

The stereochemistry at the Ha proton was determined by 2D NMR analysis



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Chapter 4. Toward the biomimetic synthesis of grayanane diterpenoids via skeletal rearrangement

4-1. Abstract

The author challenged the construction of grayanane framework through skeletal rearrangement as a key reaction from A-ring aromatic *ent*-kaurane-like tetracyclic skeleton. The 1,2-diol structure which is necessary for the skeletal rearrangement was successfully obtained through the oxidative dearomatization of phenol and the oxa-Michael addition reaction of quinol.

4-2. Introduction

Grayanane diterpenoids, isolated from the *Ericaceae* family, have been discovered in over 300 species to date.[1] These diterpenoids feature a [5.7.6.5] tetracyclic framework bearing a bicyclo[3.2.1]octane ring, numerous stereogenic centers, and an abundance of oxygen functional groups such as hydroxyl and carbonyl groups (Figure 1). These families are known for their broad range of bioactivities, such as voltage-gated sodium channel modulating,[2] analgesic, sedative, insecticidal, antifeeding,[3] anti-inflammatory,[4] protein tyrosine phosphatase 1B (PTP1B) inhibitory [5] and antiviral activities.[6] Representative grayanane diterpenoids, grayanotoxin II (**1**), rhodomollein XX (**2**), principinol D (**3**), are shown in Figure 1.

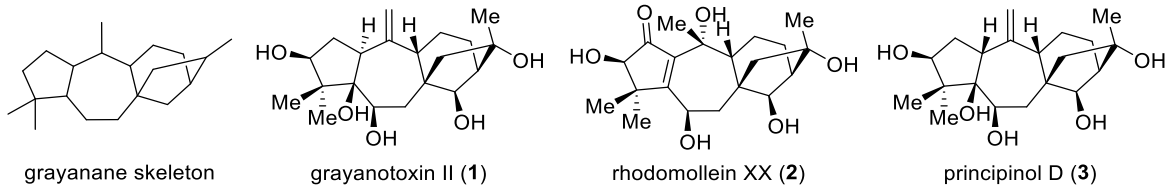


Figure 1. Grayanane diterpenoids

Figure 2 shows the proposed biosynthetic pathway of grayanane diterpenoids. The *ent*-kaurane framework is formed through sequential cationic cyclization and methyl rearrangement of geranylgeranyl pyrophosphate (GGPP). Subsequently, a Wagner–Meerwein-type skeletal rearrangement proceeds to construct the grayanane skeleton.

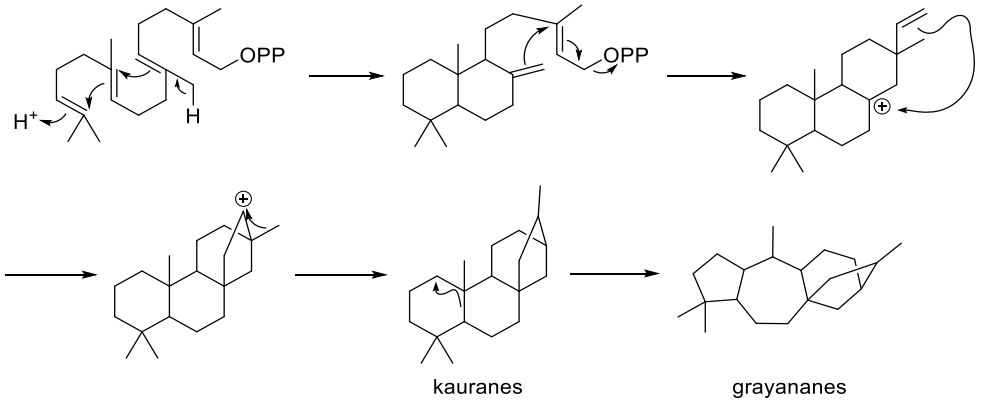


Figure 2. Proposed biosynthetic pathway of grayanane diterpenoid

Grayanane diterpenoids include several skeletons formed from the [5.7.6.5] tetracyclic

framework in biosynthesis. Figure 3 shows representative subtypes of the grayanane skeleton, constructed through bond cleavage, methyl and skeletal rearrangement.

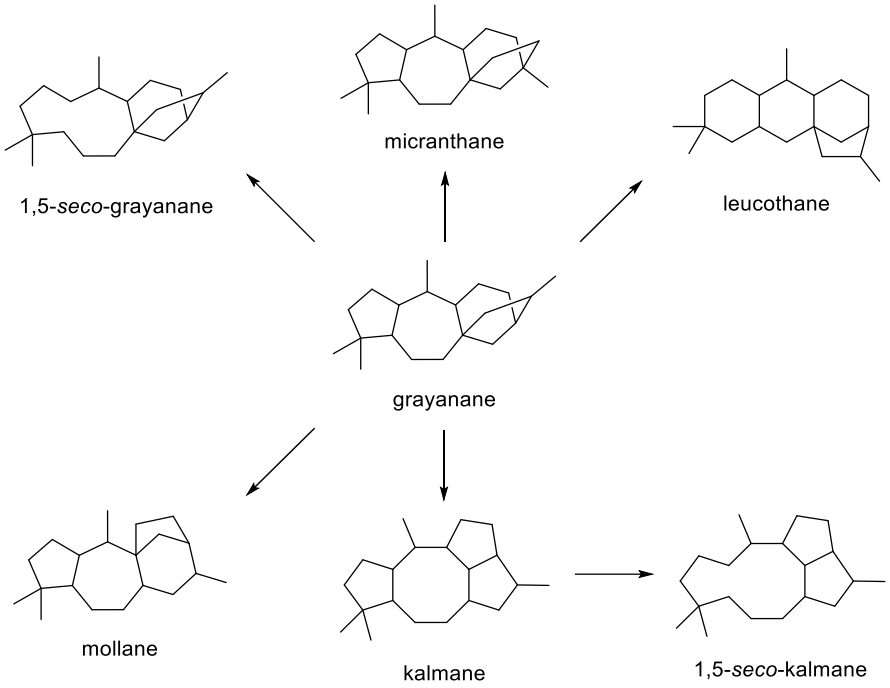
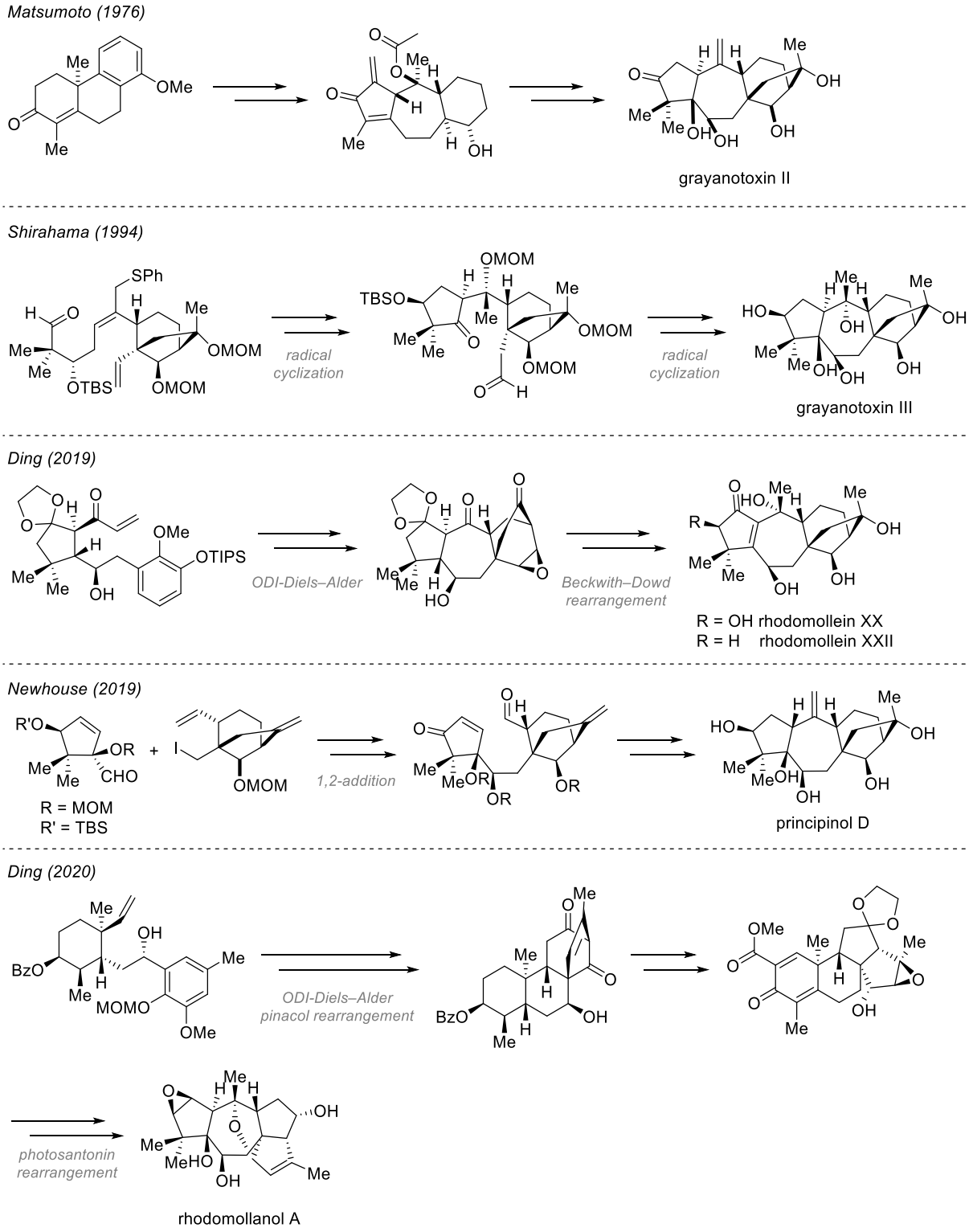


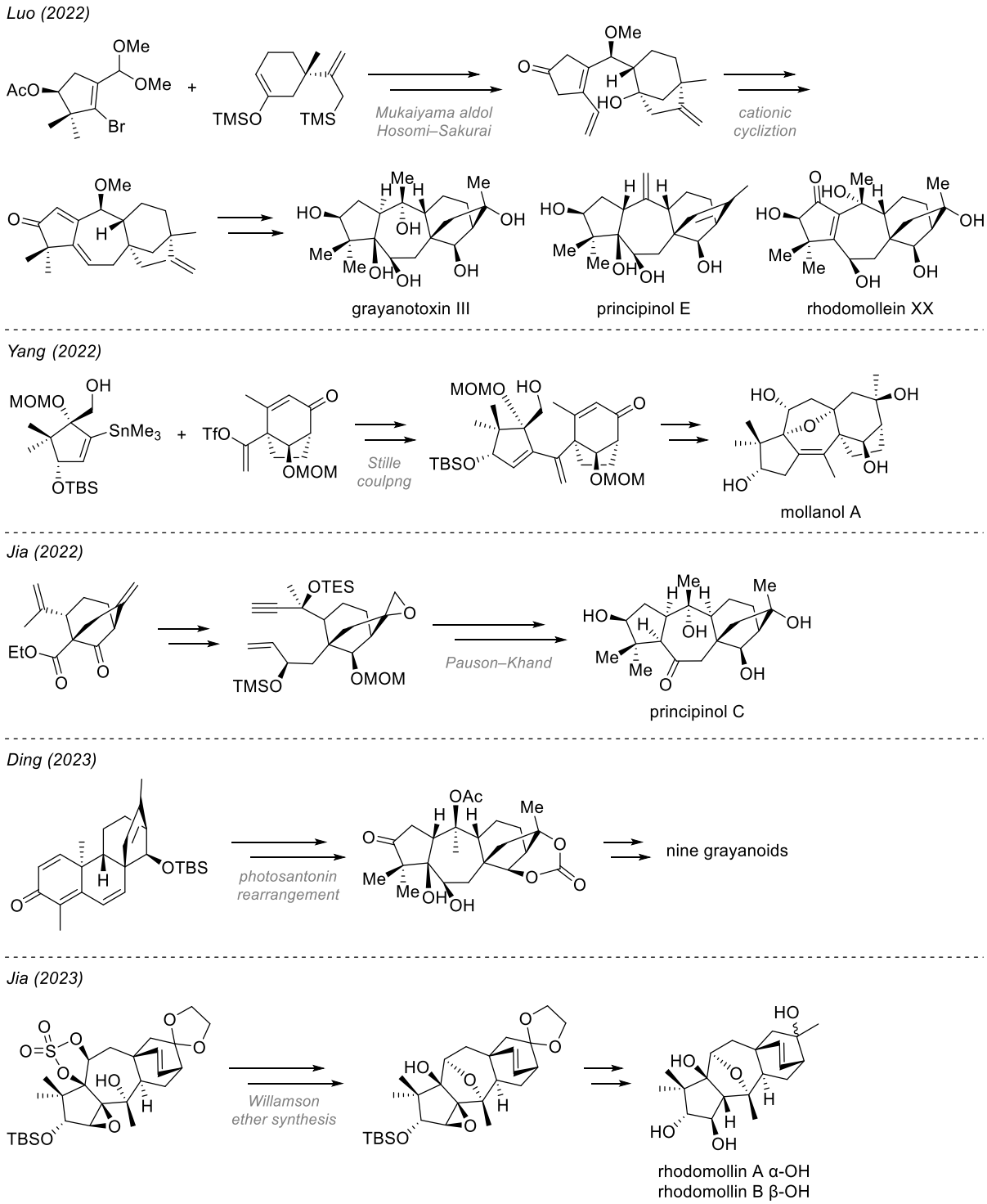
Figure 3. The subtypes of grayanoids

Since these families are very attractive due to their useful biological activities and complex polycyclic skeletons in biosynthesis, several synthetic methods have been reported (Scheme 1,2). In 1976, Matsumoto and co-workers reported a relay total synthesis of grayanotoxin II (**1**).[7] In 1994, Shirahama and co-workers described total synthesis of grayanotoxin III featuring a radical cycliczation using SmI_2.[8] In 2019, Ding and co-workers achieved total synthesis of rhodomollein XX (**2**) and rhodomollein XXII, utilizing a reductive epoxide-opening/Beckwith–Dowd rearrangement.[9] Newhouse and co-workers reported convergent synthesis of principinol D (**3**).[10] In 2020, Ding and co-workers described total synthesis of rhodomollanol A featuring a photo-Nazarov cyclization.[11] In 2022, Luo and co-workers achieved total syntheses of granayotoxin III, principinol E, rhodomollein XX (**2**) featuring an 7-*endo*-trig cyclization based on a bridgehead carbocation.[12] Yang and co-workers described convergent synthesis of mollanol A.[13] Jia and co-workers reported total synthesis of principinol C utilizing an intramolecular Pauson−Khand reaction.[14] In 2023, Ding and co-workers achieved divergent synthesis of nine grayanane diterpenoids based on an ODI-[5+2] cycloaddition/pinacol rearrangement.[15] Yang and co-workers reported total syntheses of rhodomollins A and B via a convergent strategy.[16]

With the development of the organic synthesis field, the number of synthetic reports has increased rapidly since the 2020s.[17]



Scheme 1. Total syntheses of grayanane diterpenoid-1



Scheme 2. Total syntheses of grayanane diterpenoid-2

As described in Chapter 1, the author considered developing a new synthetic method for grayanane diterpenoids based on biomimetic synthesis (Figure 4). In detail, the construction of grayanane skeleton could be achieved by modifying the Wagner–Meerwein rearrangement into a pinacol-type rearrangement through the appropriate placement of a hydroxy group.

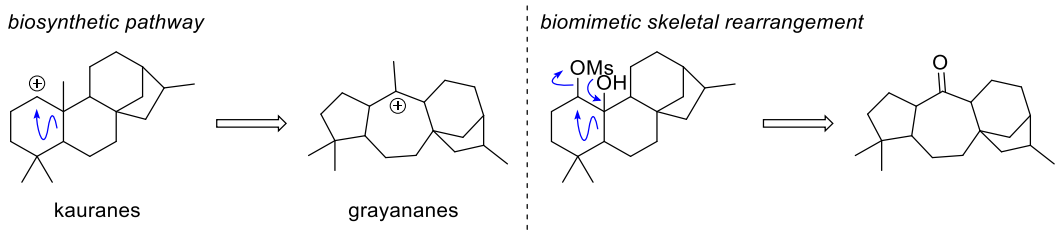
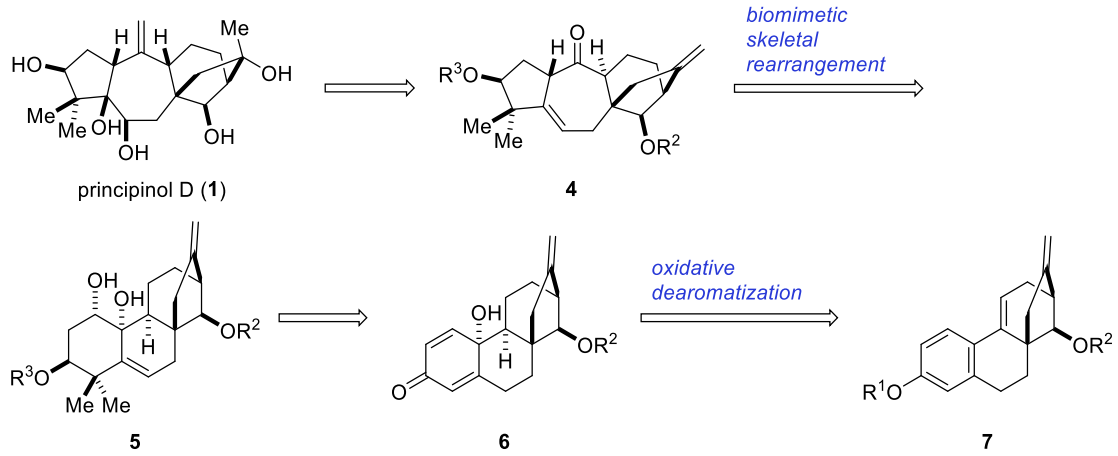


Figure 4. Synthetic plan of biomimetic construction of grayanane skeleton

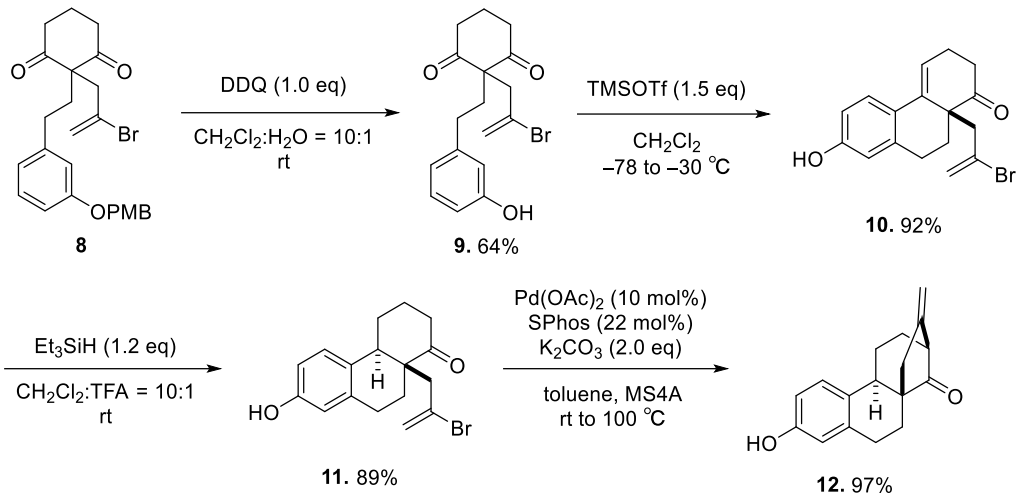
4-3. Results and discussions

In Chapter 3, the author described a rapid construction method for the *ent*-kaurane-type tetracyclic skeleton. Scheme 3 shows the retrosynthetic pathway from this tetracyclic skeleton to the synthesis of principinol D (**1**). **1** could be obtained by functional group transformation of ketone **4**. **4** could be planned to be convertd from the *ent*-kaurane-type tetracyclic compound **5** through the skeletal rearrangement reaction. This 1,2-diol **5** would be derived from quinol **6**, which is obtained by oxidative dearomatization of phenol **7**.



Scheme 3. Synthetic plan of grayanane skeleton

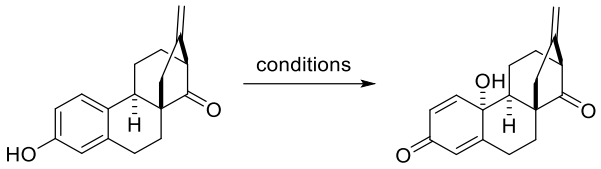
In Chapter 3, a methyl group was used as a protecting group for phenol, but it was found that demethylation was difficult. Therefore, the optimal protecting group for phenol was first explored. Surprinsingly, various protecting groups, such as TBDPS, TIPS, THP, and Bz, for phenol were considered, but these protecting group was removed, or the reaction failed before symmetrical diketones was synthesized. Fortunately, only when protected with a PMB group and attempting the synthesis of the symmetric diketone **8**, it was possible to synthesize the symmetric diketone **8** with a yield similar to that of the methyl group. When the desymmetric Friedel–Crafts cyclization with the PMB-protected symmetric diketone **8**, it was unsuccessful. Therefore, it was decided to remove the PMB group at this stage. Phenol **9** was obtained using DDQ (Scheme 4). Using TMSOTf as a Lewis acid, a desymmetric Friedel–Crafts cyclization was performed on phenol **9** to obtain a tricyclic compound **10**, which was then reduced to styrene. Subsequently, an intramolecular α-vinylation of ketone **11** was carried out to construct a tetracyclic skeleton bearing a bicyclo[3.2.1]octane ring **12**.



Scheme 4. The construction of A-ring aromatic *ent*-kaurane framework

An oxidative dearomatization reaction was performed on the obtained phenol **12** (Table 1). In entry 1, using PIDA as a hypervalent reagent, about half of the starting material was recovered, but the desired quinol **13** was successfully obtained in 40% yield. However, this consition showed inconsistent yields, other conditions were explored. In entry 2, when the solvent was changed from acetonitrile to acetone, the yield of quinol **13** decreased, and a compound with a styrene structure was obtained, although its detailed structure was unknown. Therefore, as an alternative reaction condition, an oxidative dearomatization reaction utilizing singlet oxygen was conducted. Quinol **13** was obtained under an oxygen atmosphere without forming a styrene structure, employing Rose Bengal [18] (entry 3) and a ruthenium complex [19] (entry 4) as photosensitizers, although in moderate yield.

Table 1. Investigation of oxidative dearomatization of phenol **12**

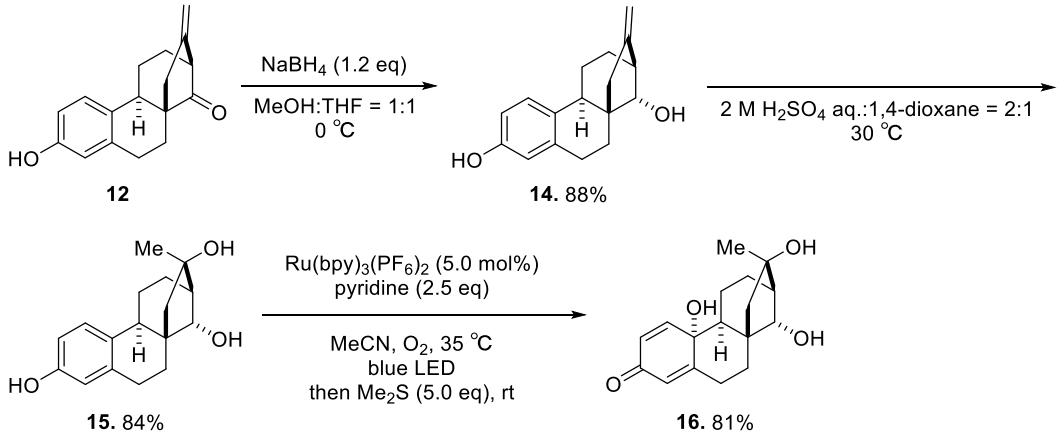


12 **13**

Entry	conditions	results
1	PIDA (1.0 eq) MeCN:H_2O = 20:1. 0 ℃	**12** 50% **13** 40%
2	PIDA (1.0 eq) acetone:H_2O = 2:1. –10 to 0 ℃	**13** 16% Styrene was obtained
3	O_2, Rose Bengal (1.0 mol%), Cs_2CO_3 (15 mol%) MeOH, rt, blue LED	**13** 45%
4	O_2, $Ru(bpy)_3(PF_6)_2$ (5.0 mol%), Cs_2CO_3 (15 mol%) MeOH, rt, blue LED then $Na_2S_2O_3$ aq. rt	**13** 31%

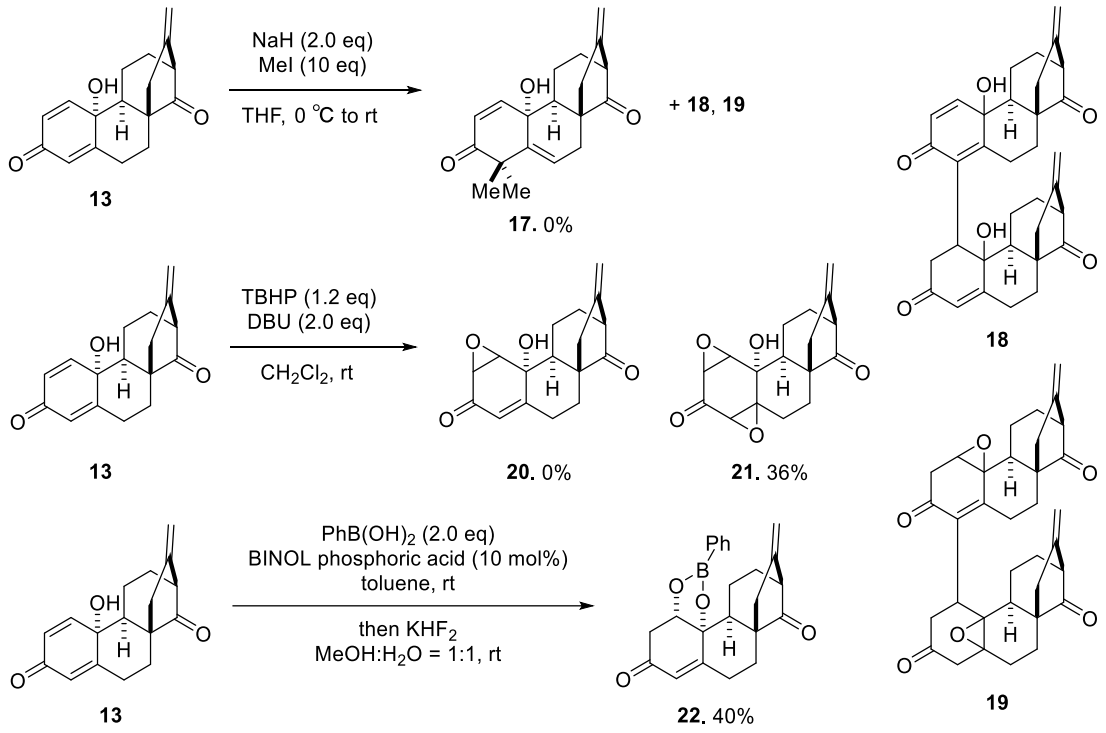
Considering that a side reaction between singlet oxygen and the alkene on bicyclo[3.2.1]octane moiety was proceeding, it was decided to perform a functional group transformation of the alkene prior to the oxidation dearomatization of the phenol.

After examining the optimal synthetic route, the ketone **13** was subjected to diastereoselective reduction, followed by a hydration reaction using sulfuric acid to obtain a triol **15** (Scheme 5). Subsequently, an oxidative dearomatization reaction of **15** was carried out, the correspomding quinol **16** was obtained in 81% yield.



Scheme 5. Synthesis of quinol **16**

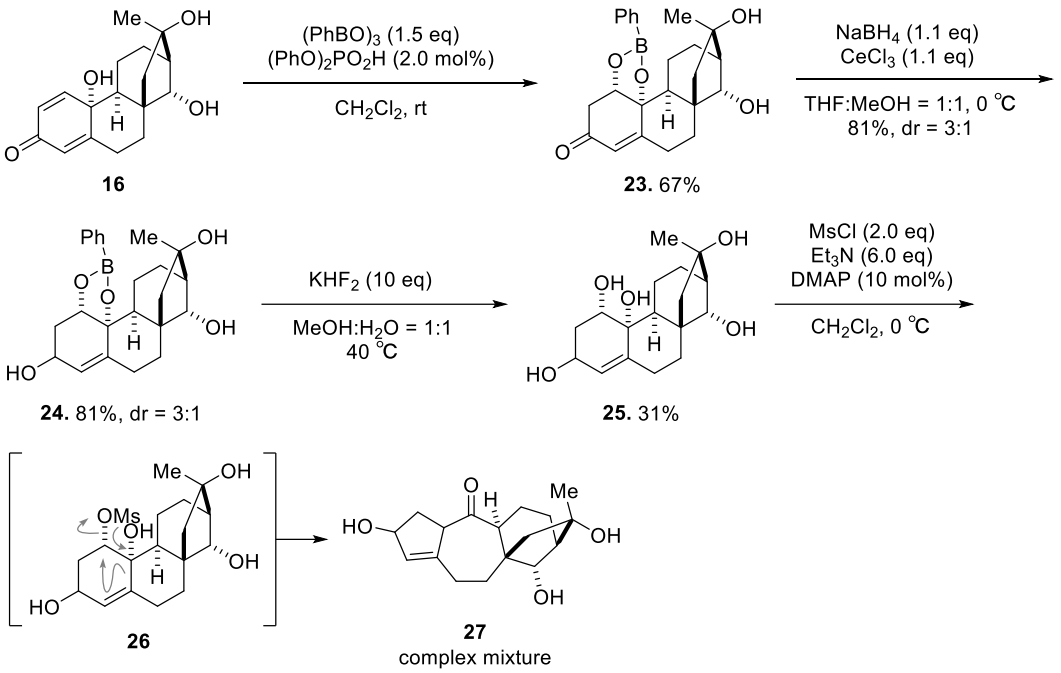
With quinol **16** in hand, the author aimed to synthesize 1,2-diol **5** for skeletal rearrangement and attempted functionalization on the quinol moiety using quinol **13** as a model substrate. Initially, dimethylation of **13** was performed using methyl iodine and sodium hydride, but only two types of dimerized product **18**,**19** of **13** were obtained (Scheme 6). This reason was attributed to the high electrophilicity of quinol. Therefore, it was decided to attempt oxygen functionalization of the quinol moiety prior to dimethylation. Taking advantage of its high electrophilicity, it was anticipated that regioselective nucleophilic epoxidation would readily obtain epoxyquinol **20**, but only yielding doubly epoxidized product **21**. Based on the report by Toste,[20] phosphoric acid catalyzed the *oxa*-Michael addition reaction using boronic acid was employed, followed by the addition of KHF_2 to remove phenylboronic acid, but only the cyclic boronic ester **22** was obtained. The author considered that this result found the cyclic boronic acid was unexpectedly stable, making it an effective protecting group for 1,2-diols.



Scheme 6. Investigation of functionalization of quinol moiety

Based on the results described in Scheme 4, the *oxa*-Micheal addition reaction of quinol **16** was conducted (Scheme 7). After exploring optimal conditions, using diphenyl phosphate and the trimer of phenylboronic acid, cyclic boronic ester **23** was obtained in 67% yield. Subsequent Luche reduction of **23** was synthesized from allyl alcohol **24** with a diastereomeric ratio of 3:1. Hydrolysis of cyclic boronic ester in **24** yielded pentanol **25** in low yield. With pentanol **25** in hand, the key skeletal rearrangement reaction was attempted. Mesylation of the secondary hydroxy group of 1,2-diol **25** was performed using methanesulfonyl chloride and triethylamine, followed by a semi-pinacol rearrangement of mesylate **26**. This rearrangement was expected to

construct the grayanane skeleton. However, the reaction led to the formation of a complex mixture.



Scheme 7. Challenging to grayanane skeleton

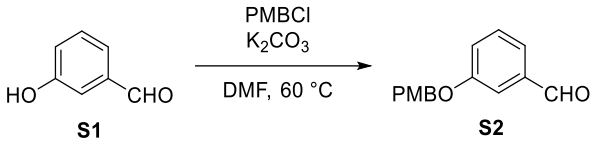
4-4. Conclusion

In this study, the author aimed to synthesize grayanane skeleton by employing a strategy that involved including skeletal rearrangement of *ent*-kaurane framework. A-ring aromatic *ent*-kaurane-like tetracyclic skeleton was converted to quinol via oxidative dearomatization, followed by *oxa*-Michael addition resulted in cyclic boronic ester as protecting group of 1,2-diol. Although the subsequent semi-pinacol rearrangement yielded a complex mixture, the author's findings suggest a promising foundation for the total synthesis of grayanane diterpenoids.

4-5. Experimental section: General Experimental Information

IR spectra were recorded on a SHIMADZU FTIR-8400 spectrometer. ^{1}H NMR spectra were measured on JEOL JNMECZ600R spectrometer (600 MHz), Varian NMR System 600 PS600 spectrometer (600 MHz), Varian 400-MR ASW spectrometer (400 MHz), and Varian Mercury-300 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from the solvent resonance employed as the internal standard ($CHCl_3$ at 7.26 ppm) on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on JEOL JNMECZ600R spectrometer (150* MHz), Varian NMR System 600 PS600 spectrometer (150 MHz) and Varian 400-MR ASW spectrometer (100 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.16 ppm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F254 0.25 mm), and Wako precoated TLC plates (silica gel 60 F254 0.25 mm) was used. Kanto Chemical Co., Inc. silica gel 60 N (spherical, neutral) and Fuji Silysia Chemical PSQ100B and PSQ60B were used for preparative column chromatography. High- and low-resolution mass spectral analysis (HRMS) was measured on a Bruker micrOTOF II (ESI) at the Chemical Instrument Facility, Okayama University. Dry toluene, tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene, dimethyl sulfoxide (DMSO), methanol (MeOH), diethyl ether (Et_2O), ethyl acetate (EtOAc) and chloroform ($CHCl_3$) were purchased from Kanto Chemical Co., Inc. or Wako Pure Chemical Industries Ltd. as the “anhydrous” and stored under nitrogen. Other materials were obtained from commercial supplies and used without further purification. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere, otherwise noted.

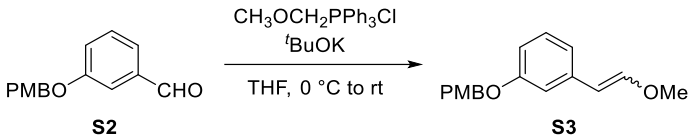
3-((4-methoxybenzyl)oxy)benzaldehyde (S2)



To a stirred solution of 3-Hydroxybenzaldehyde **S1** (7.49 g, 66.8 mmol, 1.0 eq) in DMF (67 mL) was added PMBCl (10 mL, 73.4 mmol, 1.1 eq) and K_2CO_3 (11.1 g, 88.1 mmol, 1.2 eq) sequentially at room temperature. The mixture was heated at 60 °C for X h before allowing it to cool to room temperature. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl at 0 °C, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/acetone = 4/1) to give aldehyde **S2** (15.0 g, 93%).

The characterization data are consistent with those reported in the literature.[21]

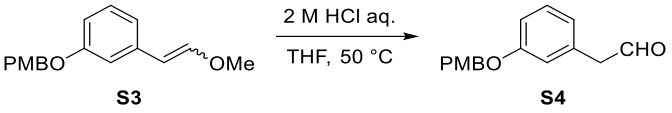
1-((4-methoxybenzyl)oxy)-3-(2-methoxyvinyl)benzene (S3)



To a stirred solution of triphenyl(methoxymethyl)phosphonium chloride (18.0 g, 74.3 mmol, 1.2 eq) in THF (380 mL) was added KO^{t}Bu (8.4 g, 74.3 mmol, 1.2 eq) at 0 °C. After being stirred for 30 min at same temperature, aldehyde **S2** (15.0 g, 61.9 mmol, 1.0 eq) in THF (120 mL) was added to the flask. The reaction mixture was stirred for 10 h at room temperature. After a period of time, the reaction was quenched with a saturated aqueous solution of NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 7/1) to give enol ether **S3** (13.9 g, 83%, E/Z = 1/2).

S3: white solid; IR (film) 3109, 2359, 1215, 757, 667 cm $^{-1}$; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.35 (m, 6H), 7.30 (t, *J* = 2.4 Hz, 1H), 7.20–7.16 (m, 3H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 12.6 Hz, 1H), 6.93–6.91 (m, 6H), 6.86–6.83 (m, 4H), 6.78–6.75 (m, 3H), 6.12 (d, *J* = 7.2 Hz, 1H), 5.79 (d, *J* = 13.2 Hz, 2H), 5.00 (s, 2H), 4.99 (s, 4H), 3.82 (s, 6H), 3.82 (s, 3H), 3.77 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.7, 159.6, 159.4, 159.0, 149.3, 148.3, 138.1, 137.4, 129.7, 129.7, 129.4, 129.4, 129.3, 129.2, 121.3, 118.2, 114.9, 114.2, 114.2, 112.7, 112.3, 112.1, 105.9, 105.3, 70.0, 60.8, 56.7, 55.4; HRMS (ESI) m/z calcd for $C_{17}H_{18}NaO_3$ $[M+Na]^+$ 293.1154, found 293.1137.

2-(3-((4-methoxybenzyl)oxy)phenyl)acetaldehyde (S4)

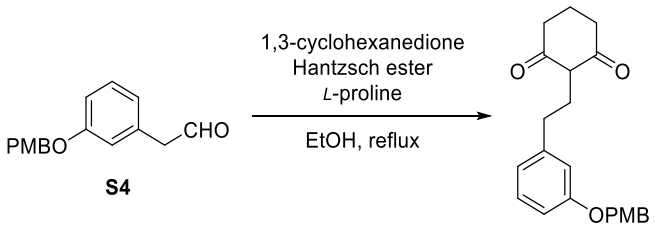


S3 **S4**

To a stirred solution of enol ether **S3** (17.6 g, 65.3 mmol) in THF (400 mL) was added 2 M HCl aq. (33 mL) at room temperature. The mixture was heated at 50 °C for 5 h before allowing it to cool to room temperature. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ at 0 °C, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 7/1) to give aldehyde **S4** (11.0 g, 66%).

S4: colorless oil; IR (film) 2949, 2880, 2843, 2360, 1722, 1699, 1599, 1516, 1301, 1246, 1177, 1067 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.93–6.91 (m, 3H), 6.84–6.81 (m, 2H), 4.99 (s, 2H), 3.82 (s, 3H), 3.64 (d, *J* = 1.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.3, 159.8, 159.6, 133.5, 130.2, 129.4, 129.1, 122.3, 116.5, 114.3, 114.0, 70.1, 55.5, 50.7; HRMS (ESI) m/z calcd for $C_{16}H_{16}NaO_3$ $[M+Na]^+$ 279.0997, found 279.0993.

2-(3-((4-methoxybenzyl)oxy)phenethyl)cyclohexane-1,3-dione (S5)



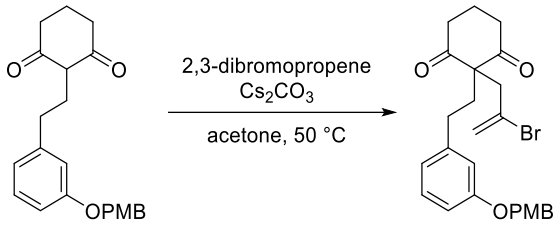
S4 **S5**

To a stirred solution of aldehyde **S4** (11.0 g, 43.0 mmol, 1.0 eq) in EtOH (86 mL) was added 1,3-cyclohexanedione (4.8 g, 43.0 mmol, 1.0 eq), Hantzsch ester (10.9 g, 43.0 mmol, 1.0 eq) and *L*-proline (990 mg, 8.60 mmol, 0.2 eq) sequentially at room temperature. The reaction mixture was heated to reflux for 9.5 h before allowing it to cool to room temperature. EtOH was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to give diketone **S5** (12.7 g, 84%).

S5: white solid; IR (film) 3019, 2359, 2336, 1701, 1611, 1541, 1420, 1217, 745 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.0 Hz, 2H), 7.21 (t, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.84–6.82 (m, 1H), 6.80–6.78 (m, 2H), 5.04 (s, 1H), 4.98 (s, 2H), 3.82 (s, 3H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.37–2.34 (m, 4H), 1.92 (tt, *J* = 12.6, 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 170.6, 159.6, 159.3, 144.1, 130.0, 129.3, 129.2, 121.0, 115.2, 114.8,

114.2, 112.8, 69.8, 55.5, 36.8, 34.8, 28.8, 24.8, 20.7; HRMS (ESI) m/z calcd for $C_{22}H_{24}NaO_4$ $[M+Na]^+$ 279.0997, found 375.1567.

2-(2-bromoallyl)-2-(3-((4-methoxybenzyl)oxy)phenethyl)cyclohexane-1,3-dione (8)

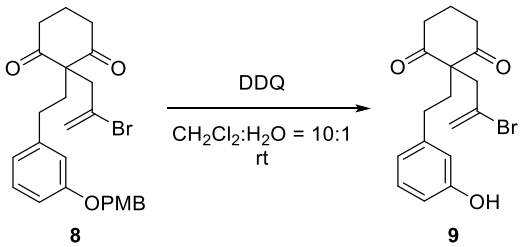


S5 **8**

To a stirred solution of diketone **S5** (5.4 g, 15.3 mmol, 1.0 eq) in acetone (135 mL) was added cesium carbonate (6.0 g, 18.4 mmol, 1.2 eq) at room temperature. The mixture was heated at 50 °C for 50 min before allowing it to cool to room temperature. 2,3-Dibromopropene (1.8 mL, 18.4 mmol, 1.2 eq) was then added to the flask, and the reaction mixture was stirred for 3 h at 50 °C. The reaction mixture was cooled to room temperature, and acetone was removed under reduced pressure. EtOAc and water were added to the residue and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to give symmetric diketone **8** (4.37 g, 61%).

8: colorless oil; IR (film) 2926, 2361, 2322, 1719, 1603, 1516, 1020 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.80 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.72 (t, *J* = 2.4 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.56 (s, 1H), 5.48 (d, *J* = 1.8 Hz, 1H), 4.96 (s, 2H), 3.82 (s, 3H), 3.07 (s, 2H), 2.77 (app ddd, *J* = 17.4, 7.8, 4.8 Hz, 2H), 2.64 (app ddd, *J* = 17.4, 8.4, 5.4 Hz, 2H), 2.38–2.35 (m, 2H), 2.16–2.09 (m, 1H), 2.06–1.97 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.3, 159.5, 159.1, 142.2, 129.6, 129.3, 129.1, 127.9, 121.8, 120.9, 115.0, 114.1, 112.8, 69.8, 67.3, 55.4, 47.7, 40.6, 40.1, 31.3, 16.8; HRMS (ESI) m/z calcd for $C_{25}H_{27}BrNaO_4$ $[M+Na]^+$ 493.0990, found 493.0967.

2-(2-bromoallyl)-2-(3-hydroxyphenethyl)cyclohexane-1,3-dione (9)



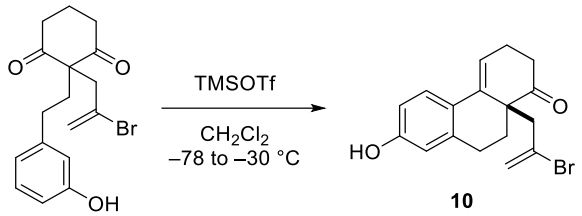
8 **9**

To a stirred solution of diketone **8** (2.06 g, 4.37 mmol, 1.0 eq) in dichloromethane (4.4 mL) and H_2O (4.4 mL) was added DDQ (971 mg, 4.37 mmol, 1.0 eq) at room temperature. The

reaction mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ at 0 °C, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to give phenol **9** (2.19 g, 64%).

9: colorless oil; IR (film) 3019, 2400, 1719, 1692, 1589, 1458, 1217, 1157, 756 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.12 (t, *J* = 1.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 2H), 6.58 (t, *J* = 1.8 Hz, 1H), 5.56 (s, 1H), 5.48 (d, *J* = 1.8 Hz, 1H), 5.09 (br s, 1H), 3.06 (s, 2H), 2.78 (app ddd, *J* = 17.4, 8.4, 5.4 Hz, 2H), 2.65 (app ddd, *J* = 17.4, 8.4, 5.4 Hz, 2H), 2.35–2.32 (m, 2H), 2.16–2.11 (m, 1H), 2.06–1.99 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.6, 155.9, 142.5, 129.9, 127.8, 122.0, 120.8, 115.4, 113.5, 67.3, 48.0, 40.5, 40.3, 31.2, 16.8; HRMS (ESI) m/z calcd for $C_{17}H_{19}BrNaO_3$ $[M+Na]^+$ 373.0415, found 373.0412.

***rac*-(*S*)-10a-(2-bromoallyl)-7-hydroxy-3,9,10,10a-tetrahydrophenanthren-1(2H)-one (10)**

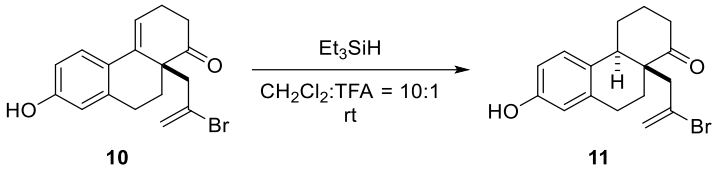


9 **10**

To a stirred solution of symmetric diketone **9** (1.6 g, 4.56 mmol, 1.0 eq)in dichloromethane (91 mL) was added TMSOTf (1.0 mL, 5.47 mmol, 1.2 eq) at –78 °C. The mixture was stirred for X h while gradually warming up the temperature to –30 °C. The reaction mixture was quenched with a saturated aqueous solution of Et_3N and $NaHCO_3$ at –30 °C, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to give cyclized product **10** (1.4 g, 92%).

10: white solid; IR (film) 3019, 2401, 2359, 1701, 1609, 1215, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.23 (dd, *J* = 5.4, 4.2 Hz, 1H), 5.41 (d, *J* = 1.8 Hz, 1H), 5.34 (s, 1H), 4.97 (br s, 1H), 3.03 (d, *J* = 14.4 Hz, 1H), 2.99 (ddd, *J* = 18.0, 12.0, 6.6 Hz, 1H), 2.83 (ddd, *J* = 18.0, 8.4, 1.8 Hz, 1H), 2.79–2.68 (m, 3H), 2.60–2.53 (m, 2H), 2.16 (ddd, *J* = 13.2, 6.0, 1.8 Hz, 1H), 1.86 (ddd, *J* = 13.2, 12.0, 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.0, 155.1, 137.9, 135.8, 128.8, 127.3, 127.2, 121.0, 120.8, 114.8, 114.3, 50.6, 44.7, 36.9, 30.4, 25.4, 24.7; HRMS (ESI) m/z calcd for $C_{17}H_{17}BrNaO_2$ $[M+Na]^+$ 355.0310, found 355.0291.

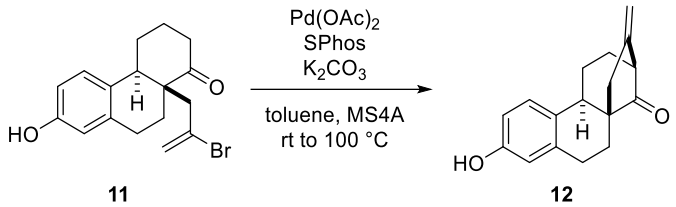
rac-(4a*R*,10a*S*)-10a-(2-bromoallyl)-7-hydroxy-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one (11)



To a stirred solution of ketone **10** (2.32 g, 6.92 mmol, 1.0 eq) in dichloromethane (70 mL) was added Et_3SiH (1.3 mL, 8.30 mmol, 1.2 eq) and TFA (7.0 mL) at 0 °C, and the reaction mixture was stirred for 6 h at the room temperature. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ at 0 °C, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to give vinyl bromide **11** (2.06 g, 89%).

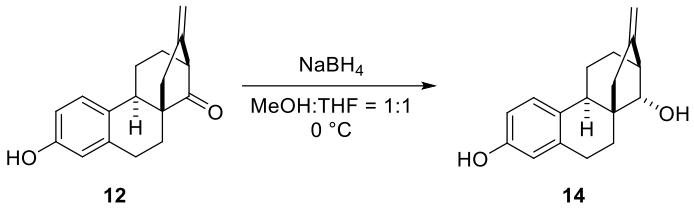
11: white solid; IR (film) 3019, 2361, 1699, 1611, 1505, 1215, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 5.54 (s, 1H), 5.50 (d, *J* = 1.2 Hz, 1H), 4.76 (br s, 1H), 3.06–2.99 (m, 2H), 2.88–2.77 (m, 3H), 2.55 (d, *J* = 16.2 Hz, 1H), 2.47–2.45 (m, 1H), 2.35 (d, *J* = 9.0 Hz, 1H), 2.31–2.28 (m, 1H), 2.20 (ddd, *J* = 14.4, 6.6, 2.4 Hz, 1H), 2.04–1.98 (m, 1H), 1.87–1.81 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 215.0, 154.1, 137.4, 129.2, 129.1, 127.0, 120.5, 115.5, 113.3, 51.5, 48.4, 40.9, 38.6, 27.0, 25.6, 25.4, 23.4; HRMS (ESI) m/z calcd for $C_{17}H_{19}BrNaO_2$ $[M+Na]^+$ 357.0446, found 357.0456.

rac-(6a*S*,9*S*,11a*R*)-3-hydroxy-8-methylene-5,6,7,8,9,10,11,11a-octahydro-6a,9-methanocyclohepta[a]naphthalen-12-one (12)



Vinylbromide **11** (1.28 g, 3.82 mmol, 1.0 eq), $Pd(OAc)_2$ (85.7 mg, 0.382 mmol, 0.10 eq), SPhos (580 mg, 0.840 mmol, 0.22 eq), K_2CO_3 (1.05 g, 7.64 mmol, 2.0 eq) and MS4A (2.8 g) in toluene (28 mL) was stirred for 13 h at 100 °C. After cooling to room temperature, the solution was filtrated through a short pad of silica gel (EtOAc) to give the crude mixture. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to give ketone **12** (938 mg, 97%). Since the impurities could not be separated, the mixture was used in the next reaction without further purification.

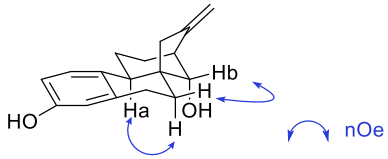
rac-(6a*S*,9*S*,11a*R*,12*S*)-8-methylene-5,6,7,8,9,10,11,11a-octahydro-6a,9-methanocyclohepta[a]naphthalene-3,12-diol (14)



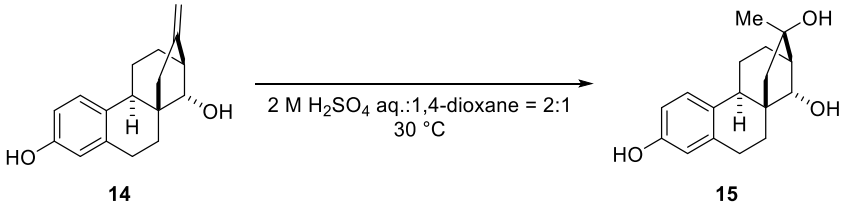
To a stirred solution of ketone **12** in MeOH (13 mL) and THF (13 mL) was slowly added $NaBH_4$ (83.4 mL, 2.21 mmol, 1.2 eq) at 0 °C, and the reaction mixture was stirred for 20 min at the same temperature. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl at the same temperature, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to give alcohol **14** (417 mg, 89%).

14: white solid; IR (film) 3019, 2362, 2344, 1701, 1508, 1217, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 1H), 6.64 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 4.90 (s, 1H), 4.76 (s, 1H), 4.47 (br s, 1H), 3.80 (d, *J* = 4.8 Hz, 1H), 3.08 (dd, *J* = 13.2, 6.0 Hz, 1H), 2.77–2.75 (m, 2H), 2.68 (s, 1H), 2.30 (d, *J* = 17.4 Hz, 1H), 2.20–2.14 (m, 2H), 1.99–1.92 (m, 2H), 1.56–1.50 (m, 1H), 1.47–1.44 (m, 1H), 1.40–1.34 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.2, 149.9, 137.6, 132.5, 128.3, 114.9, 113.3, 106.3, 78.5, 47.5, 43.5, 36.0, 35.9, 32.1, 27.7, 26.2, 24.5; HRMS (ESI) m/z calcd for $C_{17}H_{20}NaO_2$ $[M+Na]^+$ 279.1361, found 279.1349.

The stereochemistry at the Ha and Hb protons was determined by 2D NMR analysis



rac-(6a*S*,8*S*,9*R*,11a*R*,12*S*)-8-methyl-5,6,7,8,9,10,11,11a-octahydro-6a,9-methanocyclohepta[a]naphthalene-3,8,12-triol (15)

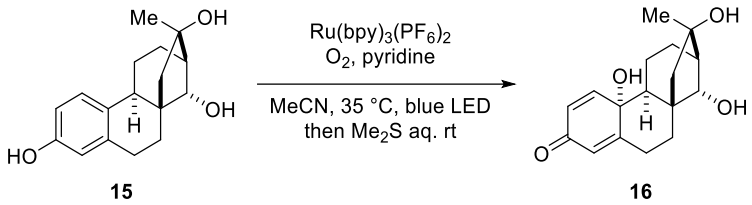


To a stirred solution of alcohol **14** (69.7 mg, 0.272 mmol, 1.0 eq) in 1,4-dioxane (1.6 mL) was added 2 M H_2SO_4 aq. (4.1 mL) at room temperature. The mixture was heated at 30 °C for 12 h before allowing it to cool to room temperature. The reaction mixture was quenched with a

saturated aqueous solution of $NaHCO_3$ at 0 °C, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to give triol **15** (63.1 g, 84%).

15: white solid; IR (film) 3019, 2401, 1699, 1516, 1418, 1215, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 1H), 6.64 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 4.51 (br s, 1H), 4.33 (d, *J* = 4.2 Hz, 1H), 3.09 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.76–2.73 (m, 2H), 2.21 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.07 (ddd, *J* = 13.8, 6.0, 3.0 Hz, 1H), 1.96–1.90 (m, 2H), 1.71 (d, *J* = 12.0 Hz, 1H), 2.20–2.14 (m, 2H), 1.33 (s, 3H), 1.26–1.20 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.2, 137.7, 132.4, 128.4, 114.9, 113.4, 77.8, 76.3, 52.2, 44.8, 44.1, 35.2, 32.5, 27.7, 25.2, 24.9, 20.4; HRMS (ESI) m/z calcd for $C_{17}H_{22}NaO_3$ $[M+Na]^+$ 297.1467, found 297.1456.

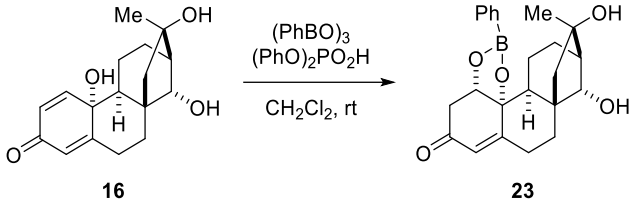
rac-(6a*S*,8*S*,9*R*,11a*S*,11b*R*,12*S*)-8,11b,12-trihydroxy-8-methyl-5,6,8,9,10,11,11a,11b-octahydro-6a,9-methanocyclohepta[a]naphthalen-3(7H)-one (16)



To a stirred solution of triol **15** (99.0 mg, 0.358 mmol, 1.0 eq) in MeCN (3.6 mL) was added $Ru(bpy)_3(PF_6)_2$ (15.4 mg, 17.9 μmol, 0.05 eq) and pyridine (70 μL, 0.90 mmol, 2.5 eq) at room temperature. An oxygen balloon was attached. The mixture was heated at 35 °C and then irradiated with blue LED light (X nm, X mW) for 36 h. After reaction mixture was allowed to cool to room temperature and a nitrogen balloon was attached, added Me_2S (0.13 mL, 1.8 mmol, 5.0 eq) at the same temperature for 5 h. solvents was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (dichloromethane/MeOH = 15/1) to give quinol **16** (83.5 g, 81%).

16: white solid; IR (film) 3021, 2359, 1734, 1559, 1506, 1215, 763 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.18 (d, *J* = 10.2 Hz, 1H), 6.09 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.00 (s, 1H), 4.07 (d, *J* = 4.8 Hz, 1H), 3.06 (d, *J* = 15.0 Hz, 1H), 2.83 (ddd, *J* = 12.6, 12.6, 4.8 Hz, 1H), 2.29 (dt, *J* = 11.4, 3.0 Hz, 1H), 1.99 (td, *J* = 12.6, 5.4 Hz, 1H), 1.93–1.84 (m, 2H), 1.82–1.77 (m, 2H), 1.76–1.72 (m, 1H), 1.68–1.64 (m, 1H), 1.53–1.47 (m, 2H), 1.40 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 189.3, 171.2, 155.4, 127.6, 123.5, 78.3, 77.6, 72.7, 53.3, 48.3, 47.5, 46.5, 42.2, 32.1, 25.7, 21.6, 21.4; HRMS (ESI) m/z calcd for $C_{17}H_{22}NaO_4$ $[M+Na]^+$ 313.1416, found 313.1406.

rac-(3a_S_,8a_S_,10_S_,11_R_,13a_S_,13b_R_,14_S_)-10,14-dihydroxy-10-methyl-2-phenyl-3a,4,7,8,9,10,11,12,13,13a-decahydro-5H-8a,11-methanocyclohepta[7,8]naphtho[1,8a-d][1,3,2]dioxaborol-5-one (23)

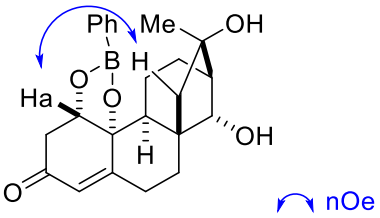


16 **23**

To a stirred solution of quinol **16** (74.5 mg, 0.258 mmol, 1.0 eq) in CH_2Cl_2 (5.0 mL) was added $(PhBO)_3$ (121 mg, 0.387 mmol, 1.5 eq) and diphenyl phosphoric acid (1.3 mg, 5.16 μmol, 0.02 eq) at room temperature. The reaction mixture was stirred for 12 h at the same temperature. CH_2Cl_2 was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (dichloromethane/MeOH = 10/1) to give boronic ester **23** (76.2 mg, 67%).

23: white solid; IR (film) 3019, 1711, 1418, 1364, 1217, 766, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.6 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 5.87 (s, 1H), 4.87 (dd, *J* = 4.2, 3.6 Hz, 1H), 4.24 (s, 1H), 3.01 (d, *J* = 15.0 Hz, 1H), 2.95 (dd, *J* = 16.8, 3.0 Hz, 1H), 2.83–2.78 (m, 1H), 2.71 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.26–2.20 (m, 2H), 2.00–1.94 (m, 1H), 1.88 (s, 1H), 1.82 (td, *J* = 14.4, 4.2 Hz, 1H), 1.76 (ddd, *J* = 12.6, 4.2, 3.0 Hz, 1H), 1.65–1.54 (m, 2H), 1.40 (s, 3H), 1.32–1.25 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.0, 160.5, 135.1, 132.0, 128.1, 123.8, 82.9, 76.8, 76.2, 51.8, 47.0, 46.3, 40.7, 39.2, 38.3, 31.7, 30.3, 25.4, 22.8, 19.4, 19.0.

The stereochemistry at the Ha proton was determined by 2D NMR analysis



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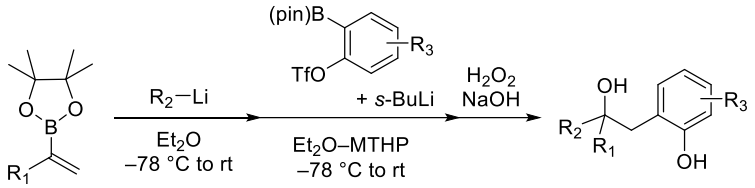
Chapter 5. Grand Summary

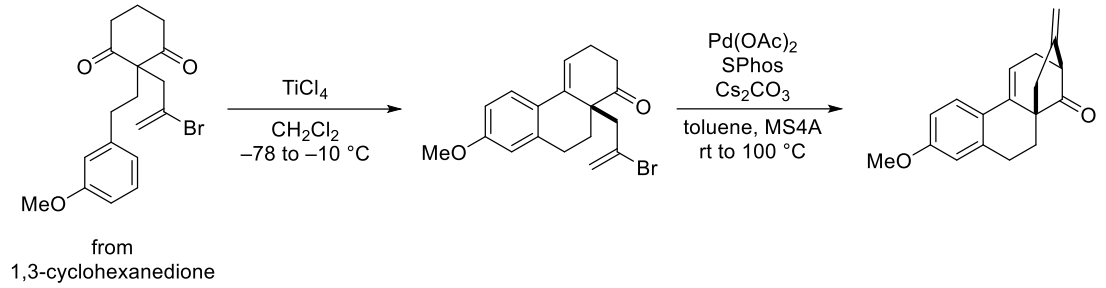
This paper describes the synthesis of complex and useful organic compounds through 1,2-rearrangement reactions, such as 1,2-metallate rearrangement and skeletal rearrangement, as key reactions.

In chapter 2, a novel 1,2-metallate rearrangement reaction of vinylboronic esters employing arynes as carbon electrophiles was developed. By treating vinylboronate, generated from vinylboronic esters and organolithium reagents, with arynes, coupling, 1,2-metallate rearrangement, and cyclization of aryl anion proceeded to afford a cyclic borinic ester ate-complex bearing two newly formed carbon–carbon bonds and one newly formed carbon–boron bond. Upon oxidation, this intermediate could be converted into the corresponding hydroxyphenols.



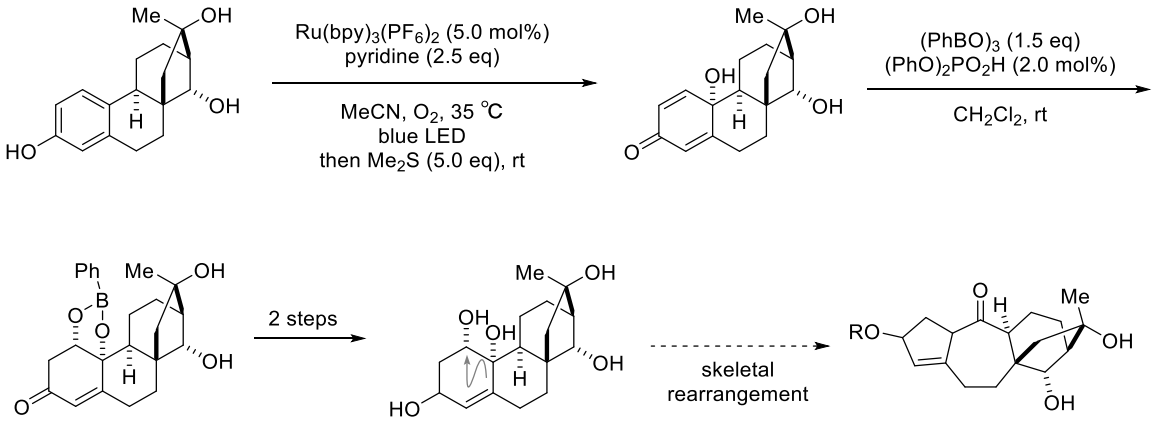
Scheme 1. Aryne-triggered 1,2-metallate rearrangement of vinylboronic esters

In Chapters 3 and 4, a biomimetic synthetic study of grayanane diterpenoids was undergone, with a focus on skeletal rearrangement as the key reaction. Inspired by the biosynthetic pathway, a new approach to construct the grayanane framework via a skeletal rearrangement was proposed. First, a rapid method was established to build an A-ring aromatic *ent*-kaurane-type tetracyclic core, as described in Chapter 3. The author proposed based on desymmetrization of 1,3-diketones, a symmetrical diketone bearing both an aromatic ring and a vinyl bromide side chain was synthesized in two steps from 1,3-cyclohexanedione (Scheme 2). Desymmetric Friedel–Crafts cyclization of the symmetric diketone afforded a tricyclic compound. A Pd-catalyzed intramolecular α-vinylation of the ketone then induced the formation of a bicyclo[3.2.1]octane ring. Through this four-step sequence, the A-ring aromatic *ent*-kaurane-like tetracyclic framework was successfully constructed from 1,3-cyclohexanedione.



Scheme 2. Rapid construction of A-ring aromatic *ent*-kaurane-like tetracyclic skeleton

In Chapter 4, synthetic studies toward the construction of the [5.7.6.5] tetracyclic grayanane skeleton, starting from the constructed A-ring aromatic *ent*-kaurane-type tetracyclic framework, are described (Scheme 3). Following the synthesis of the phenol, an oxidative dearomatization was conducted to afford the corresponding quinol. Subsequently, an *oxa*-Michael addition was employed to introduce the 1,2-diol functionality required for the skeletal rearrangement. After several steps, the synthetic route to the rearrangement precursor was successfully established.



Scheme 3. Toward the biomimetic construction of grayanane skeleton

In conclusion, the author aimed to construct two complex frameworks using 1,2-rearrangement reactions. The results obtained demonstrate potential for broader applications, to which the author's work is expected to make a significant contribution.

List of Publications

1) Annulative coupling of vinylboronic esters: aryne triggered 1,2-metallate rearrangement
Haruki Mizoguchi, Hidetoshi Kamada, Kazuki Morimoto, Ryuji Yoshida, Akira Sakakura
Chem. Sci. **2022**, *13*, 9580.
(*Chapter 2*)

2) Rapid construction of a diterpene-inspired tetracyclic skeleton bearing bicyclo[3.2.1]octane rings based on desymmetrization of 1,3-diketones
Hidetoshi Kamada, Haruki Mizoguchi, Akira Sakakura
Tetrahedron Lett. accepted.
(*Chapter 3*)

Acknowledgments

The studies presented in this thesis have been carried out under the direction of Professor Akira Sakakura at the Division of Applied Chemistry, Graduate School of Natural Science and Technology, Okayama University during 2019–2025.

I would like to express my grateful acknowledgments to my supervisors, Professor Akira Sakakura, Professor Ichiro Hayakawa (Nihon University), and Associate Professor Haruki Mizoguchi, whose encouragements and helpful suggestions have been indispensable to the completion of the present thesis. The excitement with which they approach the synthesis and their dedication to the goal of producing good science always inspired me.

I'm also very grateful to Mr. Kazuki Morimoto and Mr. Ryuji Yoshida as my helpful research colleagues. It is also pleasant to express my appreciation to the former colleagues, especially Mr. Tomoki Isogai, Mr. Masaya Seriu, Mr. Keita Fujita, Mr. Ryuji Yoshida.

I would like to express my deepest gratitude to the Public Interest Incorporated Foundation''Ohmoto Ikueikai'' for their generous financial support over the past three years in carrying out this research.

Finally, I would like to express my deepest appreciation to my parents Mr. Hidemichi Kamada, Mrs. Kazuyo Kamada, my young brother Mr. Shinji Kamada, and young sister Ms. Mami Kamada for their constant assistance and encouragement.

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