

**Studies on Enantioselective Synthesis of Cyclic Compounds
by Organo-catalyzed Dearomatization and
Metal-catalyzed C–H Functionalization Reactions**

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Chapter 1

Introduction and General Summary

1.1 Introduction

Since Friedrich Wöhler's synthesis of urea from inorganic materials in 1828,¹ the rapid development of synthetic organic chemistry has enriched our daily lives through the production of agrochemicals, pharmaceuticals, and materials.² The development of a new chemical reaction that offers a reliable methodology for the synthesis of fine chemicals could be a game-changer in modern society. From this perspective, the advent of asymmetric reactions should be one of the most striking events, enabling easier access to complex molecules containing chiral center(s).³ Traditionally, chemical researchers have been focusing on the use of chiral pool strategies, which rely on the stoichiometric amount of naturally occurring chiral compounds such as amino acids and sugars.⁴ However, due to the limited number of options, this approach alone does not suffice to address the ever-expanding chemical space.⁵ Additionally, the use of stoichiometric amounts of natural products would not be sustainable.⁶ In this context, the key should be the development of catalytic asymmetric constructions of chiral complex molecules starting from easily accessible and modifiable materials.^{3g,7}

Owing to the rapid development of synthetic methods in recent decades, we can easily access highly functionalized C(sp²)-rich molecules from simple starting materials like benzenes, phenols, and indoles.⁸ One possible way to access complex chiral cyclic compounds would be to dearomatize aromatic compounds after the functionalization of C(sp²)-H bonds starting from simple molecules (Figure 1-1, left). Additionally, achieving the direct asymmetric functionalization of strong C(sp³)-H bonds at any position with the perfect site- and stereo-selectivities is probably the ultimate goal for synthetic organic chemists (Figure 1-1, right).



Figure 1-1 Possible ideal synthetic pathways of complex three-dimensional molecules

The author focused on designing a novel catalytic system for the construction of a chiral center in cyclic compounds starting from easily modifiable arenols and aryl

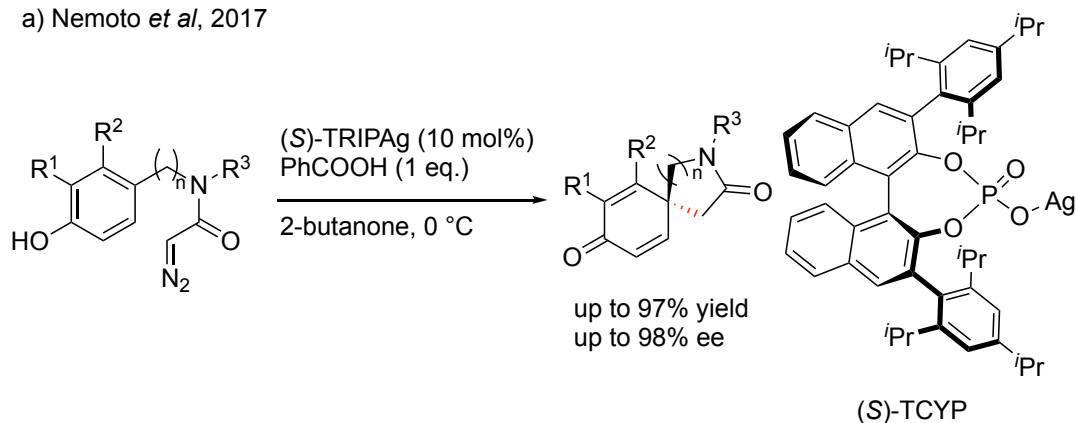
amines (flat molecules), as well as readily available cyclic C(sp³)-rich three-dimensional structures.

1.2 Catalytic asymmetric dearomatization

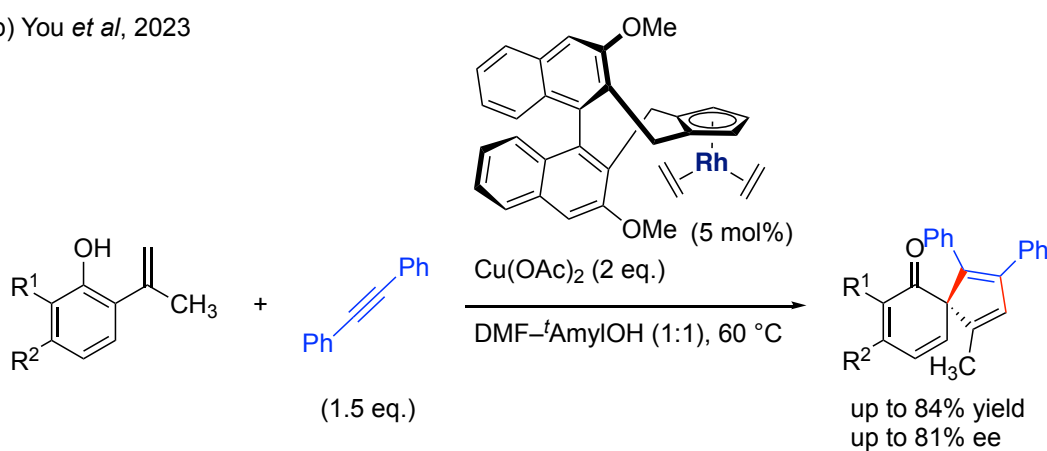
1.2.1 Background

Over the past few decades, catalytic asymmetric dearomatization (CADA) reactions have gathered significant attention owing to their remarkable ability to transform chemically robust flat molecules into chiral complex three-dimensional compounds.⁹ In this field, thanks to the tremendous contributions of You and other groups, both transition-metal- and organo-catalysis have been recognized as reliable methodologies. Among these, indoles and naphthols have been viable substrates for the CADA reactions due to their relatively weak aromaticity.¹⁰ In contrast, the CADA reactions of phenol derivatives have only been intermittently reported in the last decades.^{11,12} For example, Nemoto and co-workers reported a silver-catalyzed C–C bond-forming dearomatization of phenols *via* a silver-carbenoid in 2017 (Figure 1-2 (a)),^{11e} and You and co-workers reported rhodium-catalyzed enantioselective dearomative spiroannulation of phenol in 2023 (Figure 1-2 (b)).^{11f} Despite the significant efforts, most of the reactions that achieve high enantioselectivity are limited to intramolecular reactions and reactions at the *ortho*-position.^{12a} A notable example of an intermolecular CADA reaction at the *para*-position of phenols was reported by the Toste group in 2013 by chiral anion phase-transfer catalysis (Figure 1-2 (c)).^{11g}

a) Nemoto *et al*, 2017



b) You *et al*, 2023



c) Toste *et al*, 2013

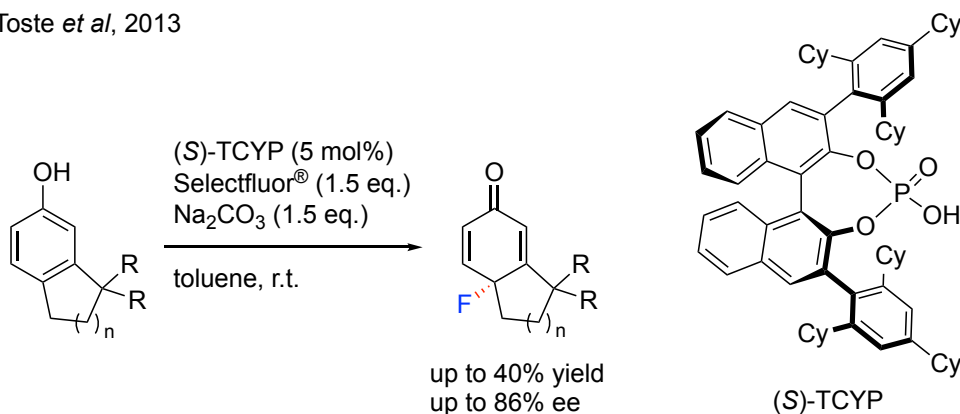


Figure 1-2 Representative examples of enantioselective dearomatization of phenols

1.2.2 Organoiodine-catalyzed asymmetric dearomatization

Organoiodine catalysis has played a key role in the CADA reactions due to its accessibility, mild reactivity, and low toxicity.⁹ⁱ Hypervalent organoiodine compounds

such as (diacetoxyiodo)benzene (PIDA) and Dess–Martin periodinane (DMP) have been used as oxidants in the field of natural product synthesis, due to their chemoselectivity and environmentally friendly nature.^{13,14} In these cases, a stoichiometric amount of hypervalent organoiodine is needed. Aryl iodide can be easily oxidized *in situ* in the presence of oxidants to give organoiodine(III).^{9c,9f,9h,9i,12} A catalytic cycle involving organoiodine species in the +I and +III oxidation states has captivated the interest of many researchers in the last few decades as a way to implement oxidation reactions with low environmental impact, and the emergence of chiral organoiodine compounds has become a game-changer in the field of asymmetric synthesis as they enable the synthesis of otherwise inaccessible compounds, such as chiral 1,2-difluoroalkanes from alkenes.¹⁵ In particular, chiral organoiodine compounds have been developed for the CADA reactions by Kita, Fujita, Ishihara, and other groups.^{9i,12} Due to their dedication to this field, many dearomatization reactions involving the formation of C–C and C–heteroatom bonds have been reported with broad substrates. To achieve high site- and enantioselectivity, however, they have been limited largely to intramolecular reactions and reactions near key functional groups due to the limited number of effective chiral organoiodine catalysts and the possible dissociative reaction pathways (Figure 1-3).¹²

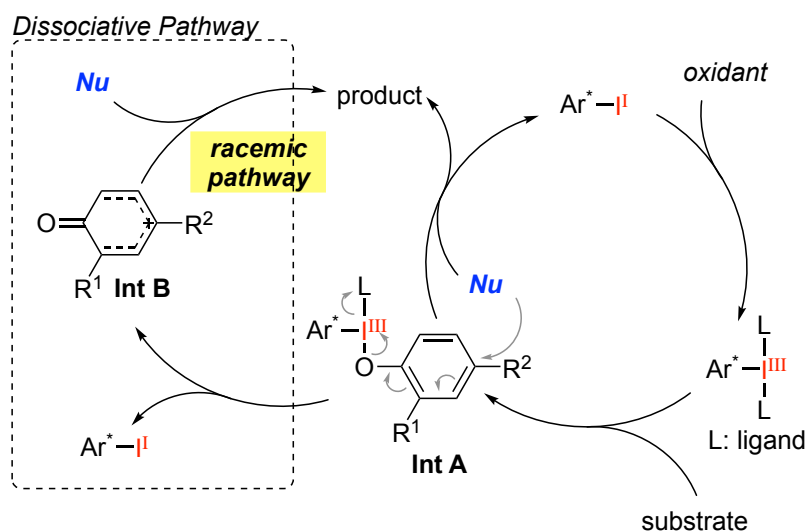
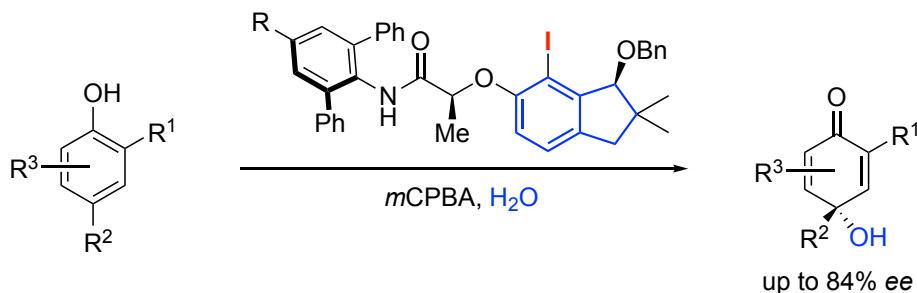


Figure 1-3 General reaction pathway of organoiodine-catalyzed dearomatization

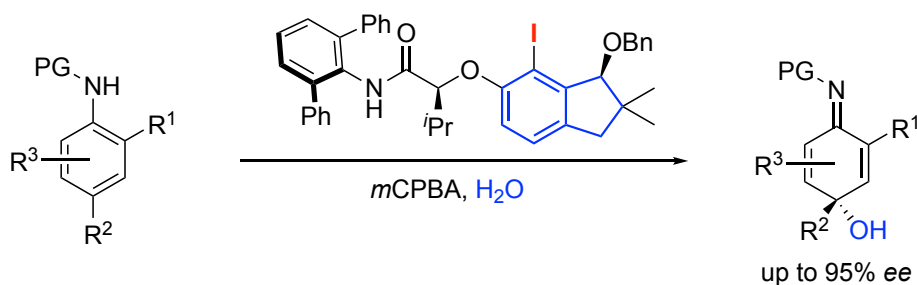
1.2.3 The author's Ph.D. studies on the development of CADA reactions

In Chapter 2, the organoiodine-catalyzed enantioselective *para*-dearomatization of arenols with water as a nucleophile is described (Scheme 1-1). The use of a newly designed indanol-based catalyst core is crucial to achieve higher activity and enantioselectivities.¹⁶



Scheme 1-1 Indanol-based chiral organoiodine catalysts for enantioselective hydrative dearomatization

In Chapter 3, the author shows the enantioselective hydrative dearomatization of *N*-protected anilines with indanol-based chiral organoiodine catalysts (Scheme 1-2). In the course of the development of the organoiodine-catalyzed dearomatization of phenol (Scheme 1-1), aniline derivatives were found to serve as reactants. A proper *N*-protecting group of substrates and a catalyst structure play important roles to achieve high yields and enantioselectivities.



Scheme 1-2 Enantioselective *para*-dearomatization of sulfonanilides by an indanol-based organoiodine catalyst

1.3 Catalytic asymmetric C(sp³)-H bond functionalization

1.3.1 Background

Traditionally, the synthesis of complex organic molecules has relied on converting one functional group into another or installing functional groups by cleaving C-C unsaturated bonds.^{8f} If the most ubiquitous and inactive C-H bonds found in almost all organic molecules were regarded as “functional groups” that could be chemically transformed, new strategies for the synthesis of complex organic molecules can be available. In this context, the pioneering work was reported by Murahashi in 1955, demonstrating cobalt-catalyzed C(sp²)-H bond functionalization of *N*-phenyl aldimine.¹⁷ Since then, various types of C(sp²)-H functionalization reactions have been reported.¹⁸ In contrast, there have been less reports on C(sp³)-H bond functionalization, compared with C(sp²)-H functionalization reactions. It is because the C-H bonds of arenes are relatively sterically accessible, and the arenes can coordinate as arene complexes, making the activation of the C-H bonds in arenes kinetically more favorable than alkanes, and the difficulty in differentiating various C(sp³)-H bonds within the same molecule.¹⁹ Moreover, the control of enantioselectivity has remained highly challenging. In the last few decades, nevertheless, there has been substantial progress in catalytic asymmetric C(sp³)-H functionalizations. They can be classified into different strategies as follows: 1) radical hydrogen atom abstraction,²⁰ 2) asymmetric cross-dehydrogenative coupling,²¹ 3) transition-metal-catalyzed insertion of carbenoid or nitrenoid,^{21,22} and 4) coordination-directed metallation²³ (Figure 1-4). It is easy to imagine that in coordination-directed metallation, only the C(sp³)-H bond near the directing group could be activated. To achieve C(sp³)-H bond functionalization at a more distal site, there are certain requirements, such as the use of complicated ligands and the installation of very elaborate and stubborn directing groups,²⁴ thus rendering the promising reactions less practical.

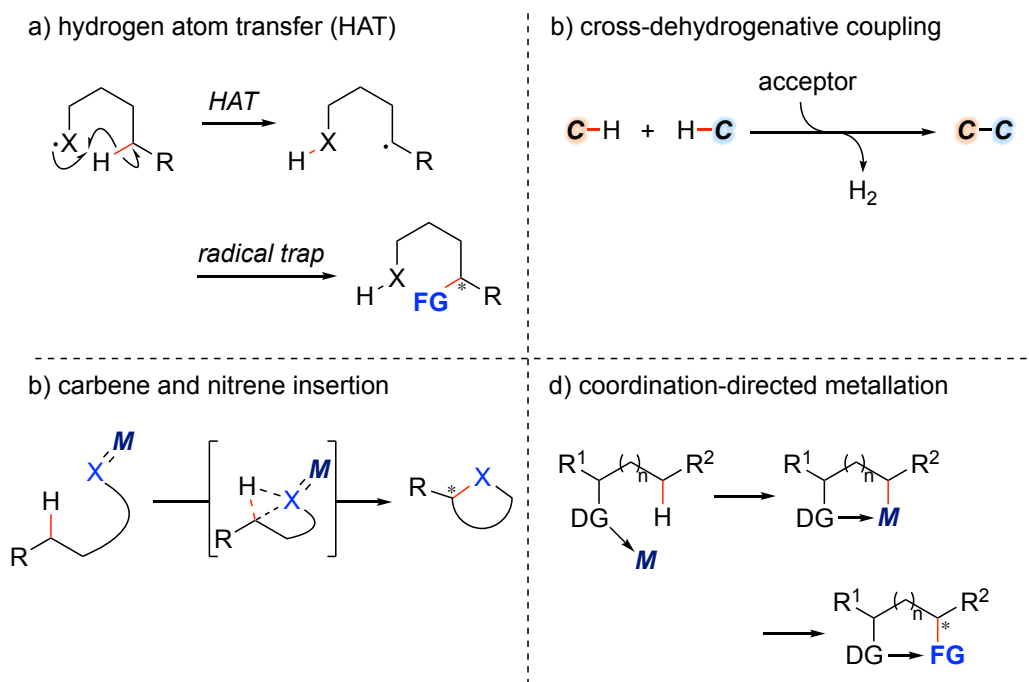


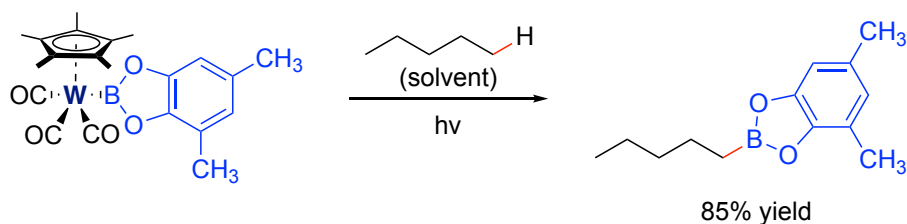
Figure 1-4 Representative approach to C(sp³)-H functionalizations

1.3.2 Transition-metal-catalyzed C(sp³)-H bond borylation

Among various transformations, the C(sp³)-H bond borylation is considered one of the most useful reactions mainly due to the versatile reactivity of the boryl group, which can be transformed into other functional groups through various reactions such as the Suzuki-Miyaura cross-coupling reaction, Matteson homologation, alkenylation, alkynylation, oxidative hydroxylation, and halogenation.²⁵ The rapid diversification of simple molecules into various complex compounds can thus be achieved through a selective C(sp³)-H borylation-post C(sp³)-B transformation sequence.

The first conversion of C(sp³)-H bond into C(sp³)-B bond was accomplished by the Hartwig group in 1997 with a stoichiometric amount of a tungsten boryl complex (Figure 1-5 (a)).²⁶ They later reported the first rhenium-catalyzed borylation of alkanes with bis(pinacolato)diboron (B₂(pin)₂) as a boron source under photochemical conditions in 1999, where they disclosed the photochemically generated a 16-electron borylrhenium complex is responsible for the cleavage of alkane C-H bonds (Figure 1-5 (b)).^{27,28}

a) Hartwig *et al*, 1997



b) Hartwig *et al*, 1999

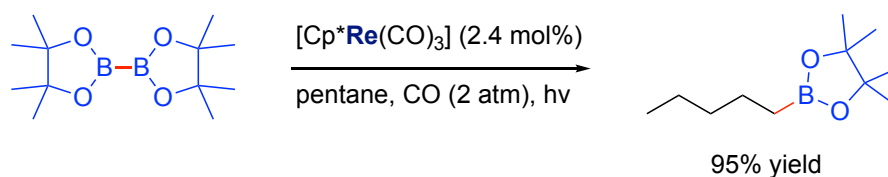


Figure 1-5 Pioneering works on transition-metal-catalyzed terminal C(sp³)-H borylation

Later, researchers' attention was turned to the development of a catalytic system for methylene C(sp³)-H bond borylations. In 2012, the Hartwig group reported the first C(sp³)-H borylation of cyclic ethers at the C3-position (Figure 1-6 (a)).²⁹ Around the same time, the Sawamura group reported the Rh/Silica-TRIP-catalyzed *N*-adjacent methylene C(sp³)-H borylation (Figure 1-6 (b)).³⁰ Recently, Aggarwal and co-workers reported photo-induced C(sp³)-H borylation under metal-free conditions *via* a HAT mechanism (Figure 1-7 (c)).³¹ The C(sp³)-H bond has lower bond dissociation energy than the C(sp²)-H bond, and this reaction proceeds exclusively with C(sp³)-H bonds.

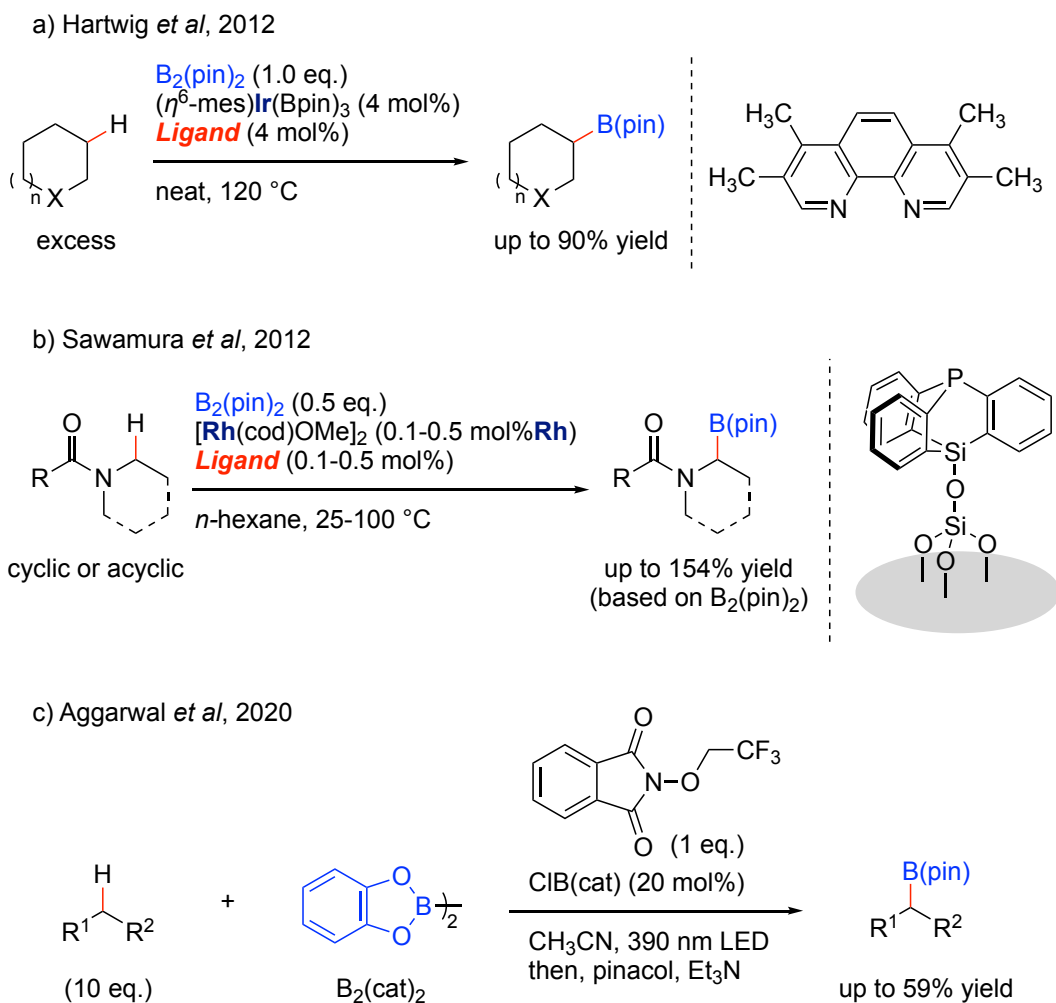


Figure 1-6 Pioneering work on methylene $\text{C}(\text{sp}^3)\text{-H}$ bond borylation

In 2017, Yu and co-workers disclosed the $\text{Pd}(\text{II})$ -catalyzed asymmetric borylation (Figure 1-7).³² The key to success was to introduce an elaborate directing group and the use of aminomethyl oxazoline chiral ligands. The β -borylated amides could be easily converted into β -hydroxy, -fluoro, and -aryl carboxylic acids in short steps.

Yu *et al*, 2017

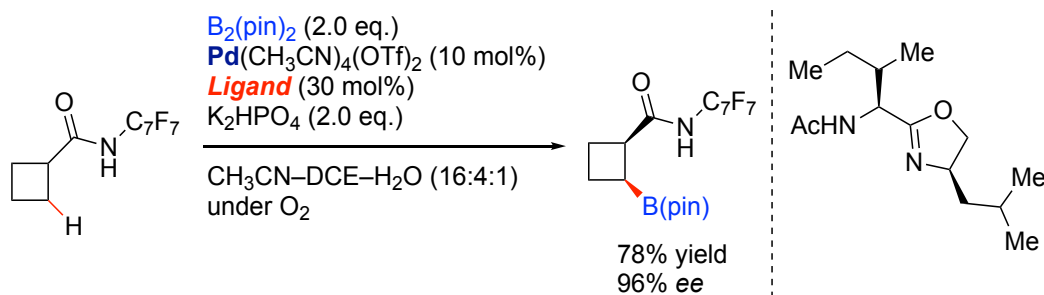
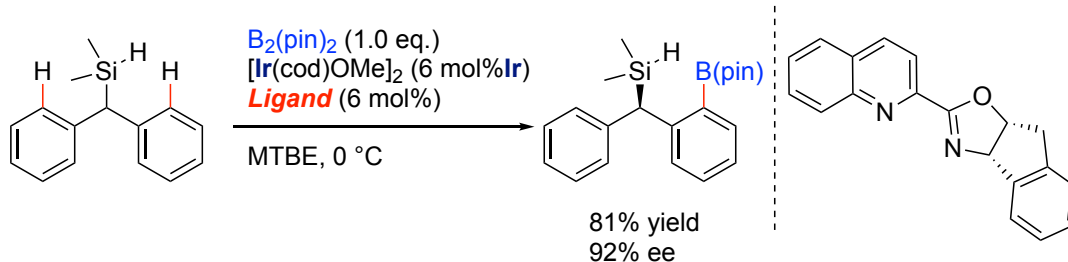


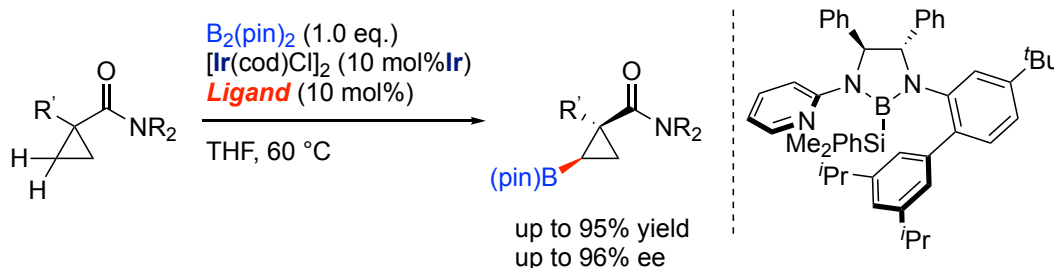
Figure 1-7 Representative works on catalytic $\text{C}(\text{sp}^3)\text{-H}$ borylations

Asymmetric iridium catalysis has recently become one of the most reliable methodologies. The pioneering work was accomplished by Hartwig and co-workers through the use of chiral bidentate dinitrogen ligand.³³ The key to success is the introduction of Si-H moiety into the substrate, which enables the first enantioselective $\text{C}(\text{sp}^2)\text{-H}$ borylation through a relay-directed mechanism (Figure 1-8 (a)). However, the need for very specific silicon functionalities to achieve high selectivity makes this reaction less practical, in terms of offering a methodology to synthesize a variety of structures. To develop a more general strategy to achieve such transformations with high stereoselectivity, it seems necessary to create novel chiral ligands. In this context, Xu and co-workers reported a novel chiral B,N -bidentate ligand in 2019, and the ligand of this type has made versatile asymmetric $\text{C}(\text{sp}^3)\text{-H}$ borylation possible (Figure 1-8 (b), (c)).³⁴ The ligated iridium complex has two available coordination sites, which could control site-selectivity, while the elaborated chiral backbone could control the enantioselectivity. Indeed, their achievements are remarkable, but it is still essential to provide new methodologies to access the ever-expanding chemical space.

a) Hartwig *et al*, 2017



b) Xu *et al*, 2019



c) Xu *et al*, 2021

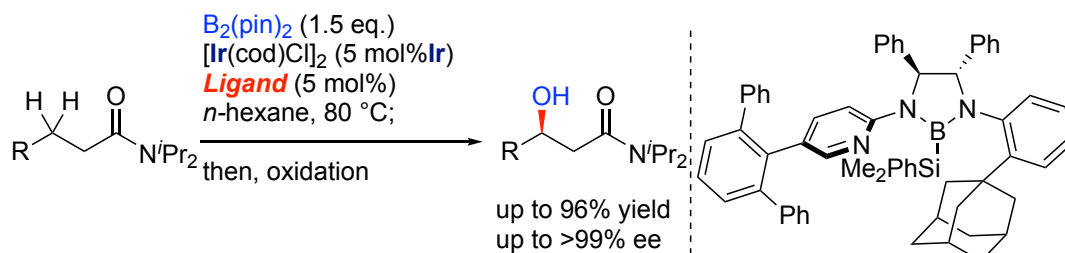
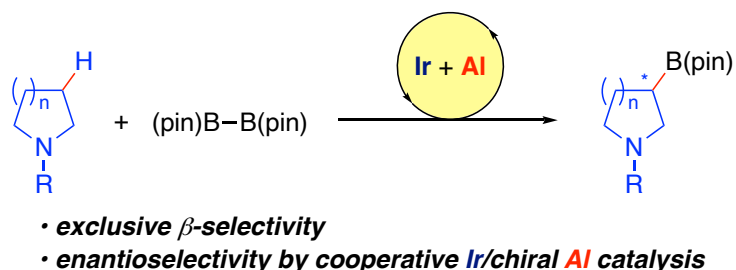


Figure 1-8 Representative works on iridium-catalyzed enantioselective C(sp³)-H borylation

1.3.3 The author's Ph.D. studies on the development of enantioselective C(sp³)-H borylation reactions

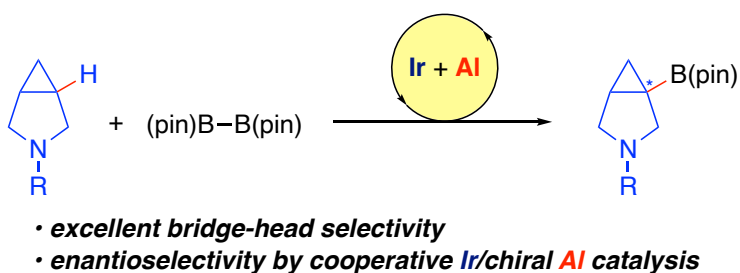
In Chapter 4, the iridium/aluminum cooperative catalysis for site-selective C(sp³)-H borylation of cyclic amines and lactams is reported (Scheme 1-3). The DFT calculation reveals that the aluminum co-catalyst lowers the energy barrier of the rate-determining C-B bond-forming reductive elimination. Besides, the use of chiral aluminum BINOLate allows the C-B bond formation in a highly stereoselective manner. The distinct feature of this strategy, compared with the previous contributions, is the synergistic catalysis by a non-chiral iridium catalyst and a chiral Lewis acid without

relying on the chirality at the iridium catalyst center where the enantioselective C–H functionalization proceeds.



Scheme 1-3 β -C(sp³)–H borylation of saturated cyclic amines by cooperative iridium/aluminum catalysis

In Chapter 5, the site-selective C(sp³)–H borylation of bicyclo[3.1.0]hexanes by cooperative iridium/aluminum catalysis is disclosed (Scheme 1-4). The reaction proceeds under mild reaction conditions to afford tertiary alkyl boronates. As described in Chapter 4, enantioselective borylation reactions are accomplished by using a chiral aluminum catalyst.



Scheme 1-4 Site-selective C(sp³)–H borylation of 3-azabicyclo[3.1.0]hexanes by cooperative iridium/aluminum catalysis

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Chapter 2

Indanol-Based Chiral Organoiodine Catalysts for Enantioselective Hydrative Dearomatization

Rapid development in the last decade has rendered chiral organoiodine(I/III) catalysis a reliable methodology in asymmetric catalysis. However, due to the severely limited numbers of effective organoiodine catalysts, many reactions still give low to modest enantioselectivity. The author reports herein a solution to this issue through the introduction of a pivotal indanol scaffold to the catalyst design. The author's catalyst architecture exhibits the advantage of high modularity and thereby expedites catalyst optimization. The catalyst was optimized for the challenging and highly sought-after hydrative dearomatization of 2-substituted phenols at the 4-position.

2.1 Introduction

Organoiodine compounds possess unique catalytic properties based on their iodine(I/III) cycle in the presence of a stoichiometric amount of oxidant. This organoiodine catalysis has recently attracted considerable attention in synthetic organic chemistry as a way to implement oxidation reactions with low environmental impact.¹ The current emphasis on this area has been driven by the emergence of effective chiral organoiodine catalysts, which have paved the way for highly enantioselective transformations (Figure 2-1 (a)).²⁻⁵ These chiral catalysts have already found application in a variety of reactions, giving enantioenriched products that are accessible only through the use of organoiodine catalysis.⁶ However, chiral organoiodine catalysts that surpass the selectivity achievable with these leading catalysts are virtually non-existent,⁷ and many organoiodine-catalyzed reactions are still performed with unsatisfactory levels of selectivity.^{7,8} As a solution to overcome this limitation, the author became interested in applying a chiral indanol scaffold, which has demonstrated outstanding selectivity in studies on a thiyl radical and an electrophilic selenium catalyst,⁹ to design a new chiral organoiodine catalyst (Figure 2-1 (b)).¹⁰

As a proof of concept, the author surmised that enantiocontrol of the hydrative dearomatization of phenols at the *para* position, to give *p*-quinols would be particularly challenging and rewarding (Figure 2-1 (c)).¹¹⁻¹⁴ Such organoiodine(III)-mediated oxidative dearomatizations of phenols are a common strategy in natural product synthesis, and have been practiced for more than two decades.^{15,16} However, they are mostly conducted by using a stoichiometric amount of achiral reagent like $\text{PhI}(\text{OAc})_2$. While chiral organoiodine-catalyzed hydrative dearomatization can certainly be a solution as presented by Harned and Muñiz,¹³ the enantioselectivity remained poor to modest in both cases. It is assumed that the remote prochiral center, which is five bonds away from the organoiodine moiety, and the use of water as a small nucleophile render the chirality transfer from the catalyst to the substrate difficult.¹⁴

This study unveiled an indanol-based chiral organoiodine catalyst which performs the hydrative dearomatization of phenols to *p*-quinols in up to 84% ee. Taking advantage of the author's indanol scaffold, which is equipped with two hydroxy groups, the chiral structure was strategically diversified to expedite the optimization process. In a broader context of chiral organoiodine(I/III) catalysis, this report demonstrates the first

chiral catalyst that achieves good enantioselectivity in an intermolecular dearomatization.¹⁷

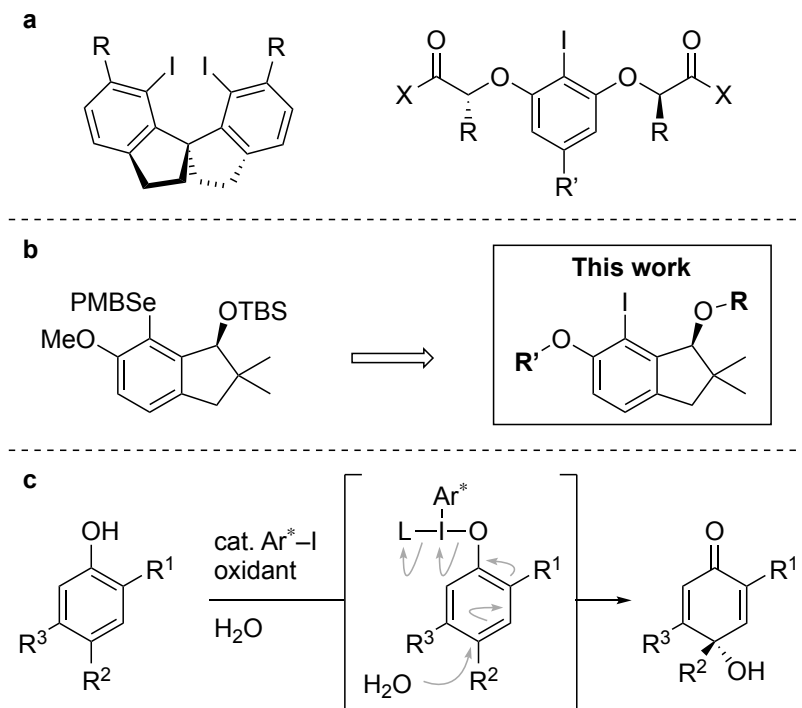
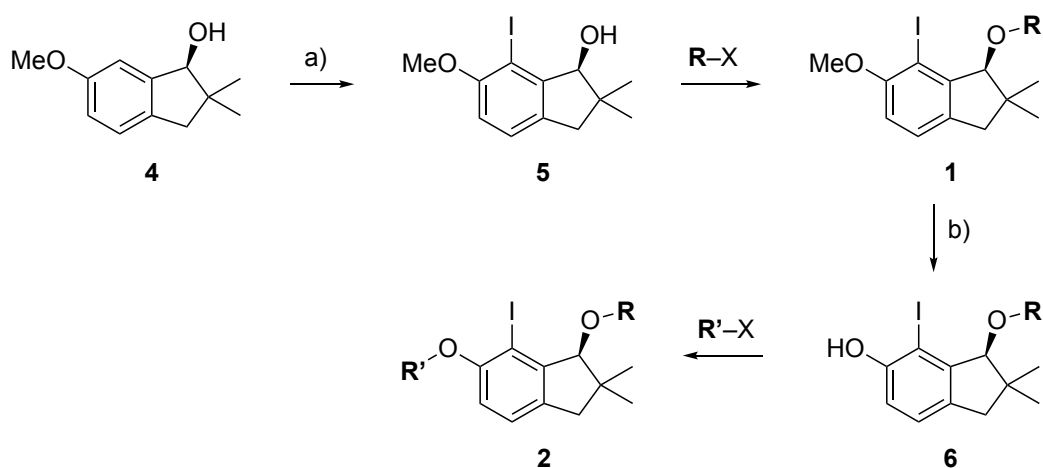


Figure 2-1 a) Representative chiral organoiodine catalysts. b) An indanol-based chiral organoiodine catalyst. c) *para*-Hydrative dearomatization of phenols.

2.2 Results and Discussion

Armed with a chromatography-free, scalable synthesis of enantiopure indanol **4**,^{9a,18} the author set up the synthesis of an indanol-based organoiodine catalyst library (Scheme 2-1). Hydroxy-group-directed lithiation was carried out to install an iodo moiety at the 7-position to give organoiodine **5**. By attaching different substituents to the hydroxy moiety, this intermediate can be derivatized to a variety of chiral organoiodine catalysts **1**. Furthermore, compound **1** can be demethylated by treatment with a thiolate, thereby allowing him to modify the phenol moiety of **6** and hence to fine tune the properties of organoiodine catalysts **2**.



Scheme 2-1 Modular synthesis of indanol-based chiral organoiodine catalysts. a) BuLi, ether, r.t., then I_2 , THF, $-78\text{ }^{\circ}\text{C}$, 47% yield (87% brsm); b) $tert-C_{12}H_{25}SH$, NaH, DMF, $130\text{ }^{\circ}\text{C}$, 86% yield (R = benzyl).

By using this strategy, the author was able to diversify the indanol scaffold **5** rapidly and create a library containing more than 80 chiral organoiodine catalysts, with which the hydrative dearomatization was optimized (Table 2-1). 2-Bromo-4-methylphenol (**7a**) was chosen as a model substrate based on the synthetic utility of the bromo moiety for further functionalization and the poor selectivity achieved in previous studies (around 40% ee).¹³ Taking the aforementioned derivatization strategy for the catalyst into account, the author split the catalyst optimization into three consecutive rounds. The first round of optimization commenced with organoiodines **1**, synthesized through the attachment of alkyl, aryl, acyl, and silyl groups on the C1-alcohol moiety of

indanol **5**. In the initial screening, benzyl substitution stood out in that the dearomatized product could be obtained with 50% ee (entries 1–4). At this stage, solvents and reaction conditions were examined, revealing the use of a 2:1 mixture of acetone/H₂O at 10 °C as optimal to give **8a** with 59% ee (entries 5–7). Encouraged by the observed enantioselectivity, which is comparable to the highest reported selectivity,¹³ the author further screened other C1-alcohol functionalities for catalyst **1** in the expectation of attaining higher selectivity (Table 2-6). However, even after thorough investigation, the ee remained in the range of 40–60 % in all cases.

The author then turned his attention to the second round of catalyst optimization using C1-benzyloxy **6** (Scheme 2-1, R = benzyl) as a template. This time, the phenolic OH group at the 6-position was modified. After a screening of achiral substituents that did not produce improved results (entries 8–10, see also Table 2-7), the author turned his focus to a chiral lactate moiety introduced by Fujita *et al.* in their development of chiral organoiodine(III) reagents.¹⁹ Examination of both enantiomers of methyl lactate revealed that one isomer (**2d**) lowered the ee by 18% and the other (**2e**) improved the ee by 11% (entries 12 and 13). It is of note that the chirality of the lactate is crucial since catalysts bearing achiral glycolate (CH₂CO₂Me) or 2-methyl lactate (CMe₂CO₂Me) had no effect on the selectivity, respectively (Table 2-8). Further improvement of the enantioselectivity was observed by the incorporation of *N*-phenyl lactamide as the supporting chiral entity (**2f**, entry 13).⁵

The last optimization round was focused on the amide *N*-substituent of organoiodines **3** (entries 14–17, see also Table 2-9). Consistent with a report by Ishihara and co-workers,^{5b} attachment of 2,6-disubstituted anilines further improved the selectivity to more than 80% ee (entries 15–17). By fixing the catalyst as **3c**, the reaction conditions were fine-tuned, resulting in the use of a butanone/H₂O solvent system at 0 °C (entry 18, see also Table 2-10). Under these conditions, *p*-quinol **8a** was obtained in 54% yield and 82% ee. It should be noted that no racemization of the product was observed in the reaction and the absolute configuration of **8a** was confirmed by X-ray crystallographic analysis.²⁰

Table 2-1 Catalyst optimization.^a

7a $\xrightarrow[\text{solvent, temp. (}^{\circ}\text{C)}]{\text{Ar}^*\text{-I (10 mol\%)}, \text{mCPBA (2.2 eq.)}}$ **8a**
11–65 h

1st round

R = Bn (**1a**), Me (**1b**), Bz (**1c**), SiPh₃ (**1d**)

2nd round

R' = Bn (**2a**), Bz (**2b**), SiPh₃ (**2c**)

(**2d**)

(**2e**)

(**2f**)

3rd round

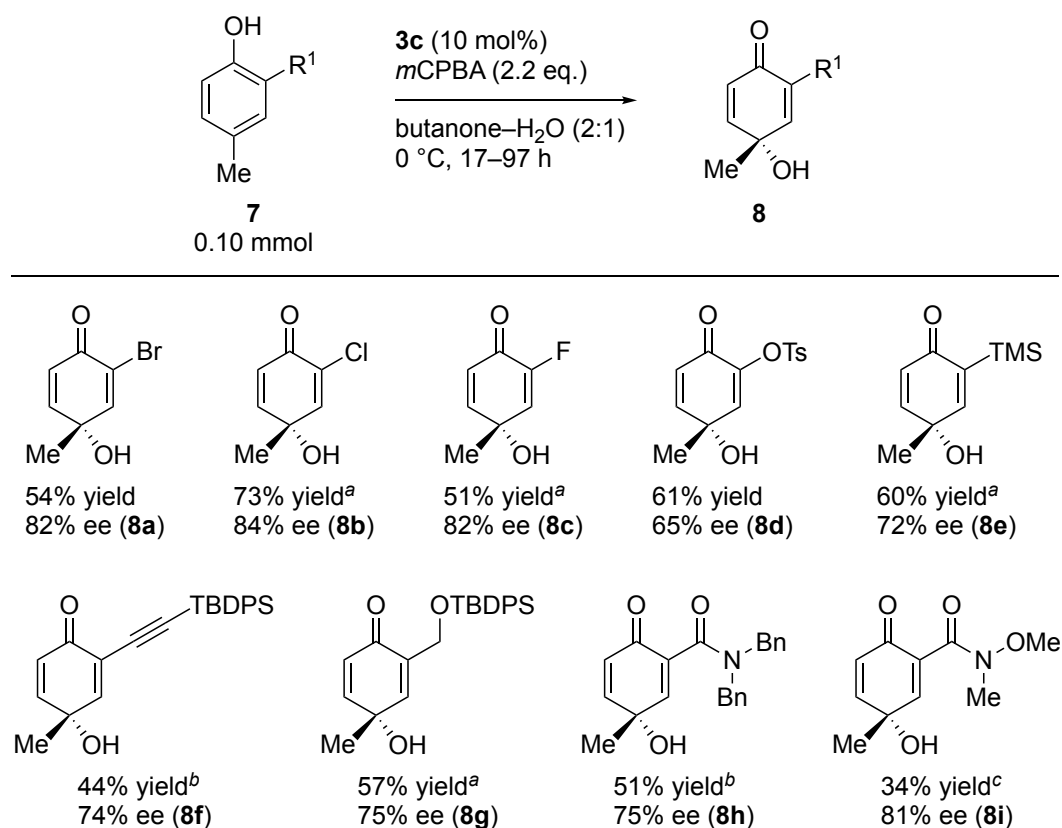
Ar = 3,5-Me₂C₆H₃ (**3a**)
 2,4,6-Me₃C₆H₂ (**3b**)
 2,6-Ph₂C₆H₃ (**3c**)
 4-Me-2,6-Ph₂C₆H₂ (**3d**)

Entry	Ar*-I	Solvent	Temp. (°C)	Yield (%)	Ee (%)
1	1a	acetone–H ₂ O (9:1)	r.t.	49	50
2	1b		r.t.	36	37
3	1c		r.t.	3	32
4	1d		r.t.	51	4
5	1a	CH ₃ CN–H ₂ O (9:1)	r.t.	31	30
6	1a	DMF–H ₂ O (9:1)	r.t.	5	68
7	1a	acetone–H ₂ O (2:1)	10	73	59
8	2a		10	63	57
9	2b		10	10	37
10	2c		10	46	52
11	2d		10	66	41
12	2e		10	68	70
13	2f		10	49	73
14	3a		10	55	74
15	3b		10	65	77
16	3c		10	46	81
17	3d		10	55	75
18	3c	butanone–H ₂ O (2:1)	0	54 ^e	82

^aReaction conditions: **7a** (0.165 mmol), *m*CPBA (0.363 mmol), and Ar*-I (0.0165 mmol) in solvent (1.0 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation. ^dPerformed on 0.100 mmol scale. ^eIsolated yield.

With the optimized catalyst and reaction conditions in hand, the author then examined the substrate scope, initially focusing on the 2-substituent of 4-methylphenols **7** (Table 2-2). The optimized reaction conditions were applicable to 2-chloro-4-methylphenol with the same level of enantioselectivity (**8b**). Interestingly, the enantioselectivity was maintained even with 2-fluoro-4-methylphenol (**8c**), thus implying that the catalyst recognizes the electronic bias of the phenol ring. In these two cases, catalyst **3d**, which bears a *N*-4-methyl-(2,6-diphenyl)phenyl group, gave a slightly higher ee. As for hetero functionalities, a tosyloxy group was tolerated albeit with lower enantioselectivity (**8d**). A 2-TMS substrate was converted into *p*-quinol **8e** with 72 % ee. The author's focus then shifted to different carbon substituents attached to the phenol ring. *p*-Quinols **8f–h**, which bear an alkynyl, siloxymethyl, or amide functionality, were obtained with 70–81 % ee by conducting the reaction in either acetonitrile/H₂O or butanone/H₂O. The use of 5-methylsalicylate (**7**, R¹=CO₂Me) resulted in an over-oxidation of the product by *m*CPBA (data not shown). The Weinreb amide, a useful synthetic handle, could be also incorporated into *p*-quinol **8i** with good enantioselectivity, although the reaction yield still needs to be improved.

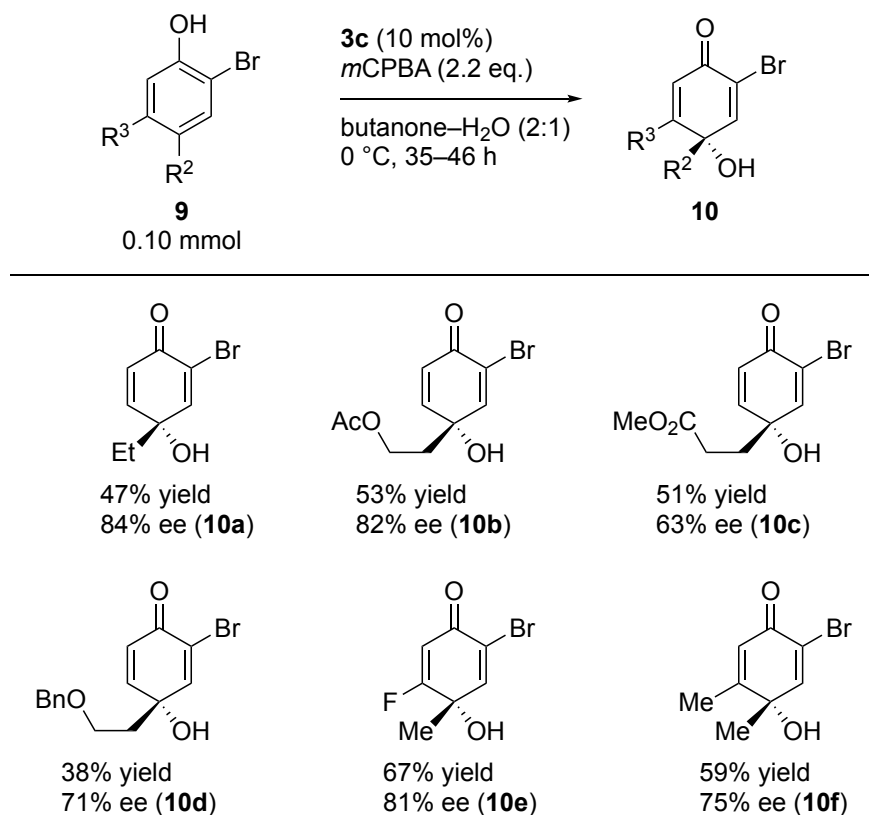
Table 2-2 4-Methylphenols substrate scope.



^aPerformed with **3d** (0.010 mmol). ^bPerformed in CH₃CN–H₂O (2:1, 1.0 mL). ^cPerformed in CH₃CN–CHCl₃–H₂O (7:1:2, 1.0 mL).

As the next step, the author turned his attention to the 4-alkyl substituent of 2-bromophenols **9** (Table 2-3). An ethyl group instead of a methyl group at the 4-position had no negative effect on the enantioselectivity (**10a**). To examine the pendant-functional-group tolerance, the author then examined substrates bearing acyl, ester, and ether moieties at the end of the alkyl chain. While these functionalities were tolerated, the reactions gave variable levels of enantioselectivity (**10b–d**). Finally, 4,5-disubstituted 2-bromophenols were briefly examined by using 5-fluoro and 5-methyl substituted phenols. In both cases, the enantioselectivity was unaffected by the additional substituent, with the reactions giving **10e** and **10f** in good yields and enantioselectivity. It is expected that subsequent debromination of these products would give access to 3,4-disubstituted *p*-quinols, which are valuable intermediates in natural product synthesis^{15c,15d,15f,15h} but are still hard to synthesize through state-of-the-art asymmetric catalysis.^{13a, 21}

Table 2-3 2-Bromophenols substrate scope.



2.3 Conclusion

In conclusion, the author has developed the first chiral organoiodine catalyst that performs the intermolecular hydrative dearomatization of phenols to give *p*-quinols with good enantioselectivity. The key to success was the use of a readily available enantiopure indanol scaffold, which allows rapid catalyst evolution and the creation of a library containing more than 80 organoiodine catalysts. Given that the selectivity of many organoiodine-catalyzed reactions still lags behind today's standards in asymmetric catalysis, the author's approach should pave the way for further progress in this flourishing field.

2.4 Experimental section

2.4.1 General information related to all the experimental parts in the Thesis

All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique under an argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck TLC silica gel 60 F₂₅₄ (0.25 mm) plates. Unless otherwise noted, visualization was accomplished with UV light (254 nm) and/or color reagents (such as phosphomolybdic acid (PMA), basic KMnO₄, or *p*-anisaldehyde), followed by gentle heating. Unless otherwise noted, the products were purified by Merck precoated preparative thin layer chromatography (PLC) plate (silica gel 60 GF₂₅₄, 0.25 mm) and/or prepacked Biotage column or Kanto Chemical silica gel (60 N, neutral, spherical, 40-50 μ m) on Biotage Isolera purification system, Yamazen EPLC-W-Prep 2XY, or SHOKO SCIENTIFIC Purif-espoir2 (λ = 254 nm) systems. Commercially obtained reagents were used without further purification.

2.4.2 Apparatus related to all the experimental parts in the Thesis

NMR spectra: measured on JEOL JNM-FX500 or ECS-400 spectrometers. ¹H NMR (500 or 400 MHz) spectra were measured with tetramethylsilane or solvent resonance as the internal standard (CDCl₃ at 7.26 ppm, benzene-*d*₆ at 7.16 ppm, acetone-*d*₆ at 2.05 ppm) and ¹³C NMR (125 or 101 MHz) spectra were measured with solvent resonance as the internal standard (CDCl₃ at 77.0 ppm, benzene-*d*₆ at 128.1 ppm, acetone-*d*₆ at 29.8 ppm, DMSO-*d*₆ at 39.5 ppm). ¹⁹F NMR (376 MHz) spectra were measured with C₆F₆ as the internal standard (−162.00 ppm). NMR Data are reported as follows: chemical shifts in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, qd = quartet of doublets, *virt* = virtual, br = broad), coupling constant(s) (Hz), and integration. Unless otherwise noted, all NMR spectra were measured at ambient temperature.

Infrared (IR) spectra: recorded on a Thermo Fisher Scientific Nicolet iS5 spectrometer.

Gas chromatography (GC): performed on a Shimadzu GC-2014 equipped with a BP1 column (SGE Analytical Science, 0.25 mm $\times$ 30 m, pressure = 149.0 kPa, detector = FID, 290 °C) with helium gas as a carrier.

High-resolution mass spectra (HRMS): obtained with Thermo Fisher Scientific MS: Exactive Plus HPLC: UltiMate 3000 (ESI).

Analytical high-performance liquid chromatography (HPLC): performed on Shimadzu 10A or 20A instruments using Daicel CHIRALPAK[®] IA-3 (4.6 mm × 25 cm), CHIRALPAK[®] IB N-3 (4.6 mm × 25 cm), Daicel CHIRALPAK[®] IC-3 (4.6 mm × 25 cm), CHIRALPAK[®] IE-3 (4.6 mm × 25 cm), CHIRALPAK[®] IG-3 (4.6 mm × 25 cm), CHIRALCEL[®] OJ-H (4.6 mm × 25 cm), Daicel CHIRALCEL[®] OJ-3 (4.6 mm × 25 cm), Daicel CHIRALCEL[®] OD-3 (4.6 mm × 25 cm), Daicel CHIRALPAK[®] AS-3 (4.6 mm × 25 cm), or Daicel COSMOSIL[®] Packed Column 5SL-II (4.6 mm × 25 cm). More detailed conditions (eluent, flow rate, wavelength, and temperature (unless otherwise noted, ambient temperature)) are indicated in each experimental section. All solvents used for chiral HPLC analysis were HPLC-grade solvents and degassed prior to use.

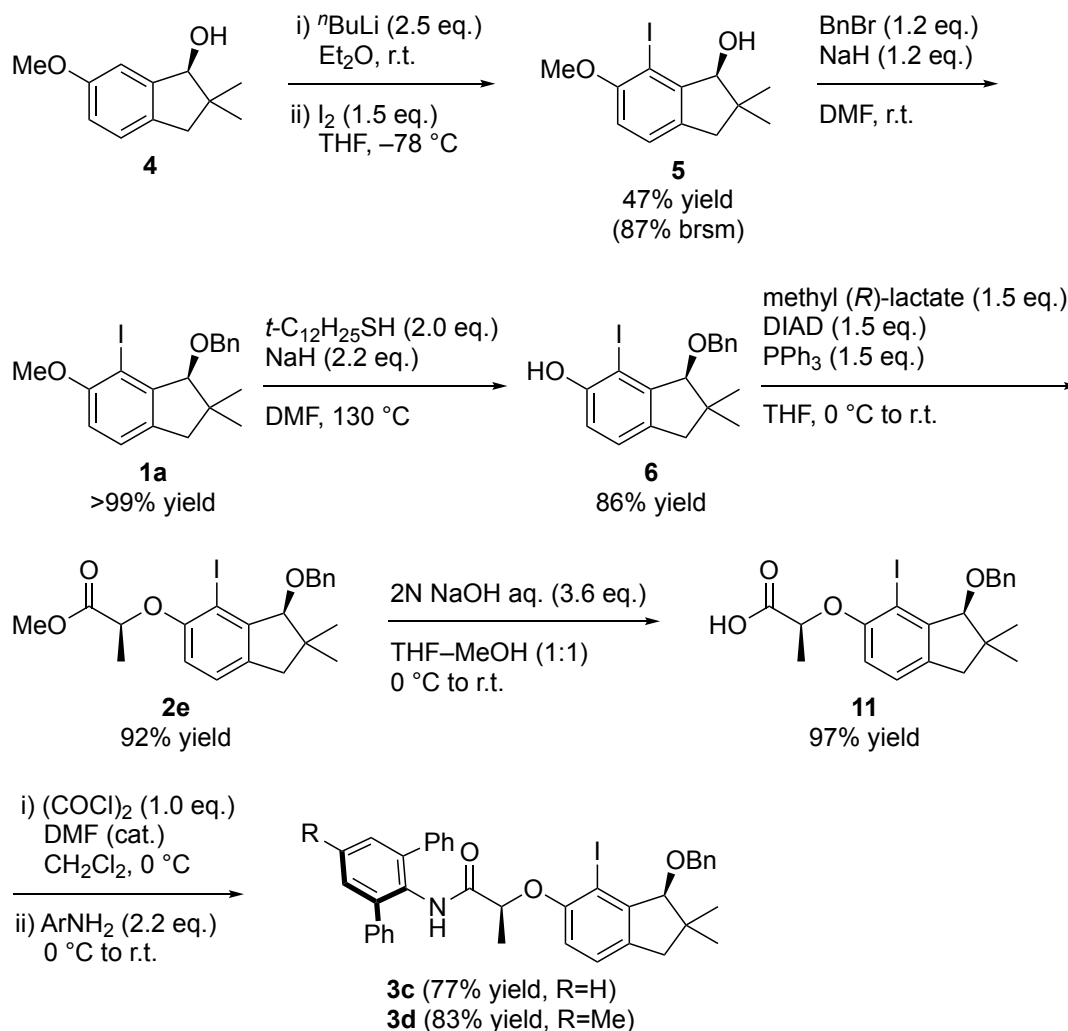
Semi-preparative recycling high-performance liquid chromatography (HPLC): performed on Shimadzu instruments (equipped with CBM-20A communications bus module, SPD- 20A UV/Vis detector, FRC-10A fraction collector, and LC-6AD solvent delivery pump unit) using Daicel COSMOSIL[®] packed column (5SL-II, 20 mm× 25 cm), or Daicel COSMOSIL[®] packed column (5C₁₈-AR-II, 20 mm × 25 cm). All solvents used for chiral HPLC analysis were HPLC-grade solvents and degassed prior to use.

Preparative recycling high-performance liquid chromatography (HPLC): performed on Shimadzu instruments (equipped with CBM-20A communications bus module, SPD-20A UV/Vis detector, RID-20A refractive index detector, FRC-10A fraction collector, and LC-20AP solvent delivery pump unit) using Daicel COSMOSIL[®] packed column (15SL-II, 50 mm× 50 cm). All solvents used for chiral HPLC analysis were HPLC-grade solvents and degassed prior to use.

Preparative recycling gel permeation chromatography (GPC): performed on Japan Analytical Industry LC-9201 (equipped with UV-50 detector, RI-50s detector, and MDL-102 recorder) using JAIGEL-1H/2H column. Chloroform used for recycling GPC resolution was guaranteed reagent grade purchased from Wako.

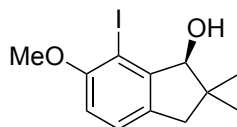
Optical rotation: measured on a JASCO DIP-1000 digital polarimeter or HORIBA SEPA-200.

2.4.3 Preparation of catalysts 3c and 3d



Scheme 2-2 Preparation of catalyst **3c** and **3d**.

(S)-7-Iodo-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-ol (**5**)

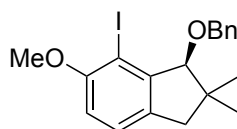


To a stirred solution of **4** (Prepared according to the literature procedure,¹⁸ 15.8 mmol, 3.04 g) in Et₂O (16 mL) was added ⁿBuLi (2.5 M in hexane, 39.5 mmol, 15.8 mL) at 0 °C under Ar atmosphere. The reaction warmed up to room temperature and stirred for 4 hours at the same temperature. After that, the reaction was cooled down to −78 °C,

followed by the addition of THF (10 mL). To this reaction was added dropwise the solution of I₂ (23.7 mmol, 6.02 g) in THF (10 mL) at the same temperature via cannula. After stirring for 90 min, 1 N Na₂SO₃ aq. was added and warmed up to room temperature, followed by the addition of saturated NaHCO₃ aq. and AcOEt. Two layers were separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 9/1 to 2/1) to afford the title compound as a white solid in 47% yield and compound **4** was recovered as an orange oil in 46% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.08 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 4.52 (d, *J* = 4.3 Hz, 1H), 3.87 (s, 3H), 2.99 (d, *J* = 15.3 Hz, 1H), 2.63 (d, *J* = 15.3 Hz, 1H), 2.04 (d, *J* = 4.3 Hz, 1H), 1.24 (s, 3H), 1.02 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 156.9, 149.7, 137.0, 125.8, 111.5, 86.6, 86.3, 56.9, 45.5, 43.0, 27.8, 22.5; **IR** (neat) 3368, 2953, 2836, 1464, 1434, 1382, 1255, 1061 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₁₂H₁₅O₂INa: *m/z* 341.0009 ([M+Na]⁺), found: *m/z* 341.0009 ([M+Na]⁺); **Optical rotation** [α]_D¹⁴ = +54.1 (*c* = 1.0, CHCl₃).

(S)-1-(Benzyloxy)-7-iodo-6-methoxy-2,2-dimethyl-2,3-dihydro-1*H*-indene (1a)

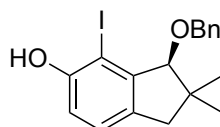


To a stirred solution of **5** (7.39 mmol, 2.35 g) in DMF (20 mL) was added NaH (60% in mineral oil, 8.8 mmol, 0.35 g) and BnBr (8.8 mmol, 1.1 mL) at room temperature under Ar atmosphere. After stirring overnight at the same temperature, the reaction was quenched with saturated NaHCO₃ aq. and diluted with AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 95/5) to afford the title compound as a colorless oil in >99% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.23-7.42 (m, 5H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.90 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 10.5 Hz, 1H), 4.36 (s, 1H), 3.87 (s, 3H), 3.08 (d, *J* = 15.3 Hz, 1H), 2.57 (d, *J* = 15.3 Hz, 1H), 1.36 (s, 3H), 1.04 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 156.9, 148.9, 138.8, 137.4, 128.2, 128.0, 127.5, 125.4, 111.4,

93.8, 87.2, 73.8, 56.8, 46.2, 43.7, 28.1, 22.8; **IR (neat)** 2955, 2927, 1497, 1465, 1434, 1271, 1256, 1064 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_2\text{INa}$: m/z 431.0478 ($[\text{M}+\text{Na}]^+$), found: m/z 431.0481 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = +116.8$ ($c = 0.4$, CHCl_3).

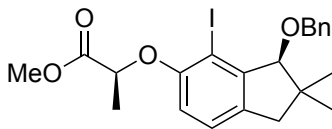
(S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-ol (6)



To a suspension of NaH (60% in mineral oil, 16 mmol, 0.65 g) in DMF (10 mL) was added dropwise *tert*-dodecanethiol (14.8 mmol, 3.48 mL) at 0 °C under Ar atmosphere. After stirring for 5 min at the same temperature, the solution of **1a** (7.38 mmol, 3.02 g) in DMF (20 mL) was added to the reaction at the same temperature. After the addition, the reaction was thoroughly degassed under reduced pressure for 20 min at the same temperature, followed by the refilling of Ar gas. The reaction was warmed up to 130 °C and stirred for 70 min at the same temperature. After that, the reaction was cooled down to 0 °C, and saturated NH_4Cl aq. and AcOEt were added. Two layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 95/5 to 80/20) to afford the title compound as a white solid in 86% yield.

^1H NMR (500 MHz, CDCl_3) δ 7.27-7.41 (m, 5H), 6.99 (d, $J = 8.2$ Hz, 1H), 6.87 (d, $J = 7.9$ Hz, 1H), 5.27 (s, 1H), 4.83 (d, $J = 10.5$ Hz, 1H), 4.73 (d, $J = 10.5$ Hz, 1H), 4.31 (s, 3H), 3.04 (d, $J = 15.3$ Hz, 1H), 2.58 (d, $J = 15.3$ Hz, 1H), 1.35 (s, 3H), 1.08 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 153.7, 147.3, 138.6, 137.1, 128.4, 128.1, 127.8, 126.2, 115.4, 94.0, 86.6, 73.8, 46.5, 43.9, 28.5, 23.0; **IR (neat)** 3317, 3030, 2954, 2925, 2867, 1454, 1286, 1065 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_2\text{INa}$: m/z 417.0322 ($[\text{M}+\text{Na}]^+$), found: m/z 417.0326 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{24} = +106.0$ ($c = 1.0$, CHCl_3).

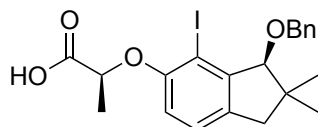
Methyl (S)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanoate (2e)



To a stirred solution of **6** (6.21 mmol, 2.45 g) in THF (20 mL) were added methyl (*R*)-lactate (9.3 mmol, 0.89 mL) and PPh₃ (9.32 mmol, 2.44 g) at 0 °C under Ar atmosphere. To this solution was added dropwise DIAD (9.3 mmol, 1.8 mL). After stirring overnight at 0 °C to room temperature, THF was removed under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 95/5 to 80/20) to afford the title compound as a colorless oil in 92% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.41-7.43 (m, 2H), 7.29-7.32 (m, 2H), 7.23-7.25 (m, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 10.5 Hz, 1H), 4.70 (q, *J* = 6.8 Hz, 1H), 4.35 (s, 1H), 3.76 (s, 3H), 3.06 (d, *J* = 15.3 Hz, 1H), 2.56 (d, *J* = 15.6 Hz, 1H), 1.69 (d, *J* = 6.8 Hz, 3H), 1.36 (s, 3H), 1.04 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 172.5, 155.7, 149.3, 138.8, 138.7, 128.4, 128.2, 127.7, 125.5, 114.7, 94.0, 89.0, 75.1, 74.1, 52.4, 46.4, 43.8, 28.3, 23.0, 18.9; **IR (neat)** 2953, 1756, 1737, 1455, 1317, 1272, 1253, 1126 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₂H₂₅O₄INa: *m/z* 503.0690 ([M+Na]⁺), found: *m/z* 503.0688 ([M+Na]⁺); **Optical rotation** [α]_D²⁵ = +79.8 (*c* = 1.3, CHCl₃).

(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanoic acid (11)

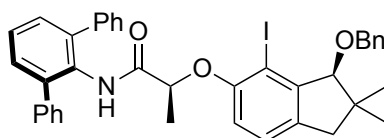


To a stirred solution of **2e** (5.54 mmol, 2.66 g) in THF (10 mL) and MeOH (10 mL) was added 2 N NaOH aq. (10 mL) at 0 °C. After stirring for 3 hours at 0 °C to room temperature, 1 N HCl aq. and AcOEt were added. Two layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The crude material was pure enough to be used for next step without further purification.

¹H NMR (500 MHz, CDCl₃) δ 7.41-7.43 (m, 2H), 7.30-7.33 (m, 2H), 7.27-7.24 (m, 1H),

7.05 (d, $J = 8.2$ Hz, 1H), 6.68 (d, $J = 8.2$ Hz, 1H), 4.91 (d, $J = 10.5$ Hz, 1H), 4.80 (q, $J = 6.8$ Hz, 1H), 4.78 (d, $J = 10.5$ Hz, 1H), 4.35 (s, 1H), 3.08 (d, $J = 15.6$ Hz, 1H), 2.59 (d, $J = 15.6$ Hz, 1H), 1.71 (d, $J = 6.8$ Hz, 3H), 1.37 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.7, 155.0, 149.4, 139.1, 138.7, 128.4, 128.2, 127.7, 125.6, 114.6, 94.0, 88.9, 74.5, 74.2, 46.4, 43.8, 28.3, 23.0, 18.6; **IR** (neat) 2963, 2924, 2872, 1729, 1463, 1319, 1138, 1126 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{21}\text{H}_{23}\text{O}_4\text{INa}$: m/z 489.0533 ($[\text{M}+\text{Na}]^+$), found: m/z 489.0537 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{25} = +104.5$ ($c = 1.1$, CHCl_3).

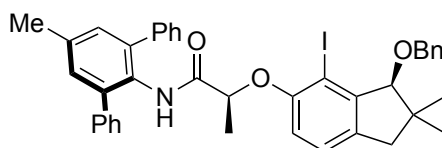
(S)-N-([1,1':3',1''-Terphenyl]-2'-yl)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanamide (3c)



To stirred solution of **11** (0.50 mmol, 0.23 g) in CH_2Cl_2 (15 mL) was added catalytic amount of DMF (4 drops) at 0 °C under Ar atmosphere, followed by the drop of oxalyl chloride (0.60 mmol, 52 μL) at the same temperature. After stirring for 20 min, [1,1':3',1''-terphenyl]-2'-amine (1.2 mmol, 0.31 g) was added to the reaction in one portion at the same temperature. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 N HCl aq., and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: CH_2Cl_2 only) to afford the title compound as a white solid in 77% yield.

^1H NMR (500 MHz, CDCl_3) δ 8.20 (s, 1H), 7.47-7.23 (m, 18H), 6.92 (d, $J = 7.9$ Hz, 1H), 6.32 (d, $J = 8.2$ Hz, 1H), 4.86 (d, $J = 10.5$ Hz, 1H), 4.73 (d, $J = 10.2$ Hz, 1H), 4.40 (q, $J = 6.6$ Hz, 1H), 4.29 (s, 1H), 3.03 (d, $J = 15.3$ Hz, 1H), 2.57 (d, $J = 15.3$ Hz, 1H), 1.35 (s, 3H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.1, 154.2, 149.0, 141.1, 139.7, 138.7, 138.6, 130.7, 130.1, 129.1, 128.4, 128.3, 128.2, 127.8, 127.8, 127.4, 125.8, 114.1, 93.9, 88.7, 76.4, 74.2, 46.4, 43.9, 28.4, 23.0, 18.0; **IR** (neat) 1662, 1527, 1497, 1456, 1284, 1271, 1248, 1092 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{39}\text{H}_{36}\text{O}_3\text{NINa}$: m/z 716.1632 ($[\text{M}+\text{Na}]^+$), found: m/z 716.1627 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{26} = +59.7$ ($c = 1.0$, CHCl_3).

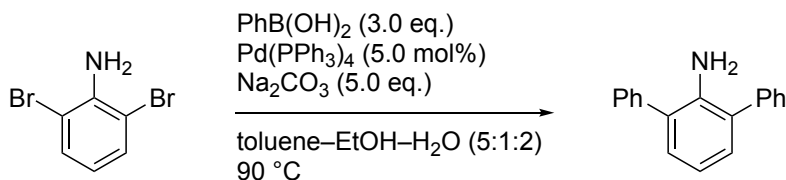
(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)propenamide (3d)



To stirred solution of **11** (0.50 mmol, 0.23 g) in CH₂Cl₂ (15 mL) was added catalytic amount of DMF (4 drops) at 0 °C under Ar atmosphere, followed by the drop of oxalyl chloride (0.60 mmol, 52 µL) at the same temperature. After stirring for 20 min, 5'-methyl-[1,1':3',1''-terphenyl]-2'-amine (1.2 mmol, 0.32 g) was added to the reaction in one drop at the same temperature. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 N HCl aq. and two layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: CH₂Cl₂ only) to afford the title compound as a white solid in 83% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.13 (s, 1H), 7.26-7.42 (m, 15H), 7.20 (s, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.31 (d, *J* = 7.9 Hz, 1H), 4.86 (d, *J* = 10.5 Hz, 1H), 4.74 (d, *J* = 10.2 Hz, 1H), 4.40 (q, *J* = 6.7 Hz, 1H), 4.29 (s, 1H), 3.03 (d, *J* = 15.6 Hz, 1H), 2.57 (d, *J* = 15.3 Hz, 1H), 2.42 (s, 3H), 1.35 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.4, 154.2, 149.0, 140.9, 139.8, 138.7, 138.5, 137.6, 130.8, 129.1, 128.4, 128.3, 128.2, 128.0, 127.8, 127.3, 125.8, 114.1, 93.9, 88.7, 76.5, 74.2, 46.4, 43.8, 28.4, 23.0, 21.2, 18.0; **IR (neat)** 3244, 1663, 1599, 1533, 1456, 1251, 1093, 1069 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₄₀H₃₈O₃NINa: *m/z* 730.1789 ([M+Na]⁺), found: *m/z* 730.1783 ([M+Na]⁺); **Optical rotation** [α]_D²⁶ = +57.1 (*c* = 1.2, CHCl₃).

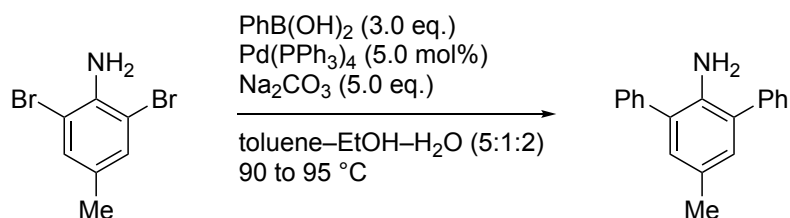
[1,1':3',1''-Terphenyl]-2'-amine



The title compound was prepared according to the literature procedure.²² To a mixture of 2,6-dibromoaniline (20.0 mmol, 5.02 g), phenylboronic acid (60.0 mmol, 7.32 g) and Na₂CO₃ (100 mmol, 10.6 g) were added toluene (50 mL), EtOH (10 mL) and H₂O (20

mL) at room temperature under Ar atmosphere. The suspension was degassed under reduced pressure, followed by the refilling of Ar gas. After that, Pd(PPh₃)₄ (1.00 mmol, 1.16 g) was added to the suspension. After stirring for 9 hours at 90 °C, the organic layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was filtered through celite pad, and evaporated. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 100/0 to 60/40) to afford the title compound as a white solid in 95% yield. The spectral data matched with those reported in the literature.²²

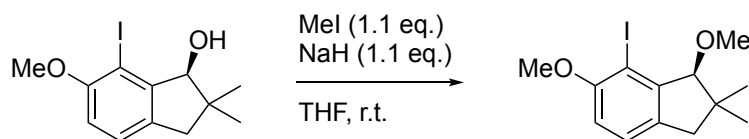
5'-Methyl-[1,1':3',1''-terphenyl]-2'-amine



To a mixture of 2,6-dibromo-4-methylaniline (10.0 mmol, 2.65 g), phenylboronic acid (30.0 mmol, 3.66 g) and Na₂CO₃ (50 mmol, 5.3 g) were added toluene (25 mL), EtOH (5 mL) and H₂O (10 mL) at room temperature under Ar atmosphere. The suspension was degassed under reduced pressure, followed by the refilling of Ar gas. After that, Pd(PPh₃)₄ (0.50 mmol, 0.58 g) was added to the suspension. After stirring for 38 hours at 90 to 95 °C, the organic layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was filtered through celite pad, and evaporated. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 100/0 to 50/50) to afford the title compound as a white solid in 95% yield. The spectral data matched with those reported in the literature.²³

2.4.4 Preparation of other catalysts

(S)-7-Iodo-1,6-dimethoxy-2,2-dimethyl-2,3-dihydro-1H-indene (1b)

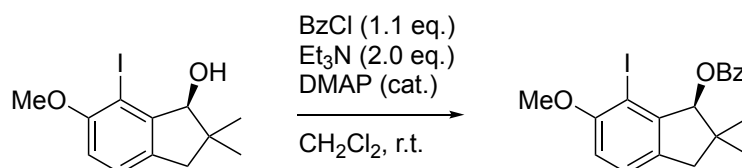


To a stirred solution of **5** (0.100 mmol, 31.8 mg) in THF (0.5 mL) were added NaH (0.11

mmol, 4.4 mg) and MeI (0.11 mmol, 6.9 μ L) at room temperature under Ar atmosphere. After stirring for 60 min at the same temperature, the reaction was quenched with saturated NaHCO₃ aq. and diluted with AcOEt. Two layers were separated, and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 85/15 to 65/35) to afford the title compound as a colorless oil in >99% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.05 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 4.07 (s, 1H), 3.86 (s, 3H), 3.62 (s, 3H), 3.01 (d, J = 15.3 Hz, 1H), 2.54 (d, J = 15.3 Hz, 1H), 1.28 (s, 3H), 1.00 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 157.1, 148.8, 137.2, 125.5, 111.6, 95.3, 87.2, 60.1, 56.9, 46.1, 43.6, 28.1, 22.5; **IR (neat)** 2954, 2926, 2823, 1463, 1434, 1271, 1255, 1124 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₃H₁₇O₂INa: m/z 355.0165 ([M+Na]⁺), found: m/z 355.0176 ([M+Na]⁺); **Optical rotation** $[\alpha]_D^{31}$ = +35.1 (c = 1.4, CHCl₃).

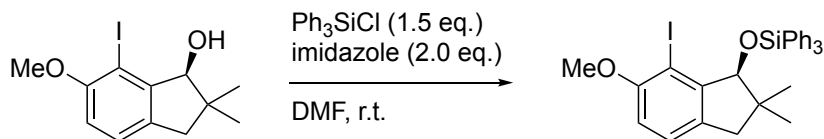
(S)-7-Iodo-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-yl benzoate (1c)



To a stirred solution of **5** (0.100 mmol, 31.8 mg) in CH₂Cl₂ (1 mL) were added catalytic amount of DMAP, Et₃N (0.20 mmol, 28 μ L) and BzCl (0.11 mmol, 13 μ L) at room temperature under Ar atmosphere. After stirring for 65 hours at the same temperature, the solvent was removed under reduced pressure. The residue was purified by PLC (eluent: hexane/AcOEt = 3/1) to afford the title compound as a white solid in 37% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, J = 7.4 Hz, 2H), 7.52-7.55 (m, 1H), 7.40 (t, J = 7.8 Hz, 2H), 7.15 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.07 (s, 1H), 3.88 (s, 3H), 3.09 (d, J = 15.6 Hz, 1H), 2.74 (d, J = 15.6 Hz, 1H), 1.20 (s, 3H), 1.17 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 166.3, 157.4, 146.2, 138.1, 132.9, 130.2, 130.0, 128.4, 125.4, 112.1, 87.8, 86.6, 56.9, 46.5, 43.1, 27.7, 22.8; **IR (neat)** 2959, 2837, 1717, 1467, 1435, 1265, 1105, 1067 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₉H₁₉O₃INa: m/z 445.0271 ([M+Na]⁺), found: m/z 445.0276 ([M+Na]⁺); **Optical rotation** $[\alpha]_D^{31}$ = +35.2 (c = 1.4, CHCl₃).

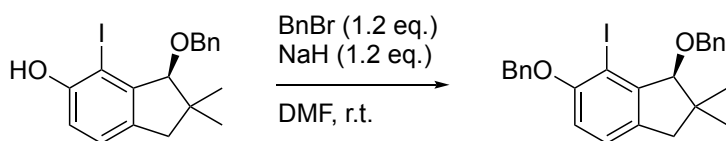
(S)-((7-Iodo-6-methoxy-2,2-dimethyl-2,3-dihydro-1*H*-inden-1-yl)oxy)triphenylsilane (1d)



To a stirred solution of **5** (0.300 mmol, 95.4 mg) in DMF (1 mL) were added imidazole (0.600 mmol, 40.8 mg) and Ph₃SiCl (0.450 mmol, 133 mg) at room temperature under Ar atmosphere. After stirring for 14 hours at the same temperature, the reaction was quenched with H₂O and diluted with AcOEt. Two layers were separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 100/0 to 80/20) to afford the title compound as a white solid in 61% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.62-7.64 (m, 6H), 7.37-7.40 (m, 3H), 7.30-7.33 (m, 6H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.64 (s, 1H), 3.84 (s, 3H), 3.26 (d, *J* = 14.7 Hz, 1H), 2.53 (d, *J* = 14.7 Hz, 1H), 1.10 (s, 3H), 0.71 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 156.8, 151.1, 137.8, 136.0, 135.3, 129.7, 127.6, 125.6, 111.2, 89.3, 87.1, 57.0, 45.5, 44.9, 26.4, 23.7; **IR (neat)** 3068, 2956, 2836, 1461, 1428, 1114, 1055, 1028 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₃₀H₂₉O₂INaSi: *m/z* 599.0874 ([M+Na]⁺), found: *m/z* 599.0883 ([M+Na]⁺); **Optical rotation** [α]_D³¹ = +31.4 (*c* = 1.0, CHCl₃).

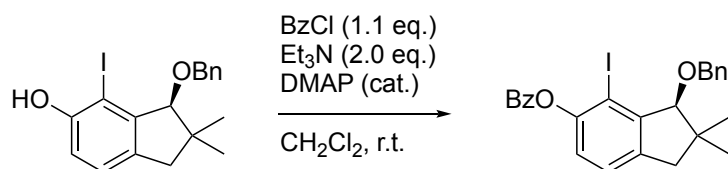
(S)-1,6-Bis(benzyloxy)-7-iodo-2,2-dimethyl-2,3-dihydro-1*H*-indene (2a)



To a stirred solution of **6** (0.300 mmol, 118 mg) in DMF (1 mL) were added NaH (60% in mineral oil, 0.36 mmol, 14 mg) and BnBr (0.36 mmol, 43 μL) at room temperature under Ar atmosphere. After stirring for 36 hours at the same temperature, the reaction was quenched with saturated NH₄Cl aq. and diluted with AcOEt. Two layers were separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 100/0 to 70/30) to afford the title compound as a colorless oil in 80% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.51-7.52 (m, 2H), 7.37-7.43 (m, 4H), 7.23-7.33 (m, 4H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.12 (s, 2H), 4.91 (d, *J* = 10.5 Hz, 1H), 4.77 (d, *J* = 10.5 Hz, 1H), 4.38 (s, 1H), 3.07 (d, *J* = 15.3 Hz, 1H), 2.56 (d, *J* = 15.3 Hz, 1H), 1.36 (s, 3H), 1.04 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 156.3, 149.2, 139.0, 137.9, 137.0, 128.7, 128.4, 128.2, 128.0, 127.7, 127.2, 125.6, 113.5, 94.0, 88.3, 74.1, 71.6, 46.4, 43.9, 28.3, 23.1; **IR (neat)** 3030, 2953, 2865, 1497, 1449, 1380, 1271, 1254 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₅H₂₅O₂INa: *m/z* 507.0791 ([M+Na]⁺), found: *m/z* 507.0799 ([M+Na]⁺); **Optical rotation** [α]_D³¹ = +97.7 (*c* = 1.7, CHCl₃).

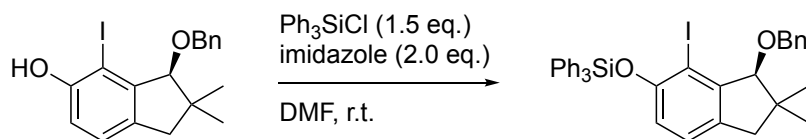
(S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl benzoate (2b)



To a stirred solution of **6** (0.300 mmol, 118 mg) in CH₂Cl₂ (1 mL) were added catalytic amount of DMAP, Et₃N (0.45 mmol, 63 μL) and BzCl (0.36 mmol, 42 μL) at room temperature under Ar atmosphere. After stirring for 36 hours at the same temperature, the reaction was quenched with saturated NH₄Cl aq. and diluted with CH₂Cl₂. Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 85/15) to afford the title compound as a colorless oil in >99% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.28 (m, 2H), 7.63-7.67 (m, 1H), 7.53 (m, 2H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.24-7.32 (m, 3H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 4.90 (d, *J* = 10.5 Hz, 1H), 4.77 (d, *J* = 10.5 Hz, 1H), 4.39 (s, 1H), 3.14 (d, *J* = 15.6 Hz, 1H), 2.65 (d, *J* = 15.6 Hz, 1H), 1.38 (s, 3H), 1.10 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 164.7, 150.0, 149.1, 142.7, 138.7, 133.9, 130.6, 129.5, 128.8, 128.5, 128.2, 127.8, 125.8, 123.3, 93.8, 91.6, 74.2, 46.7, 44.0, 28.4, 23.0; **IR (neat)** 3030, 2955, 1739, 1601, 1450, 1262, 1218, 1056 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₅H₂₃O₃INa: *m/z* 521.0584 ([M+Na]⁺), found: *m/z* 521.0594 ([M+Na]⁺); **Optical rotation** [α]_D³¹ = +93.6 (*c* = 1.7, CHCl₃).

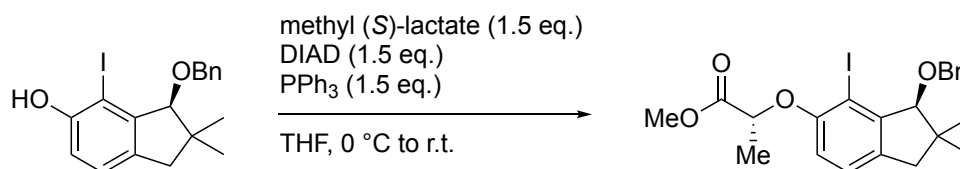
(S)-((3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)triphenylsilane (2c)



To a stirred solution of **6** (0.300 mmol, 118 mg) in DMF (1 mL) were added imidazole (0.600 mmol, 40.8 mg) and Ph_3SiCl (0.450 mmol, 133 mg) at room temperature under Ar atmosphere. After stirring for 36 hours at the same temperature, the reaction was quenched with H_2O and diluted with AcOEt. Two layers were separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/ CH_2Cl_2 = 100/0 to 70/30) to afford the title compound as a white solid in 73% yield.

^1H NMR (500 MHz, CDCl_3) δ 7.72-7.74 (m, 6H), 7.35-7.45 (m, 11H), 7.29-7.32 (m, 2H), 7.24-7.25 (m, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 4.82 (d, J = 10.5 Hz, 1H), 4.68 (d, J = 10.5 Hz, 1H), 4.32 (s, 1H), 3.02 (d, J = 15.3 Hz, 1H), 2.49 (d, J = 15.3 Hz, 1H), 1.33 (s, 3H), 1.01 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 153.5, 149.0, 139.0, 138.2, 135.9, 133.5, 130.6, 128.5, 128.3, 128.2, 127.8, 125.4, 119.4, 94.2, 91.9, 73.8, 46.6, 43.9, 28.4, 23.1; **IR (neat)** 3068, 2954, 1455, 1428, 1279, 1258, 1116, 1104 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{36}\text{H}_{33}\text{O}_2\text{INaSi}$: m/z 675.1187 ($[\text{M}+\text{Na}]^+$), found: m/z 675.1194 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{31} = +55.1$ (c = 1.1, CHCl_3).

Methyl (R)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy) propanoate (2d)

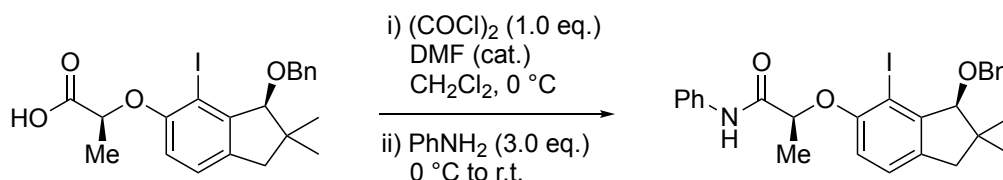


To a stirred solution of **6** (0.100 mmol, 39.4 mg) in THF (0.5 mL) were added methyl (*S*)-lactate (0.150 mmol, 14.3 μL) and PPh_3 (0.150 mmol, 39.3 mg) at 0 °C under Ar atmosphere. To this solution was added dropwise DIAD (0.150 mmol, 29.4 μL). After stirring overnight at 0 °C to room temperature, THF was removed under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 10/1) to

afford the title compound as a colorless oil in 75% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.39-7.43 (m, 2H), 7.29-7.32 (m, 2H), 7.24-7.28 (m, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 4.90 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 10.5 Hz, 1H), 4.71 (q, *J* = 6.8 Hz, 1H), 4.36 (s, 1H), 3.75 (s, 3H), 3.07 (d, *J* = 15.3 Hz, 1H), 2.56 (d, *J* = 15.3 Hz, 1H), 1.69 (d, *J* = 6.8 Hz, 3H), 1.36 (s, 3H), 1.03 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 172.5, 155.5, 149.3, 138.8, 138.7, 128.4, 128.2, 127.6, 125.5, 114.3, 93.9, 88.9, 75.0, 74.0, 52.5, 46.3, 43.8, 28.2, 22.9, 18.8; **IR** (neat) 2954, 1759, 1738, 1456, 1283, 1272, 1095, 1066 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₂H₂₅O₄INa: *m/z* 503.0690 ([M+Na]⁺), found: *m/z* 503.0694 ([M+Na]⁺); **Optical rotation** [α]_D³¹ = +77.3 (*c* = 2.8, CHCl₃).

(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-phenylpropanamide (2f)

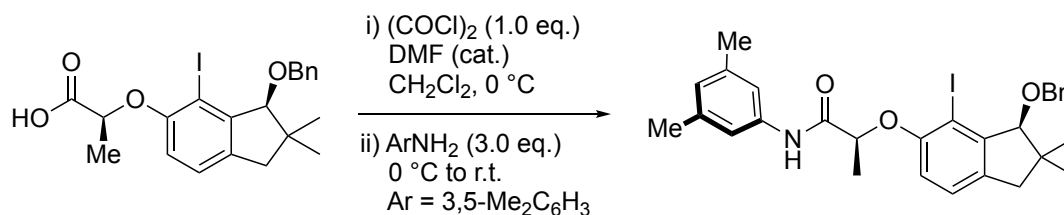


To stirred solution of **11** (0.50 mmol, 0.23 g) in CH₂Cl₂ (5 mL) was added catalytic amount of DMF (3 drops) at 0 °C under Ar atmosphere, followed by the drop of oxalyl chloride (0.50 mmol, 43 μL) at the same temperature. After stirring for 30 min, PhNH₂ (1.50 mmol, 137 μL) was added to the reaction at the same temperature. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 *N* HCl aq. and two layers were separated. Aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 75/25) to afford the title compound as a colorless oil in 77% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 7.66-7.68 (m, 2H), 7.42-7.44 (m, 2H), 7.31-7.37 (m, 4H), 7.25-7.28 (m, 1H), 7.12-7.18 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.86 (q, *J* = 6.7 Hz, 1H), 4.79 (d, *J* = 10.2 Hz, 1H), 4.38 (s, 1H), 3.08 (d, *J* = 15.6 Hz, 1H), 2.60 (d, *J* = 15.3 Hz, 1H), 1.70 (d, *J* = 6.5 Hz, 3H), 1.38 (s, 3H), 1.07 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 169.5, 154.0, 149.4, 139.0, 138.7, 137.7, 129.3, 128.5, 128.2, 127.9, 126.1, 124.8, 120.0, 113.9, 93.9, 88.8, 76.4, 74.3, 46.4, 44.0, 28.4, 23.0, 18.5; **IR** (neat) 3372, 2955, 1689, 1599, 1529, 1498,

1442, 1067 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{27}\text{H}_{28}\text{O}_3\text{NINa}$: m/z 564.1006 ($[\text{M}+\text{Na}]^+$), found: m/z 564.1017 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{31} = +149.6$ ($c = 1.9$, CHCl_3).

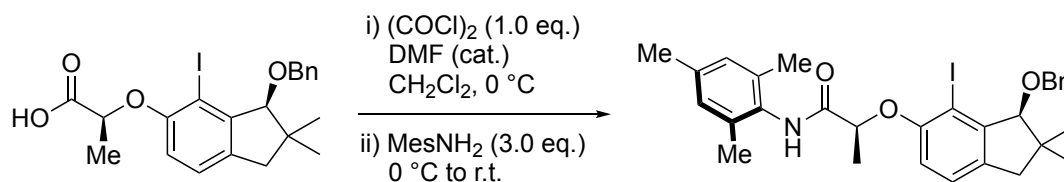
(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(3,5-dimethylphenyl)propanamide (3a)



To stirred solution of **11** (0.50 mmol, 0.23 g) in CH_2Cl_2 (5 mL) was added catalytic amount of DMF (3 drops) at $0\text{ }^\circ\text{C}$ under Ar atmosphere, followed by the drop of oxalyl chloride (0.50 mmol, 43 μL) at the same temperature. After stirring for 30 min, 3,5- $\text{Me}_2\text{C}_6\text{H}_3\text{NH}_2$ (1.50 mmol, 187 μL) was added to the reaction at the same temperature. After stirring overnight at $0\text{ }^\circ\text{C}$ to room temperature, the reaction was quenched with 1 *N* HCl aq. and two layers were separated. Aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 75/25) to afford the title compound as a colorless oil in 36% yield.

^1H NMR (500 MHz, CDCl_3) δ 8.74 (s, 1H), 7.43 (d, $J = 7.7$ Hz, 2H), 7.27-7.34 (m, 5H), 7.07 (d, $J = 7.9$ Hz, 1H), 6.79 (s, 1H), 6.71 (d, $J = 7.9$ Hz, 1H), 4.92 (d, $J = 10.5$ Hz, 1H), 4.84 (q, $J = 6.7$ Hz, 1H), 4.80 (d, $J = 10.5$ Hz, 1H), 4.38 (s, 1H), 3.08 (d, $J = 15.3$ Hz, 1H), 2.60 (d, $J = 15.3$ Hz, 1H), 2.32 (s, 6H), 1.69 (d, $J = 6.5$ Hz, 3H), 1.38 (s, 3H), 1.07 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 169.5, 154.0, 149.4, 139.0, 138.9, 138.7, 137.4, 128.5, 128.2, 127.8, 126.5, 126.0, 117.7, 113.9, 93.9, 88.8, 76.5, 74.2, 46.4, 43.9, 28.3, 23.0, 21.6, 18.5; **IR (neat)** 3375, 2954, 1689, 1612, 1539, 1454, 1268, 1062 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{29}\text{H}_{32}\text{O}_3\text{NINa}$: m/z 592.1319 ($[\text{M}+\text{Na}]^+$), found: m/z 592.1329 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{31} = +178.0$ ($c = 1.7$, CHCl_3).

(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-mesitylpropanamide (3b)

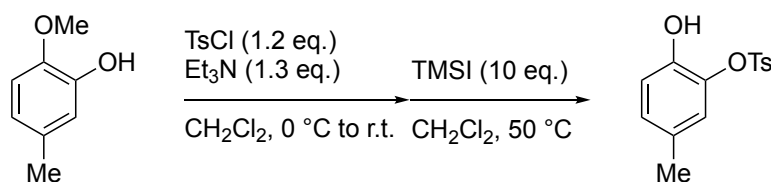


To stirred solution of **11** (0.50 mmol, 0.23 g) in CH_2Cl_2 (5 mL) was added catalytic amount of DMF (3 drops) at 0 °C under Ar atmosphere, followed by the drop of oxalyl chloride (0.50 mmol, 43 μL) at the same temperature. After stirring for 30 min, MesNH_2 (1.50 mmol, 211 μL) was added to the reaction at the same temperature. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 N HCl aq., and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 75/25) to afford the title compound as a white solid in 76% yield.

^1H NMR (500 MHz, CDCl_3) δ 8.06 (s, 1H), 7.41-7.42 (m, 2H), 7.24-7.33 (m, 3H), 7.08 (d, J = 8.2 Hz, 1H), 6.89 (s, 2H), 6.77 (d, J = 8.2 Hz, 1H), 4.95 (q, J = 6.7 Hz, 1H), 4.90 (d, J = 10.5 Hz, 1H), 4.78 (d, J = 10.5 Hz, 1H), 4.36 (s, 1H), 3.09 (d, J = 15.3 Hz, 1H), 2.59 (d, J = 15.6 Hz, 1H), 2.26 (s, 3H), 2.13 (s, 6H), 1.75 (d, J = 6.8 Hz, 3H), 1.38 (s, 3H), 1.05 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 170.2, 154.1, 149.6, 138.9, 138.7, 137.2, 135.3, 130.5, 129.2, 128.5, 128.2, 127.8, 126.0, 113.7, 93.9, 88.7, 76.3, 74.2, 46.4, 44.0, 28.3, 23.0, 21.2, 19.0, 18.5; **IR (neat)** 3376, 2954, 2926, 2866, 1693, 1498, 1456, 1252 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{30}\text{H}_{34}\text{O}_3\text{NINa}$: m/z 606.1476 ($[\text{M}+\text{Na}]^+$), found: m/z 606.1484 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{31} = +146.8$ (c = 1.1, CHCl_3).

2.4.5 Preparation of substrates

2-Hydroxy-5-methylphenyl 4-methylbenzenesulfonate (7d)

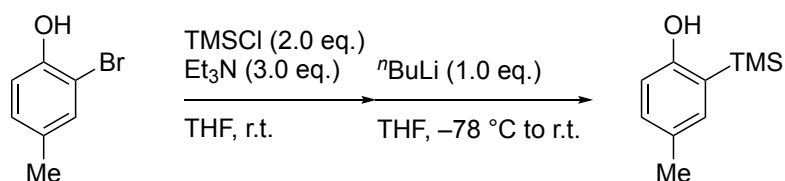


To a stirred solution of 2-methoxy-5-methylphenol (3.0 mmol, 0.41 g) in CH_2Cl_2 (5 mL)

were added Et₃N (3.9 mmol, 0.54 mL) and TsCl (3.6 mmol, 0.69 g) at 0 °C. After stirring for 3.5 hours at 0 °C to room temperature, the reaction was quenched by the addition of 1 N HCl aq. and two layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/acetone = 83/17) to afford 2-methoxy-5-methylphenyl 4-methylbenzenesulfonate as a white solid in 97% yield. To stirred solution of 2-methoxy-5-methylphenyl 4-methylbenzenesulfonate (2.0 mmol, 0.58 g) in CH₂Cl₂ (5 mL) in a sealed tube was added TMSI (20 mmol, 2.7 mL) at 0 °C. After stirring for 11 hours at 50 °C (bath temperature), the reaction was cooled down to 0 °C, and H₂O was added slowly. Two layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/acetone = 70/30) to afford the title compound as a white solid in 98% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.93 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 1.7 Hz, 1H), 5.71 (s, 1H), 2.46 (s, 3H), 2.16 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 146.2, 146.0, 136.8, 131.5, 130.7, 130.0, 129.1, 128.7, 123.6, 118.0, 21.8, 20.4; **IR (neat)** 3459, 1597, 1512, 1364, 1391, 1190, 1172, 1084 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₄H₁₃O₄S: *m/z* 277.0529 ([M-H]⁻), found: *m/z* 277.0539 ([M-H]⁻).

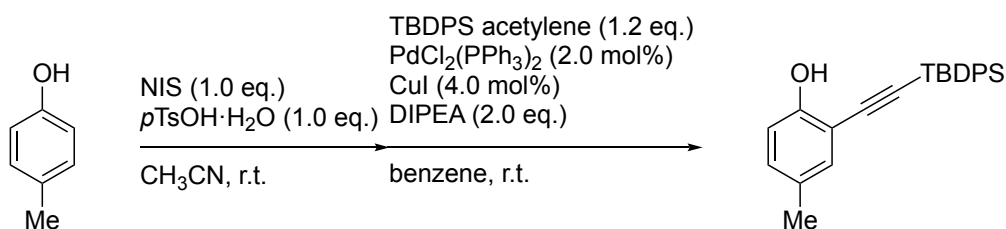
4-Methyl-2-(trimethylsilyl)phenol (7e)



To a stirred solution of 2-bromo-4-methylphenol (2.0 mmol, 0.24 mL) in THF (5 mL) were added Et₃N (0.60 mmol, 0.84 mL) and TMSCl (0.40 mmol, 0.51 mL) at room temperature under Ar atmosphere. After stirring for 8 hours at the same temperature, the solvent was removed under reduced pressure. The residue was filtered and evaporated under reduced pressure. To a stirred solution of the residue in THF (6 mL) was added ⁿBuLi (1.67 M in hexane, 1.95 mmol, 1.24 mL) at -78 °C under Ar atmosphere and the reaction was gradually warmed up to room temperature. After stirring for 2 hours at the

same temperature, the reaction was quenched with saturated NH_4Cl aq., and diluted with AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 25/1) to afford the title compound as a colorless oil in 79% yield. The spectral data matched with those reported in the literature.²⁴

2-((*tert*-Butyldiphenylsilyl)ethynyl)-4-methylphenol (7f)

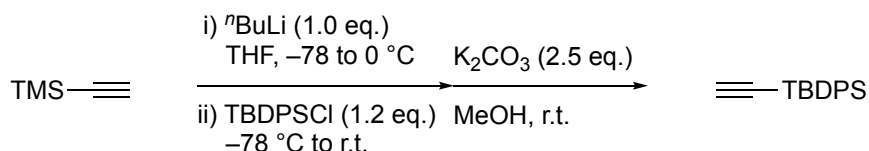


To a stirred solution of 4-methylphenol (10.0 mmol, 1.05 mL) in MeCN (10 mL) was added $p\text{TsOH}\cdot\text{H}_2\text{O}$ (10.0 mmol, 1.90 g) at room temperature. After stirring for 10 min at the same temperature, *N*-iodosuccinimide (10.0 mmol, 2.25 g) was added in one portion. After stirring for 24 hours at the same temperature, the reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ aq., and diluted with AcOEt. Two layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/ CH_2Cl_2 = 4/1) to afford the title compound as a white solid in 96% yield. To a stirred solution of 2-iodo-4-methylphenol (1.7 mmol, 0.40 g) in benzene (8 mL) were added *N,N*-diisopropylethylamine (3.4 mmol, 0.59 mL), (*tert*-butyldiphenylsilyl)acetylene (2.1 mmol, 0.54 g) and $\text{PdCl}_2(\text{PPh}_3)_2$ (34.0 μmol , 24.0 mg) at room temperature under Ar atmosphere. After stirring for 5 min at the same temperature, CuI (68.0 μmol , 13.0 mg) was added. After stirring overnight, the reaction was filtered through celite pad and evaporated. The residue was purified by column chromatography (eluent: hexane/ CH_2Cl_2 = 75/25 to 65/35) to afford the title compound as a white solid in 93% yield.

^1H NMR (500 MHz, CDCl_3) δ 7.81-7.83 (m, 4H), 7.38-7.45 (m, 6H), 7.27 (d, J = 1.7 Hz, 1H), 7.10 (dd, J = 8.5, 1.7 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 5.71 (s, 1H), 2.28 (s, 3H), 1.15 (s, 9H); **^{13}C NMR** (125 MHz, CDCl_3) δ 155.6, 135.7, 133.0, 132.1, 132.0, 129.9, 129.7, 128.1, 114.8, 109.2, 103.6, 97.4, 27.3, 20.5, 18.8; **IR** (neat) 3516, 2929, 2857,

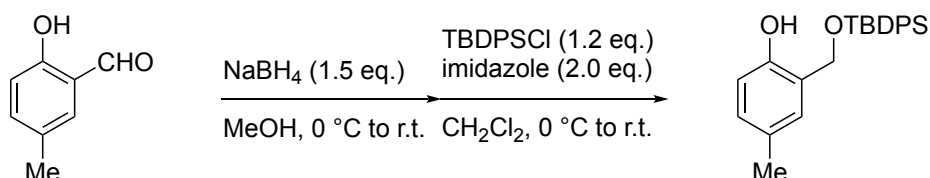
2142, 1492, 1470, 1428, 1391 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{25}\text{H}_{25}\text{OSi}$: m/z 369.1669 ($[\text{M}-\text{H}]^-$), found: m/z 369.1680 ($[\text{M}-\text{H}]^-$).

(*tert*-Butyldiphenylsilyl)acetylene



To stirred solution of (trimethylsilyl)acetylene (20 mmol, 2.8 mL) in THF (30 mL) was added $^n\text{BuLi}$ (2.5 M in hexane, 20 mmol, 8 mL) at -78°C under Ar atmosphere. After stirring for 5 min at the same temperature, TBDPSCI (23 mmol, 5.9 mL) was added to the reaction. After stirring overnight at -78°C to room temperature, the reaction was quenched with saturated NH_4Cl aq., and diluted with AcOEt. Two layers were separated and aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. To a stirred solution of the obtained crude material in MeOH (20 mL) was added K_2CO_3 (50 mmol, 6.9 g) at room temperature. After stirring for 80 min at the same temperature, the reaction was filtered and evaporated under reduced pressure. To the obtained filtrate was added H_2O , two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 95/5) to afford the title compound as a white solid in 33% yield. The spectral data matched with those reported in the literature.²⁵

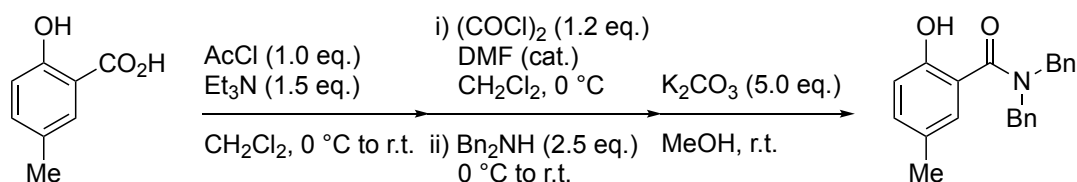
2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-methylphenol (7g)



To a stirred solution of 2-hydroxy-5-methylbenzaldehyde (3.2 mmol, 0.43 g) in MeOH (5 mL) was added NaBH_4 (4.8 mmol, 0.18 g) at 0°C . After stirring for 20 min at room temperature, MeOH was removed under reduced pressure. To the residue, saturated NH_4Cl aq. and AcOEt were added. Two layers were separated and aqueous layer was

extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude material was used for the next step without further purification. To stirred solution of 2-(hydroxymethyl)-4-methylphenol (1.0 mmol, 0.14 g) and imidazole (2.0 mmol, 0.14 g) in CH₂Cl₂ (4 mL) was added TBDPSCl (1.2 mmol, 0.31 mL) at 0 °C under Ar atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was quenched with H₂O. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt 95/5 to 90/10) to afford the title compound as a white solid in 55% yield. **¹H NMR** (500 MHz, CDCl₃) δ 7.91 (s, 1H), 7.67-7.69 (m, 4H), 7.44-7.48 (m, 2H), 7.38-7.41 (m, 4H), 6.98 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 1.7 Hz, 1H), 4.84 (s, 2H), 2.19 (s, 3H), 1.07 (s, 9H); **¹³C NMR** (125 MHz, CDCl₃) δ 154.2, 135.6, 132.0, 130.1, 129.4, 128.8, 127.9, 127.4, 123.5, 116.4, 66.7, 26.7, 20.37, 19.1; **IR (neat)** 3389, 2958, 2931, 2858, 1505, 1472, 1428, 1114 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₄H₂₇O₂Si: *m/z* 375.1775 ([M-H]⁻), found: *m/z* 375.1791 ([M-H]⁻).

***N,N*-Dibenzyl-2-hydroxy-5-methylbenzamide (7h)**

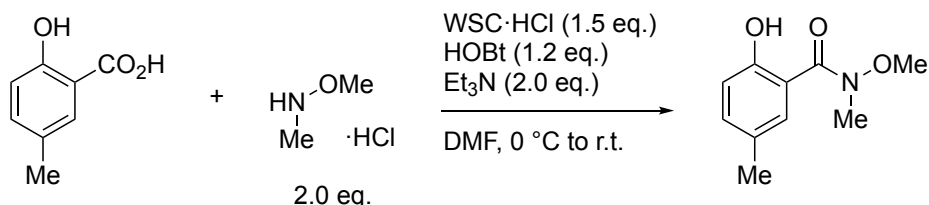


To stirred solution of 5-methylsalicylic acid (20.0 mmol, 3.04 g) in CH₂Cl₂ (20 mL) was added triethylamine (30 mmol, 4.2 mL) at 0 °C under Ar atmosphere. After stirring for 30 min at the same temperature, acetyl chloride (20 mmol, 1.4 mL) was added to the reaction at the same temperature and stirred overnight at room temperature. After that, the reaction was diluted with AcOEt. The organic phase was washed with 10 mL of 0.5 M HCl aq. (twice), H₂O, and brine. The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. To the residue, saturated NaHCO₃ aq. and AcOEt were added, and two layers were separated. To the aqueous layer, 1 N HCl aq. and AcOEt were added, and two layers were separated. The obtained organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to afford 2-acetoxy-5-methylbenzoic acid as a white solid in 66% yield. To a stirred solution of 2-acetoxy-5-

methylbenzoic acid (2.0 mmol, 0.39 g) in CH₂Cl₂ (10 mL) were added catalytic amount of DMF (10 drops) and (COCl)₂ (2.4 mmol, 0.21 mL) at 0 °C under Ar atmosphere. After stirring for 20 min at the same temperature, dibenzylamine (5.0 mmol, 0.96 mL) was added to the reaction at the same temperature. After stirring overnight at 0 °C to room temperature, MeOH (7 mL) and K₂CO₃ (10.0 mmol, 1.38 g) were added at room temperature. After stirring for 8 h at the same temperature, the reaction was acidified with 1N HCl aq. Two layers were separated and aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 75/25 to 0/100) to afford the title compound as a white solid in 55% yield.

¹H NMR (500 MHz, CDCl₃) δ 9.37 (s, 1H), 7.31-7.39 (m, 6H), 7.23-7.24 (m, 4H), 7.13 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 4.68 (s, 4H), 2.11 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 172.7, 156.4, 136.3, 133.5, 129.0, 128.1, 127.8, 127.7, 118.0, 117.6, 20.5; **IR (neat)** 3063, 3029, 1591, 1509, 1495, 1474, 1452, 1433 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₂H₂₀O₂N: *m/z* 330.1489 ([M-H]⁻), found: *m/z* 330.1504 ([M-H]⁻).

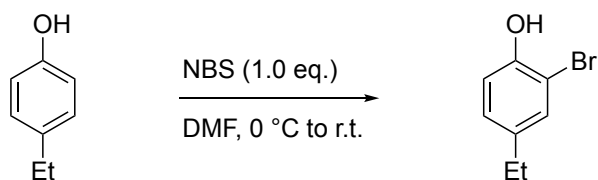
2-Hydroxy-*N*-methoxy-*N*,5-dimethylbenzamide (7i)



To a stirred solution of 2-hydroxy-5-methylbenzoic acid (5.0 mmol, 0.76 g) in DMF (15 mL) were added *N,O*-dimethylhydroxylamine hydrochloride (10 mmol, 0.98 g), WSC·HCl (7.50 mmol, 1.44 g), HOBT (6.0 mmol, 0.81 g) and Et₃N (10 mmol, 1.4 mL) at 0 °C under Ar atmosphere. After stirring for 2 days at 0 °C to room temperature, the reaction was quenched with H₂O and diluted with AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 94/6 to 51/49) to afford the title compound as an orange oil in 89% yield. The spectral data matched with those

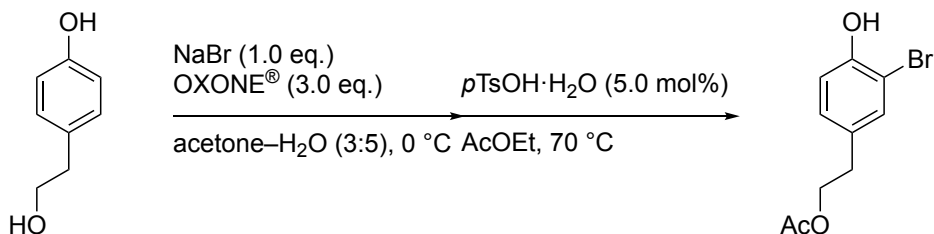
reported in the literature.²⁶

2-Bromo-4-ethylphenol (9a)



To a stirred solution of 4-ethylphenol (2.0 mmol, 0.24 g) in DMF (2 mL) was added *N*-bromosuccinimide (2.0 mmol, 0.36 g) at 0 °C under Ar atmosphere. After stirring for 15 h at 0 °C to room temperature, the reaction was quenched with saturated Na₂S₂O₃ aq. and diluted with AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 30/1) to afford the title compound as a white solid in 57% yield. The spectral data matched with those reported in the literature.²⁷

3-Bromo-4-hydroxyphenethyl acetate (9b)

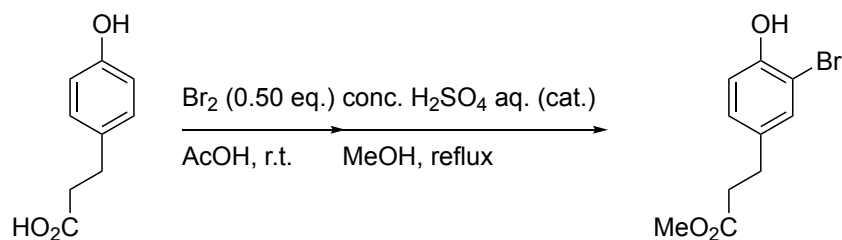


To a suspension of 4-(2-hydroxyethyl)phenol (20.0 mmol, 2.76 g) and NaBr (20.0 mmol, 2.06 g) in acetone (55 mL) was added dropwise the solution of OXONE[®] (60.0 mmol, 18.4 g) in H₂O (90 mL) at 0 °C over 90 min. After stirring for 90 min at the same temperature, the reaction was diluted with AcOEt and quenched with saturated Na₂S₂O₃ aq. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: CH₂Cl₂/MeOH = 20/1) to afford 2-bromo-4-(2-hydroxyethyl)phenol as a white solid in 86% yield. To a stirred solution of 2-bromo-4-(2-hydroxyethyl)phenol (5.00 mmol, 1.09 g) in AcOEt (15 mL) was added *p*-toluenesulfonic acid monohydrate (0.250 mmol, 47.6 mg) at room temperature. After stirring for 5 hours at 70 °C, the reaction was

cooled down to room temperature, and saturated NaHCO_3 aq. was added. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH} = 20/1$) to afford the title compound as a white solid in 84% yield.

^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, $J = 2.0$ Hz, 1H), 7.07 (dd, $J = 8.4, 2.1$ Hz, 1H), 6.95 (d, $J = 8.2$ Hz, 1H), 5.44 (s, 1H), 4.23 (t, $J = 6.9$ Hz, 2H), 2.85 (t, $J = 6.9$ Hz, 2H), 2.04 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 171.7, 151.5, 132.6, 131.2, 129.5, 116.3, 110.1, 65.1, 33.9, 21.1; **IR** (neat) 3368, 1715, 1609, 1578, 1508, 1497, 1240, 1032 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3\text{Br}$: m/z 256.9808 ($[\text{M}-\text{H}]^-$), found: m/z 256.9822 ($[\text{M}-\text{H}]^-$).

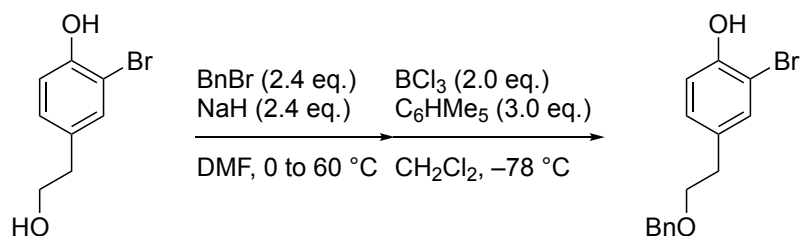
Methyl 3-(3-bromo-4-hydroxyphenyl)propanoate (9c)



To a stirred solution of 3-(4-hydroxyphenyl)propanoic acid (20.0 mmol, 3.32 g) in AcOH (30 mL) was slowly added bromine (10 mmol, 0.52 mL) in AcOH (40 mL) at room temperature over 50 min under Ar atmosphere. After stirring for 6 hours at the same temperature, the reaction was diluted with AcOEt, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: $\text{CHCl}_3/\text{MeOH} = 20/1$) to afford 3-(3-bromo-4-hydroxyphenyl)propanoic acid as a white solid in 46% yield. To a stirred solution of 3-(3-bromo-4-hydroxyphenyl)propanoic acid (3.0 mmol, 0.74 g) in MeOH (10 mL) was added conc. H_2SO_4 aq. (10 drops) at room temperature. After stirring overnight at 70 $^\circ\text{C}$ (jacket temperature), all volatiles were removed under reduced pressure, followed by the addition of saturated NaHCO_3 aq. and CH_2Cl_2 . Two layers were separated and aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 5/1) to afford the title compound as a white solid in >99% yield. The spectral data matched with those reported

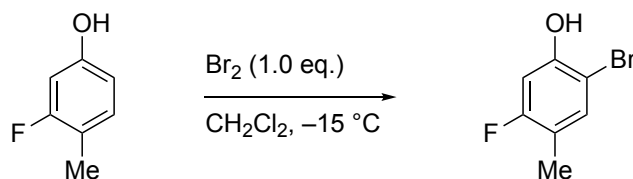
in the literature.²⁸

4-(2-(Benzyloxy)ethyl)-2-bromophenol (9d)



To a stirred solution of 2-bromo-4-(2-hydroxyethyl)phenol (1.0 mmol, 0.22 g) in DMF (3 mL) were added NaH (60% in mineral oil, 2.4 mmol, 96 mg) and BnBr (2.4 mmol, 0.29 mL) at 0 °C under Ar atmosphere. After stirring for 2 hours at 60 °C, the reaction was cooled down to room temperature, quenched with saturated NaHCO₃ aq., and diluted with AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 20/1) to afford 1-(benzyloxy)-4-(2-(benzyloxy)ethyl)-2-bromobenzene as a colorless oil in 97% yield. To a stirred solution of 1-(benzyloxy)-4-(2-(benzyloxy)ethyl)-2-bromobenzene (0.53 mmol, 0.21 g) and pentamethylbenzene (1.6 mmol, 0.24 g) in CH₂Cl₂ (10 mL) was added BCl₃ (1.0 M in hexanes, 1.1 mmol, 1.1 mL) at -78 °C under Ar atmosphere. After stirring for 20 min at the same temperature, the reaction was quenched with CHCl₃/MeOH mixture (10:1, 5.5 mL) at the same temperature, and gradually warmed up to room temperature. All volatiles were removed under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt=94/6 to 80/20) to afford the title compound as a colorless oil in 83% yield. **¹H NMR** (500 MHz, CDCl₃) δ 7.26-7.35 (m, 6H), 7.07 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 5.38 (s, 1H), 4.51 (s, 2H), 3.63 (t, *J* = 6.8 Hz, 2H), 2.83 (t, *J* = 6.9 Hz, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 150.9, 138.3, 132.8, 132.4, 129.8, 128.6, 127.8, 127.8, 116.1, 110.1, 73.2, 71.1, 35.2; **IR (neat)** 3254, 3030, 2863, 2360, 2341, 1495, 1454, 1090 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₅H₁₄O₂Br: *m/z* 305.0172 ([M-H]⁻), found: *m/z* 305.0187 ([M-H]⁻).

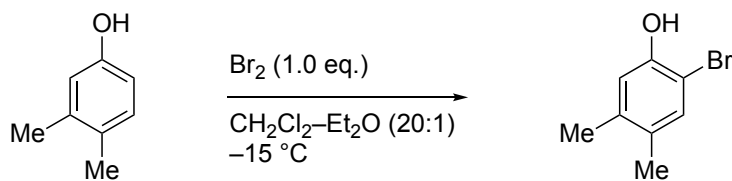
2-Bromo-5-fluoro-4-methylphenol (9e)



To a stirred solution 3-fluoro-4-methylphenol (5.0 mmol, 0.63 g) in CH_2Cl_2 (10 mL) was slowly added the solution of bromine (5.0 mmol, 0.26 mL) in CH_2Cl_2 (2.5 mL) at $-15\text{ }^\circ\text{C}$ (ice-salt bath) under Ar atmosphere. After stirring for 50 min at the same temperature, the reaction was quenched with 1 *N* Na_2SO_3 aq. Two layers were separated, and aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 25/1) to afford title compound as a colorless liquid in 90% yield.

^1H NMR (500 MHz, CDCl_3) δ 7.26 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 10.2 Hz, 1H), 5.40 (s, 1H), 2.18 (d, J = 1.1 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 161.1 (d, J = 246.6 Hz), 151.2 (d, J = 12.0 Hz), 133.4 (d, J = 7.3 Hz), 118.6 (d, J = 19.1 Hz), 104.1 (d, J = 3.6 Hz), 103.6 (d, J = 27.5 Hz), 13.7 (s); **^{19}F NMR** (466 MHz, CDCl_3) δ -115.4 (m); **IR (neat)** 3509, 1623, 1584, 1498, 1482, 1458, 1418, 1382, 1182 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_7\text{H}_5\text{OBrF}$: m/z 202.9502 ($[\text{M}-\text{H}]^-$), found: m/z 202.9507 ($[\text{M}-\text{H}]^-$).

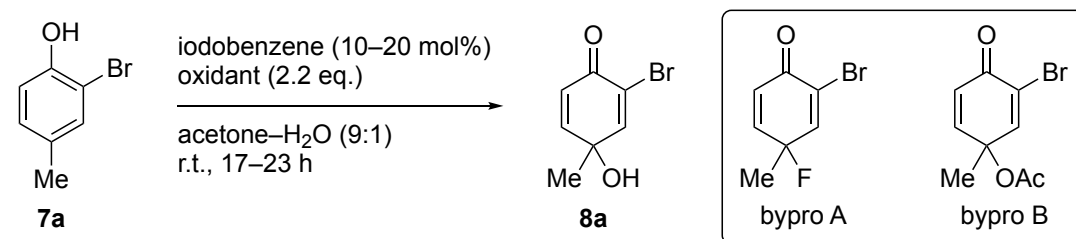
2-Bromo-4,5-dimethylphenol (9f)



To a stirred solution of 3,4-dimethylphenol (10.0 mmol, 1.22 g) in CH_2Cl_2 (60 mL) and diethylether (5 mL) was slowly added the solution of bromine (10 mmol, 0.52 mL) in CH_2Cl_2 (40 mL) at $0\text{ }^\circ\text{C}$ over 90 min. After the addition, the reaction was quenched with saturated Na_2CO_3 aq. Two layers were separated, and aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained white solid was recrystallized from hexane to afford title compound as a white solid in 44% yield. The spectral data matched with those reported in the literature.²⁹

2.4.6 Optimization of reaction conditions

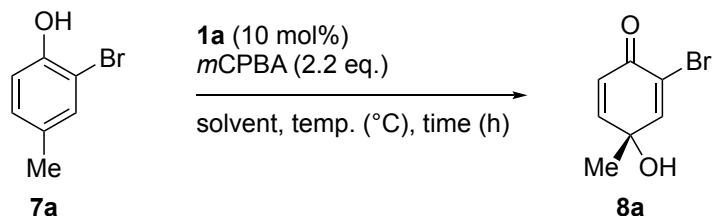
Table 2-4 Investigation of oxidants^a



Entry	Oxidant	Conv. (%)	Yield (%) ^b	Comment
1	OXONE [®]	<1	n.d.	-
2	(NH ₄) ₂ S ₂ O ₈	<1	n.d.	after 18 h, TFA was added.
3	NaBO ₃ •H ₂ O	<1	n.d.	-
4	TBHP	<1	n.d.	-
5	Selectfluor [®]	>99	55	bypro A (8% yield)
6	AcOOH	21	14	bypro B (2% yield)

^aReaction conditions: **7a** (0.165 mmol), oxidant (0.363 mmol), and iodobenzene in solvent (1.0 mL). ^bNMR yield.

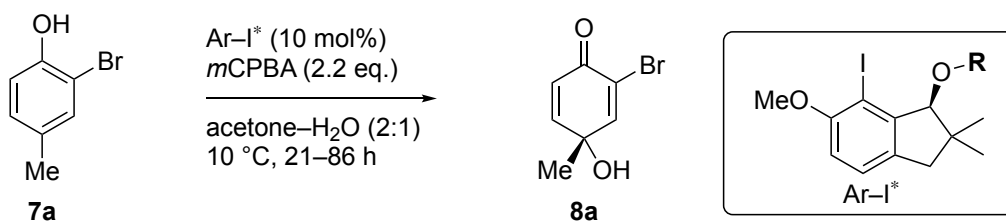
Table 2-5 Screening of solvent and reaction temperature^a



Entry	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b	Ee (%) ^c
1	acetone–H ₂ O (9:1)	r.t.	16	49	50
2	CH ₃ CN–H ₂ O (9:1)	r.t.	16	31	30
3	DME–H ₂ O (9:1)	r.t.	16	27	44
4	DMF–H ₂ O (9:1)	r.t.	16	5	68
5	Et ₂ O–H ₂ O (9:1)	r.t.	16	<1	-
6	acetone–H ₂ O (9:1)	10	21	51	54
7	acetone–H ₂ O (9:1)	0	60	31	63
8	acetone–H ₂ O (2:1)	10	21	73	59

^aReaction conditions: **7a** (0.165 mmol), *m*CPBA (0.363 mmol), and **1a** (0.0165 mmol) in solvent (1.0 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.

Table 2-6 Investigation of substituent on the C1-alcohol moiety^a



Entry	R	Time (h)	Yield (%) ^b	Ee (%) ^c
1	[1]	44	51	41
2	[2]	24	46	47
3	[3]	62	57	53
4	[4]	86	58	60
5	[5]	86	55	54
6	[6]	21	53	45
7	[7]	24	55	27
8	[8]	24	36	57
9	[9]	21	73	59

^aReaction conditions: **7a** (0.165 mmol), $m\text{CPBA}$ (0.363 mmol), and Ar-I^* (0.0165 mmol) in solvent (1.0 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.

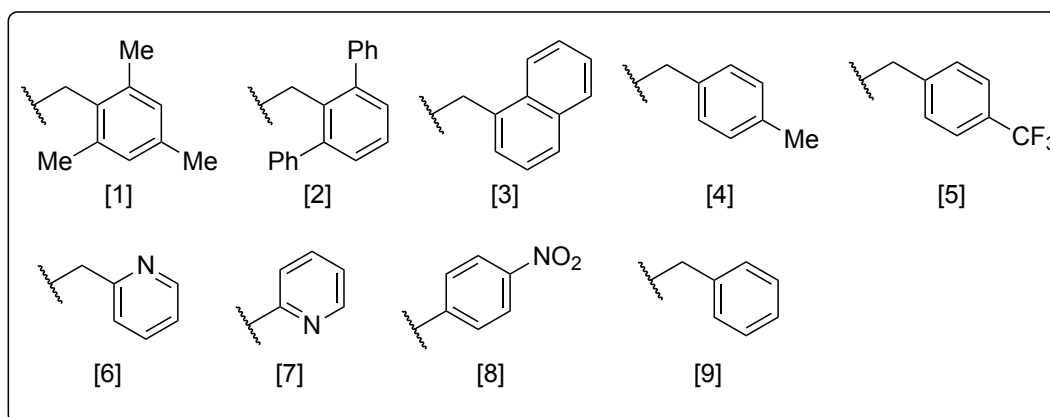
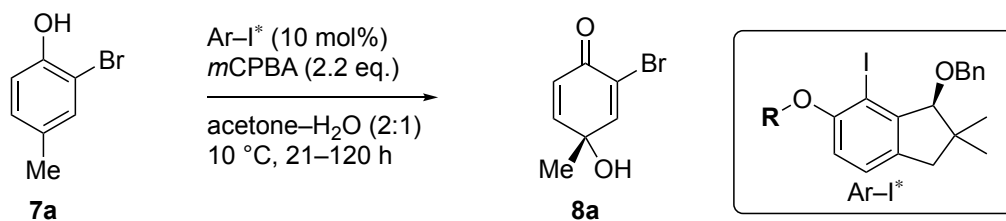


Table 2-7 Investigation of substituent on the C6-phenol moiety (i)^a



Entry	R	Time (h)	Yield (%) ^b	Ee (%) ^c
1	[1]	36	55	59
2	[2]	37	46	52
3	[3]	120	58	38
4	[4]	45	23	59
5	[5]	51	23	54
6	[6]	45	47	59
7	[7]	36	63	57
8	[8]	36	10	37
9	[9]	21	73	59

^aReaction conditions: **7a** (0.165 mmol), $m\text{CPBA}$ (0.363 mmol), and Ar-I^* (0.0165 mmol) in solvent (1.0 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.

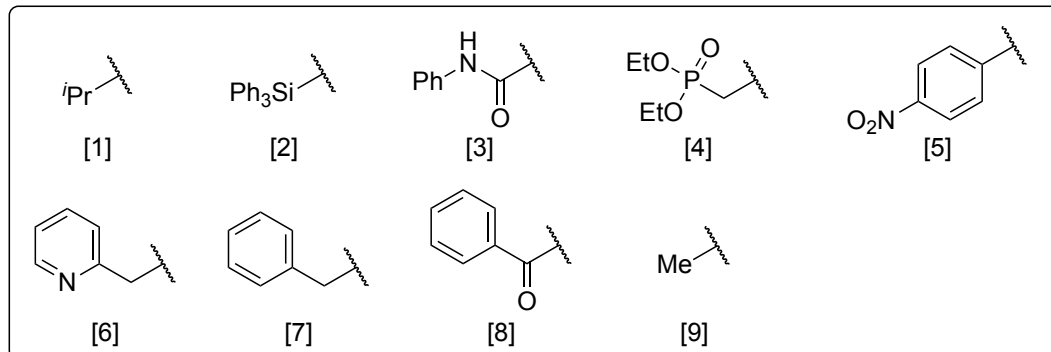
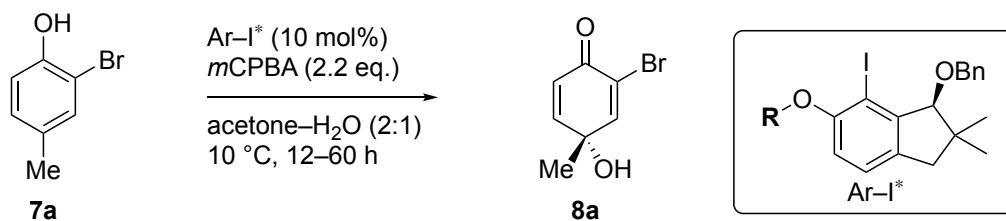


Table 2-8 Investigation of substituent on the C6-phenol moiety (ii)^a



Entry	R	Time (h)	Yield (%) ^b	Ee (%) ^c
1	[1]	60	68	70
2	[2]	60	66	41
3	[3]	60	58	60
4	[4]	62	66	62
5	[5]	12	20	59
6	[6]	60	46	65
7	[7]	13	44	64
8	[8]	26	60	63
9	[9]	26	49	73
10	[10]	26	43	74

^aReaction conditions: **7a** (0.165 mmol), $m\text{CPBA}$ (0.363 mmol), and Ar-I^* (0.0165 mmol) in solvent (1.0 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.

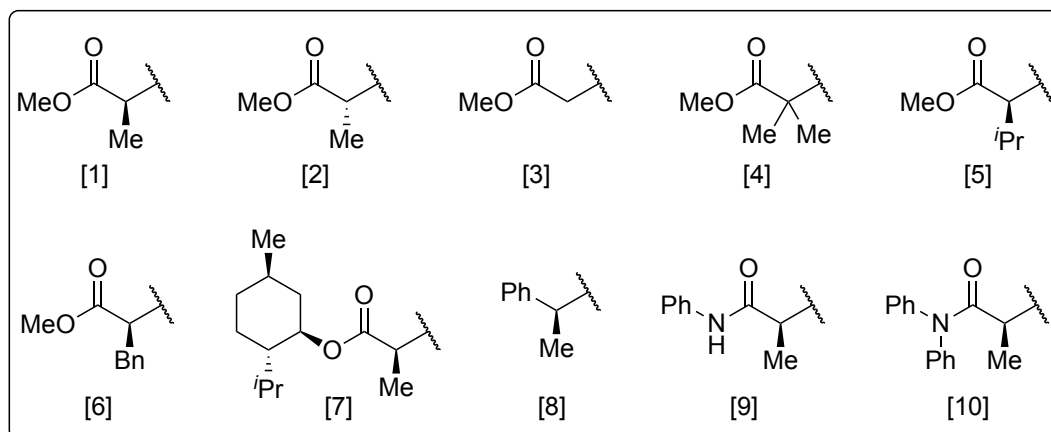
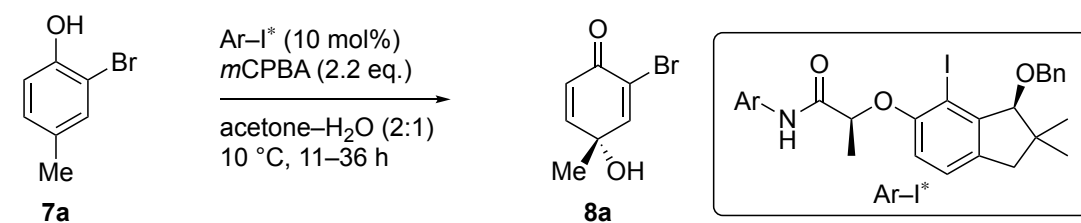


Table 2-9 Investigation of substituent on the lactamide moiety^a



Entry	Ar	Time (h)	Yield (%) ^b	Ee (%) ^c
1	[1]	26	49	77
2	[2]	16	55	74
3	[3]	20	57	71
4	[4]	16	65	77
5	[5]	20	62	78
6	[6]	20	46	81
7	[7]	24	43	73
8	[8]	11	12	71
9	[9]	16	55	75
10	[10]	36	17	70

^aReaction conditions: **7a** (0.165 mmol), $m\text{CPBA}$ (0.363 mmol), and Ar-I^* (0.0165 mmol) in solvent (1.0 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.

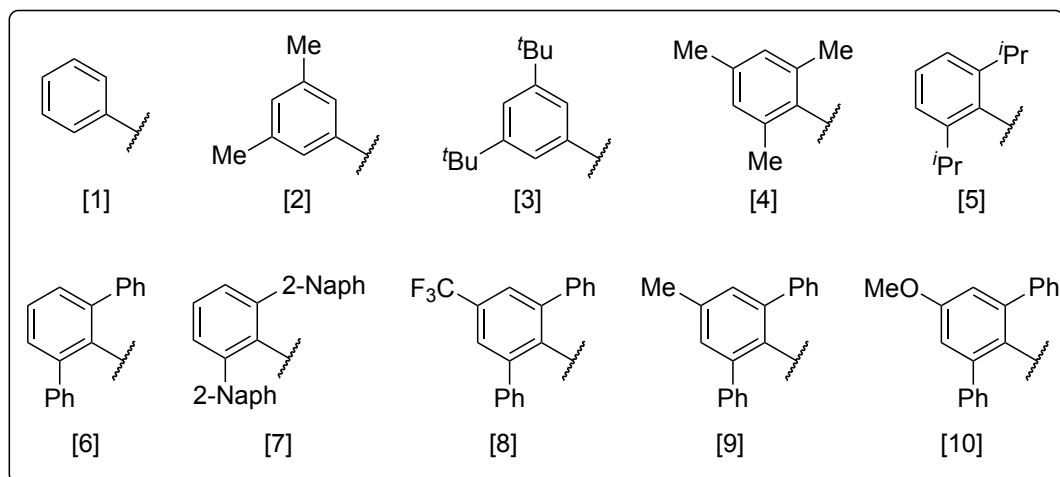
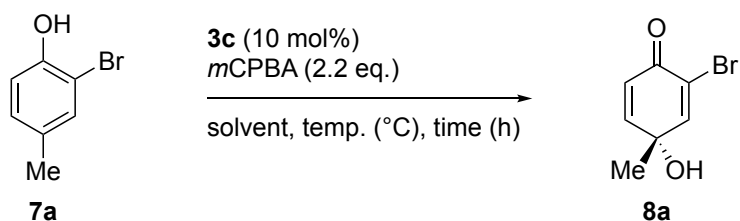
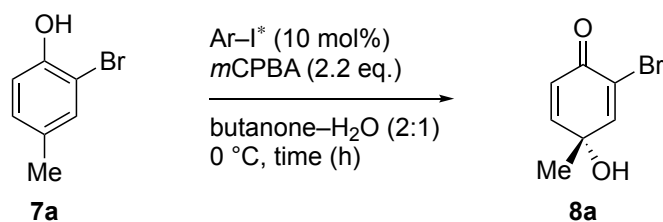


Table 2-10 Fine tuning of reaction conditions^a

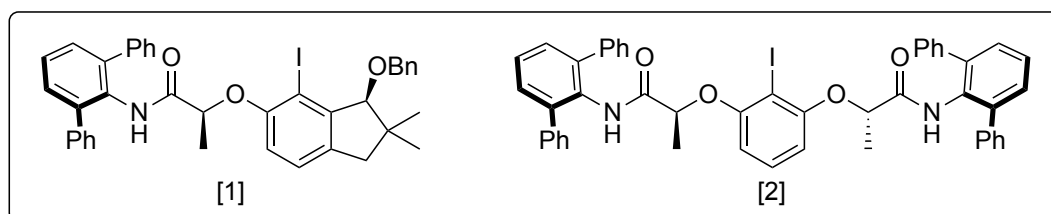
Entry	Solvent	Temp (°C)	Yield (%) ^b	Ee (%) ^c
1	acetone–H ₂ O (2:1)	10	46	81
2	butanone–H ₂ O (2:1)	10	56	79
3	3-pentanone–H ₂ O (2:1)	10	32	67
4	CH ₃ CN–H ₂ O (2:1)	10	39	66
5	DME–H ₂ O (2:1)	10	44	52
6 ^d	butanone–H ₂ O (2:1)	0	61 (54)	82

^aReaction conditions: **7a** (0.165 mmol), *m*CPBA (0.363 mmol), and **3c** (0.0165 mmol) in solvent (1.0 mL). ^bNMR yield (isolated yield in parentheses). ^cEe was determined by chiral HPLC analysis after isolation. ^d0.10 mmol scale.

Table 2-11 Comparison with Ishihara's C2-symmetric catalyst^a

Entry	Ar–I*	Time (h)	conv. (%)	Yield (%) ^b	Ee (%) ^c
1	[1]	24	>99	61	82
2	[2]	35	77	7	33

^aReaction conditions: **7a** (0.10 mmol), *m*CPBA (0.22 mmol), and Ar–I* (0.010 mmol) in solvent (0.60 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.



2.4.7 General procedure for the enantioselective *para*-hydrative dearomatization

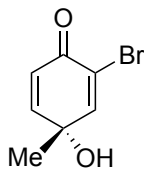
General Procedure A: A flask was charged with substrate phenol (0.10 mmol), **3c** (0.010 mmol, 6.9 mg), butanone (0.40 mL) and H₂O (0.20 mL). After sonicated for 5 min, the solution was cooled down to 0 °C. After that, *m*CPBA (*ca.* 70% purity, 0.220 mmol, 49.5 mg) was added to the solution. The reaction was monitored by TLC analysis. To the resulting solution, saturated Na₂S₂O₃ aq. (2 mL) was added and stirred for 5 min at the same temperature, followed by the addition of saturated NaHCO₃ aq. (4 mL) and AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography.

General Procedure B: A flask was charged with substrate phenol (0.10 mmol), **3c** (0.010 mmol, 6.9 mg), CH₃CN (0.67 mL) and H₂O (0.33 mL). After sonicated for 5 min, the solution was cooled down to 0 °C. After that, *m*CPBA (*ca.* 70% purity, 0.220 mmol, 49.5 mg) was added to the solution. The reaction was monitored by TLC analysis. To the resulting solution, saturated Na₂S₂O₃ aq. (2 mL) was added and stirred for 5 min at the same temperature, followed by the addition of saturated NaHCO₃ aq. (4 mL) and AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography.

General Procedure C: A flask was charged with substrate phenol (0.10 mmol), **3d** (0.010 mmol, 7.1 mg), butanone (0.40 mL) and H₂O (0.20 mL). After sonicated for 5 min, the solution was cooled down to 0 °C. After that, *m*CPBA (*ca.* 70% purity, 0.220 mmol, 49.5 mg) was added to the solution. The reaction was monitored by TLC analysis. To the resulting solution, saturated Na₂S₂O₃ aq. (2 mL) was added and stirred for 5 min at the same temperature, followed by the addition of saturated NaHCO₃ aq. (4 mL) and AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography.

2.4.8 Product identification

(*R*)-2-Bromo-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (8a)

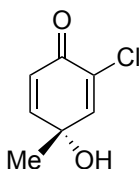


Prepared according to the general procedure A with 2-bromo-4-methylphenol (0.100 mmol, 18.7 mg) for 24 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 75/25). The obtained material contained *m*CBA as an impurity. So, the material was diluted with AcOEt, washed with saturated NaHCO₃ aq., and evaporated under reduced pressure to give the title compound as a yellowish solid in 54% yield [82% ee]. The spectral data matched with those reported in the literature.²⁴

Optical rotation $[\alpha]_{\text{D}}^{27} = -0.9$ ($c = 1.0$, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/*i*PrOH = 20/1, flow rate = 1.0 mL/min, retention time; 15.2 min (minor) and 19.3 min (major)).

(*R*)-2-Chloro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (8b)

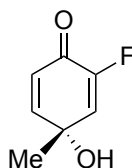


Prepared according to the general procedure C with 2-chloro-4-methylphenol (0.100 mmol, 14.3 mg) for 30 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 77/23) to give the title compound as a yellowish solid in 73% yield [84% ee]. The spectral data matched with those reported in the literature.^{13b}

Optical rotation $[\alpha]_{\text{D}}^{27} = +3.7$ ($c = 0.7$, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/*i*PrOH = 20/1, flow rate = 1.0 mL/min, retention time; 14.8 min (minor) and 17.4 min (major)).

(R)-2-Fluoro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (8c)

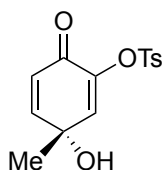


Prepared according to the general procedure C with 2-fluoro-4-methylphenol (0.100 mmol, 12.6 mg) for 24 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 75/15) to give the title compound as a yellowish solid in 51% yield [82% ee].

¹H NMR (500 MHz, CDCl₃) δ 6.91 (dd, *J* = 10.1, 2.7 Hz, 1H), 6.43 (dd, *J* = 12.2, 2.8 Hz, 1H), 6.15 (dd, *J* = 9.9, 7.1 Hz, 1H), 2.20 (s, 1H), 1.56 (d, *J* = 0.6 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 178.5 (d, *J* = 22.8 Hz), 153.3 (d, *J* = 2.4 Hz), 152.3 (d, *J* = 268.1 Hz), 127.7 (d, *J* = 9.5 Hz), 125.6 (d, *J* = 3.6 Hz), 69.3 (d, *J* = 8.4 Hz), 27.0 (s); **¹⁹F NMR** (466 MHz, CDCl₃) δ -130.6 (dd, *J* = 10.2, 7.0 Hz); **IR (neat)** 3399, 1682, 1660, 1371, 1173, 1124, 1088, 1055 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₇H₇O₂FNa: *m/z* 165.0322 ([M+Na]⁺), found: *m/z* 165.0325 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +9.0 (*c* = 0.5, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*-PrOH = 5/1, flow rate = 1.0 mL/min, retention time; 7.2 min (major) and 7.8 min (minor)).

(R)-3-Hydroxy-3-methyl-6-oxocyclohexa-1,4-dien-1-yl 4-methylbenzenesulfonate (8d)



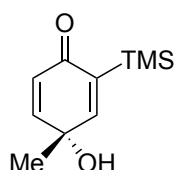
Prepared according to the general procedure A with **7d** (0.100 mmol, 27.8 mg) for 17 hours. The crude material was purified by flash chromatography (eluent: hexane/AcOEt = 75/25 to 55/45) to give the title compound as a yellowish solid in 61% yield [65% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.85 (dd, *J* = 9.9, 2.8 Hz, 1H), 6.77 (d, *J* = 2.8 Hz, 1H), 6.08 (d, *J* = 9.9 Hz, 1H), 2.46 (s, 3H), 2.25 (s, 1H), 1.53 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 178.3, 152.3, 145.9, 141.7,

140.5, 132.6, 129.9, 128.6, 126.0, 69.3, 27.0, 21.9; **IR** (neat) 3420, 1684, 1652, 1375, 1179, 1119, 1095, 1071 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_5\text{NaS}$: m/z 317.0454 ($[\text{M}+\text{Na}]^+$), found: m/z 317.0464 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{27} = +2.9$ ($c = 1.2$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/*i*PrOH = 10/1, flow rate = 1.0 mL/min, retention time; 17.4 min (major) and 19.8 min (minor)).

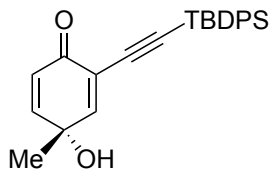
(R)-4-Hydroxy-4-methyl-2-(trimethylsilyl)cyclohexa-2,5-dien-1-one (8e)



Prepared according to the general procedure C with **7e** (0.100 mmol, 18.0 mg) for 17 hours. The crude material was purified by flash chromatography (eluent: hexane/AcOEt = 90/10 to 80/20) to give the title compound as a yellowish solid in 60% yield [72% ee]. The spectral data matched with those reported in the literature.²⁴ **Optical rotation** $[\alpha]_{\text{D}}^{27} = -11.7$ ($c = 0.9$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 20/1, flow rate = 1.0 mL/min, retention time; 7.1 min (minor) and 8.1 min (major)).

(R)-2-((tert-Butyldiphenylsilyl)ethynyl)-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (8f)



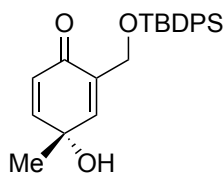
Prepared according to the general procedure B with **7f** (0.100 mmol, 37.1 mg) for 45 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 80/20) to give the title compound as a yellowish oil in 44% yield [74% ee].

¹H NMR (500 MHz, CDCl_3) δ 7.83-7.85 (m, 4H), 7.36-7.42 (m, 6H), 7.21 (d, $J = 2.8$ Hz,

1H), 6.87 (dd, $J = 10.2, 3.1$ Hz, 1H), 6.19 (d, $J = 9.9$ Hz, 1H), 2.04 (s, 1H), 1.53 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 181.8, 155.1, 151.7, 135.8, 132.9, 129.7, 127.9, 126.9, 123.0, 102.0, 95.8, 67.4, 27.2, 26.8, 18.8; **IR** (neat) 3407, 2958, 2923, 2892, 2858, 1666, 1428, 1111 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{25}\text{H}_{26}\text{O}_2\text{NaSi}$: m/z 409.1594 ($[\text{M}+\text{Na}]^+$), found: m/z 409.1601 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = +2.3$ ($c = 1.5$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/ i PrOH = 60/1, flow rate = 1.0 mL/min, retention time; 16.8 min (major) and 26.2 min (minor)).

(R)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (8g)

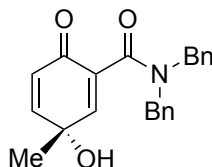


Prepared according to the general procedure C with **7g** (0.100 mmol, 37.7 mg) for 47 hours. The crude material was purified by flash chromatography (eluent: hexane/AcOEt = 100/0 to 82/18) to give the title compound as a white solid in 57% yield [75% ee].

^1H NMR (500 MHz, CDCl_3) δ 7.64-7.66 (m, 4H), 7.35-7.44 (m, 6H), 6.97-6.99 (m, 1H), 6.85 (dd, $J = 9.9, 3.1$ Hz, 1H), 6.05 (d, $J = 9.9$ Hz, 1H), 4.51-4.52 (m, 2H), 1.73 (s, 1H), 1.47 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 185.3, 152.7, 146.1, 136.1, 135.7, 135.6, 133.3, 133.2, 130.0, 127.9, 126.9, 67.6, 60.3, 27.1, 27.0, 19.4; **IR** (neat) 3397, 2959, 2930, 2892, 2858, 1672, 1637, 1112 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{24}\text{H}_{28}\text{O}_3\text{NaSi}$: m/z 415.1700 ($[\text{M}+\text{Na}]^+$), found: m/z 415.1713 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -5.5$ ($c = 2.2$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/ i PrOH = 4/1, flow rate = 0.5 mL/min, retention time; 8.2 min (minor) and 8.8 min (major)).

(R)-N,N-Dibenzyl-3-hydroxy-3-methyl-6-oxocyclohexa-1,4-diene-1-carboxamide (8h)

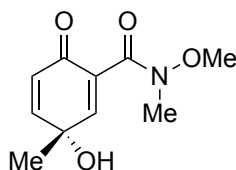


Prepared according to the general procedure B with **7h** (0.100 mmol, 33.1 mg) for 97 hours. The crude material was purified by flash chromatography (eluent: hexane/AcOEt = 100/0 to 50/50) to give the title compound as a white solid in 51% yield [70% ee].

¹H NMR (500 MHz, CDCl₃) (500 MHz, CDCl₃) δ 7.27-7.38 (m, 8H), 7.11 (d, *J* = 6.8 Hz, 2H), 6.81-6.86 (m, 2H), 6.17 (d, *J* = 9.9 Hz, 1H), 4.09-5.21 (m, 4H), 1.33 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 182.3, 167.5, 153.1, 150.3, 136.2, 136.1, 135.0, 129.0, 128.8, 128.1, 128.0, 127.6, 127.2, 126.5, 66.7, 51.2, 47.4, 26.5; **IR (neat)** 3360, 1672, 1637, 1496, 1470, 1452, 1429, 1247, 1069 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₂H₂₁O₃NNa: *m/z* 370.1414 ([M+Na]⁺), found: *m/z* 371.1419 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +9.5 (*c* = 1.9, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 1.0 mL/min, retention time; 15.2 min (major) and 85.0 min (minor)).

(R)-3-Hydroxy-N-methoxy-N,3-dimethyl-6-oxocyclohexa-1,4-diene-1-carboxamide (8i)



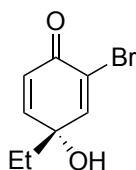
A flask was charged with **7i** (0.100 mmol, 19.5 mg), **3c** (0.010 mmol, 6.9 mg), MeCN (0.70 mL), CHCl₃ (0.10 mL) and H₂O (0.20 mL). After sonicated for 5 min, the solution was cooled down to 0 °C. After that, *m*CPBA (*ca.* 70% purity, 0.220 mmol, 49.5 mg) was added to the solution. The reaction was monitored by TLC analysis. After stirring for 30 hours at 0 °C, saturated Na₂S₂O₃ aq. (2 mL) was added and stirred for 5 min at the same temperature, followed by the addition of saturated NaHCO₃ aq. (4 mL) and AcOEt. Two layers were separated and aqueous layer was extracted with AcOEt. The combined

organic layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 50/50 to 0/100) to give the title compound as a white solid in 34% yield [81% ee].

¹H NMR (500 MHz, CDCl₃) δ 6.94 (brs, 1H), 6.90 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.17 (d, *J* = 10.2 Hz, 1H), 3.58 (s, 3H), 3.29 (s, 3H), 2.62 (brs, 1H), 1.52 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 181.5, 166.6, 152.5, 149.3, 134.5, 126.5, 66.7, 61.3, 31.9, 26.8; **IR (neat)** 3374, 1676, 1441, 1389, 1128, 1059 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₃O₄NNa: *m/z* 234.0737 ([M+Na]⁺), found: *m/z* 234.0735 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +8.0 (*c* = 0.5, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 1/1, flow rate = 0.8 mL/min, retention time; 13.4 min (major) and 28.7 min (minor)).

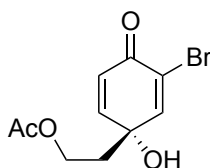
(*R*)-2-Bromo-4-ethyl-4-hydroxycyclohexa-2,5-dien-1-one (10a)



Prepared according to the general procedure A with **9a** (0.100 mmol, 20.1 mg) for 36 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 80/20) to give the title compound as a white solid in 47% yield [84% ee]. The spectral data matched with those reported in the literature.³⁰ [α]_D²⁸ = +22.5 (*c* = 0.8, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/*i*PrOH = 20/1, flow rate = 1.0 mL/min, retention time; 14.4 min (minor) and 17.1 min (major)).

(*R*)-2-(3-Bromo-1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl acetate (10b)

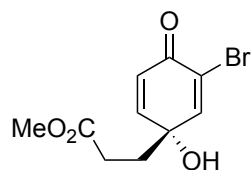


Prepared according to the general procedure A with **9b** (0.100 mmol, 25.9 mg) for 36 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 67/33) to give the title compound as a yellowish oil in 53% yield [82% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.34 (d, *J* = 2.8 Hz, 1H), 6.90 (dd, *J* = 10.2, 2.8 Hz, 1H), 6.32 (d, *J* = 9.9 Hz, 1H), 4.14-4.24 (m, 2H), 2.37 (s, 1H), 2.08-2.20 (m, 2H), 2.05 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 177.9, 170.7, 150.7, 150.2, 126.8, 124.1, 71.2, 59.3, 38.7, 20.9; **IR** (neat) 3430, 1737, 1671, 1636, 1602, 1367, 1235, 1069 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₁O₄BrNa: *m/z* 296.9733 ([M+Na]⁺), found: *m/z* 298.9710 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +24.1 (*c* = 1.1, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/*i*PrOH = 10/1, flow rate = 1.0 mL/min, retention time; 19.5 min (minor) and 28.1 min (major)).

Methyl (*R*)-3-(3-bromo-1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)propanoate (10c)

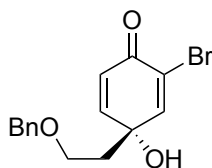


Prepared according to the general procedure A with **9c** (0.100 mmol, 25.9 mg) for 36 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 67/33) to give the title compound as a yellowish oil in 51% yield [63% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.28 (d, *J* = 2.8 Hz, 1H), 6.86 (dd, *J* = 9.9, 2.8 Hz, 1H), 6.32 (d, *J* = 10.2 Hz, 1H), 3.69 (s, 3H), 2.66 (s, 1H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.10-2.21 (m, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 178.0, 173.3, 150.7, 150.5, 126.9, 124.4, 71.9, 52.1, 34.3, 28.6; **IR** (neat) 3445, 1784, 1732, 1638, 1438, 1219, 1175, 1101 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₁O₄BrNa: *m/z* 296.9733 ([M+Na]⁺), found: *m/z* 298.9713 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +17.4 (*c* = 1.3, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/*i*PrOH = 10/1, flow rate = 1.0 mL/min, retention time; 20.3 min (minor) and 24.4 min (major)).

(R)-4-(2-(Benzyloxy)ethyl)-2-bromo-4-hydroxycyclohexa-2,5-dien-1-one (10d)

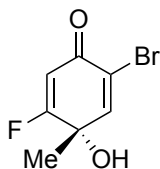


Prepared according to the general procedure A with **9d** (0.100 mmol, 30.7 mg) for 35 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 71/29) to give the title compound as a white solid in 38% yield [71% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.32-7.40 (m, 6H), 6.92 (dd, *J* = 10.2, 2.8 Hz, 1H), 6.25 (d, *J* = 9.9 Hz, 1H), 4.55 (s, 2H), 3.82 (s, 1H), 3.74 (t, *J* = 5.7 Hz, 2H), 2.00-2.13 (m, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 178.4, 151.4, 151.3, 137.1, 128.7, 128.3, 128.0, 126.0, 123.6, 73.8, 72.1, 66.6, 39.5; **IR (neat)** 3410, 1670, 1635, 1601, 1454, 1364, 1334, 1101 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₅H₁₅O₃BrNa: *m/z* 345.0097 ([M+Na]⁺), found: *m/z* 345.0103 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +13.2 (*c* = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/*i*PrOH = 20/1, flow rate = 1.0 mL/min, retention time; 36.8 min (minor) and 39.1 min (major)).

(S)-2-Bromo-5-fluoro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (10e)



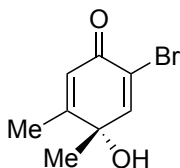
Prepared according to the general procedure A with **9e** (0.100 mmol, 20.5 mg) for 46 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 75/25) to give the title compound as a white solid in 67% yield [81% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.19 (d, *J* = 10.2 Hz, 1H), 6.00 (d, *J* = 12.5 Hz, 1H), 2.33 (s, 1H), 1.65 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 180.0 (d, *J* = 16.8 Hz), 176.3 (d, *J* = 294.5 Hz), 147.6 (s), 123.1 (s), 106.7 (d, *J* = 13.1 Hz), 69.5 (d, *J* = 24.0 Hz), 24.2 (s); **¹⁹F NMR** (466 MHz, CDCl₃) δ -97.25 (dd, *J* = 12.1, 9.8 Hz); **IR (neat)** 3392, 1678, 1612, 1372, 1339, 1164, 1131, 1061 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₇H₆O₂BrFNa:

m/z 242.9427 ($[M+Na]^+$), found: m/z 242.9428 ($[M+Na]^+$); **Optical rotation** $[\alpha]_D^{28} = +1.5$ ($c = 0.6$, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/ i PrOH = 20/1, flow rate = 1.0 mL/min, retention time; 10.2 min (minor) and 15.4 min (major)).

(S)-2-Bromo-4-hydroxy-4,5-dimethylcyclohexa-2,5-dien-1-one (10f)



Prepared according to the general procedure A with **9f** (0.100 mmol, 20.1 mg) for 37 hours. The crude material was purified by column chromatography (eluent: hexane/AcOEt = 100/0 to 60/40) to give the title compound as a white solid in 59% yield [75% ee]. The spectral data matched with those reported in the literature.²⁴ **Optical rotation** $[\alpha]_D^{28} = +9.1$ ($c = 1.1$, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/ i PrOH = 20/1, flow rate = 1.0 mL/min, retention time; 13.8 min (minor) and 19.5 min (major)).

2.5 References and notes

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Chapter 3

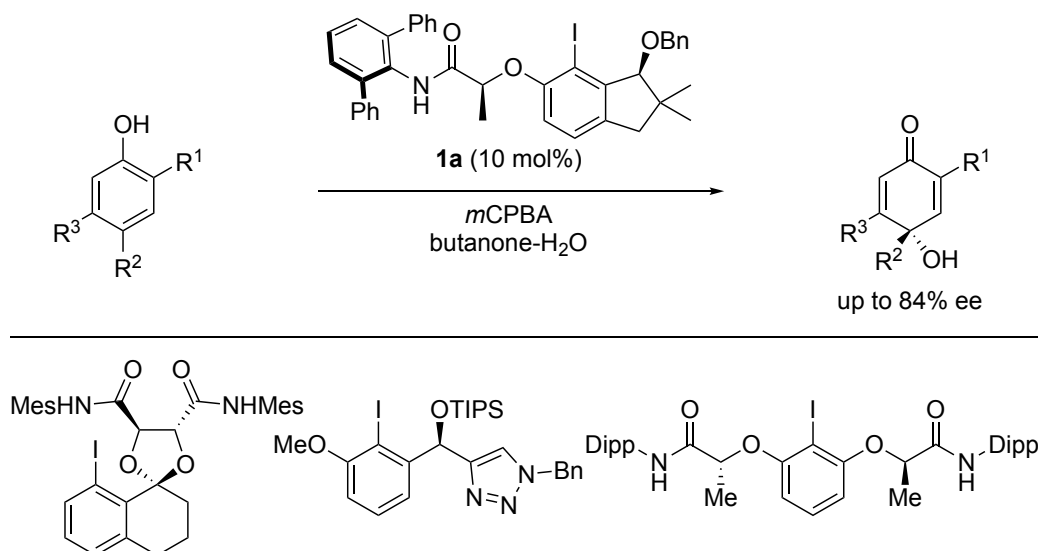
Enantioselective Hydrative *para*-Dearomatization of Sulfonanilides by an Indanol-based Chiral Organoiodine Catalyst

The author reports herein the development of an enantioselective oxidative *para*-dearomatization of sulfonanilides with water by use of an indanol-based chiral organoiodine catalyst, originally developed in his group. This reaction proceeds efficiently by the use of *N*-mesyl-protected anilines as substrates, giving functionalized *p*-quinol imines in good yields and moderate to high enantioselectivities.

3.1 Introduction

High oxidation state organoiodine (III) and (V) compounds are frequently used in synthetic organic chemistry,¹ including natural product synthesis,² to perform selective oxidative transformations that operate under mild reaction conditions and with low environmental impact. One well-investigated transformation in this area is the oxidative dearomatization of arenols which takes place *via* the intra- or intermolecular addition of a nucleophile to the aromatic core at the *ortho* or *para* position.³ In the early studies, organoiodine(III) reagents such as (diacetoxyiodo)benzene and [bis(trifluoroacetoxy)iodo]benzene were often used as a stoichiometric oxidant to provide valuable functionalized six-membered rings.^{4,5}

In the last decade, the emergence of chiral organoiodine(I/III) catalysis has opened up a new opportunity in the oxidative dearomatization,^{1c,6-9} although the successful examples are mostly limited to intramolecular *ortho*-dearomatizations.¹⁰⁻¹⁴ Oxidative intermolecular *para*-dearomatization of arenols^{15,16} has been regarded as a formidable challenge due to the difficulty of constructing an effective chiral environment at the remote *para*-position by the conventional chiral organoiodine catalysts.¹⁷ In this context, the author have recently developed new chiral organoiodine catalysts based on a structurally rigid indanol scaffold,¹⁸ and succeeded in the first highly enantioselective hydrative *para*-dearomatization of arenols (Scheme 3-1).^{19,20}



Scheme 3-1 Indanol-based chiral organoiodine catalyst for the enantioselective oxidative dearomatization of arenols

As the further application of this study, the author became interested in an enantioselective oxidative dearomatization of anilides.^{7, 21–23} In the literature, oxidative *ortho*- and *para*-dearomatizations of anilides with oxygen nucleophiles have been accomplished using a stoichiometric amount of organoiodine (III) and (V) reagents (Figure 3-1 (a) and (b)).^{24–27} More recently, Muñiz and co-workers reported the first catalytic enantioselective oxidative *para*-dearomatization of an anilide using water as a nucleophile and a C2 symmetric catalyst,^{17d} albeit with a moderate yield and enantioselectivity (Figure 3-1 (c)).

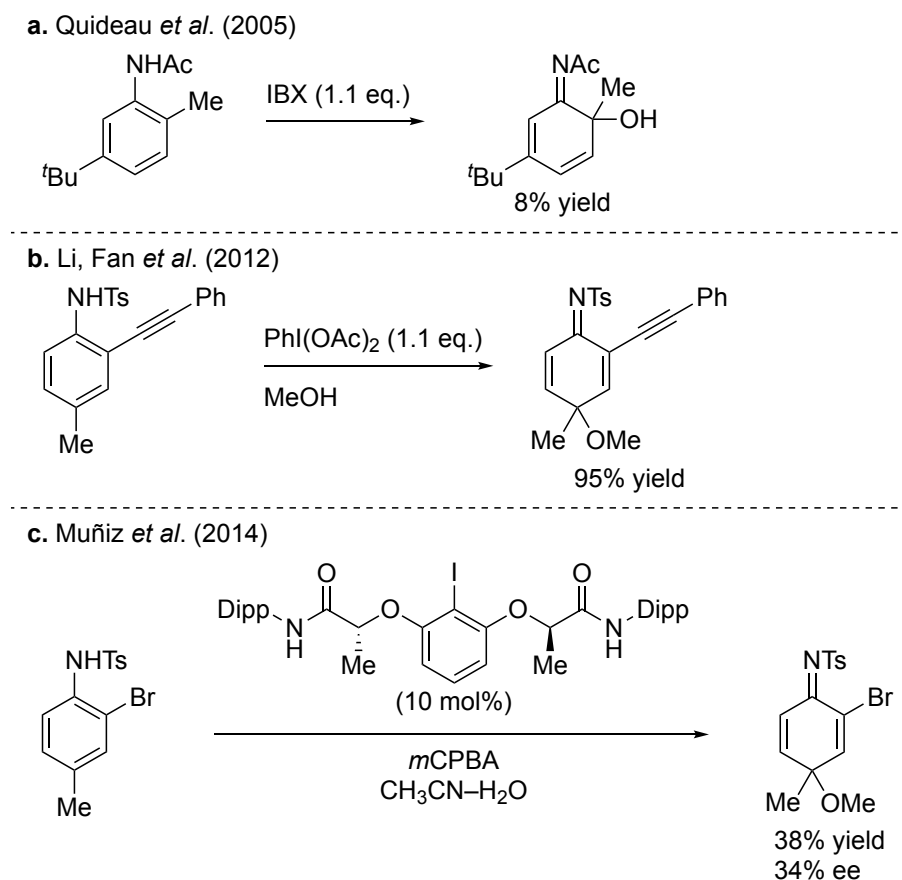


Figure 3-1 (a) and (b) Previous works on oxidative dearomatization of anilides using a stoichiometric amount of organoiodine (III) and (V) reagents. (c) The first enantioselective oxidative *para*-dearomatization of a sulfonanilide with water.

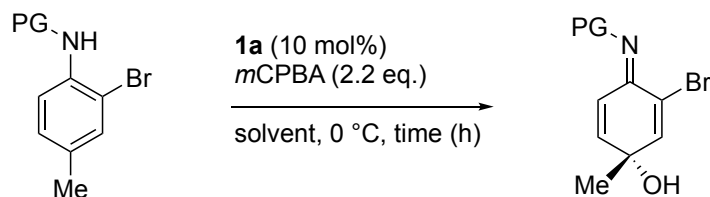
Herein, the author reports the development of an enantioselective hydrative *para*-dearomatization of anilides using the author's indanol-based chiral organoiodine catalyst. This oxidative dearomatization using *N*-mesyl anilines as substrate affords

enantioenriched *p*-quinol imines in good yields with enantioselectivities ranging from 35 to 95% ee.

3.2 Results and Discussion

The author commenced with the identification of a proper *N*-protecting group for 2-bromo-4-methylaniline, while applying the optimized conditions used in the author's hydrative *para*-dearomatization of arenols (Scheme 3-1).¹⁹ The reactions were performed with 10 mol% of catalyst **1a**, 2.2 equivalents of *m*CPBA as an external oxidant in butanone–H₂O (2:1) co-solvent at 0 °C (Table 3-1). By introducing the tosyl (Ts) group on the aniline, the corresponding *p*-quinol imine was obtained in 83% yield with 44% ee (entry 1). Encouraged by this promising result, the author further examined other sulfonyl groups for the model aniline. Almost no reaction took place when an *o*-nitrobenzenesulfonyl (Ns) group was introduced (entry 2). In contrast, attachment of a methanesulfonyl (Ms) group resulted in slightly higher enantioselectivity without deteriorating the product yield (entry 3). Protecting groups other than sulfonyl groups such as acetyl (Ac) and benzyl (Bn) groups gave no desired products (entries 4 and 5).

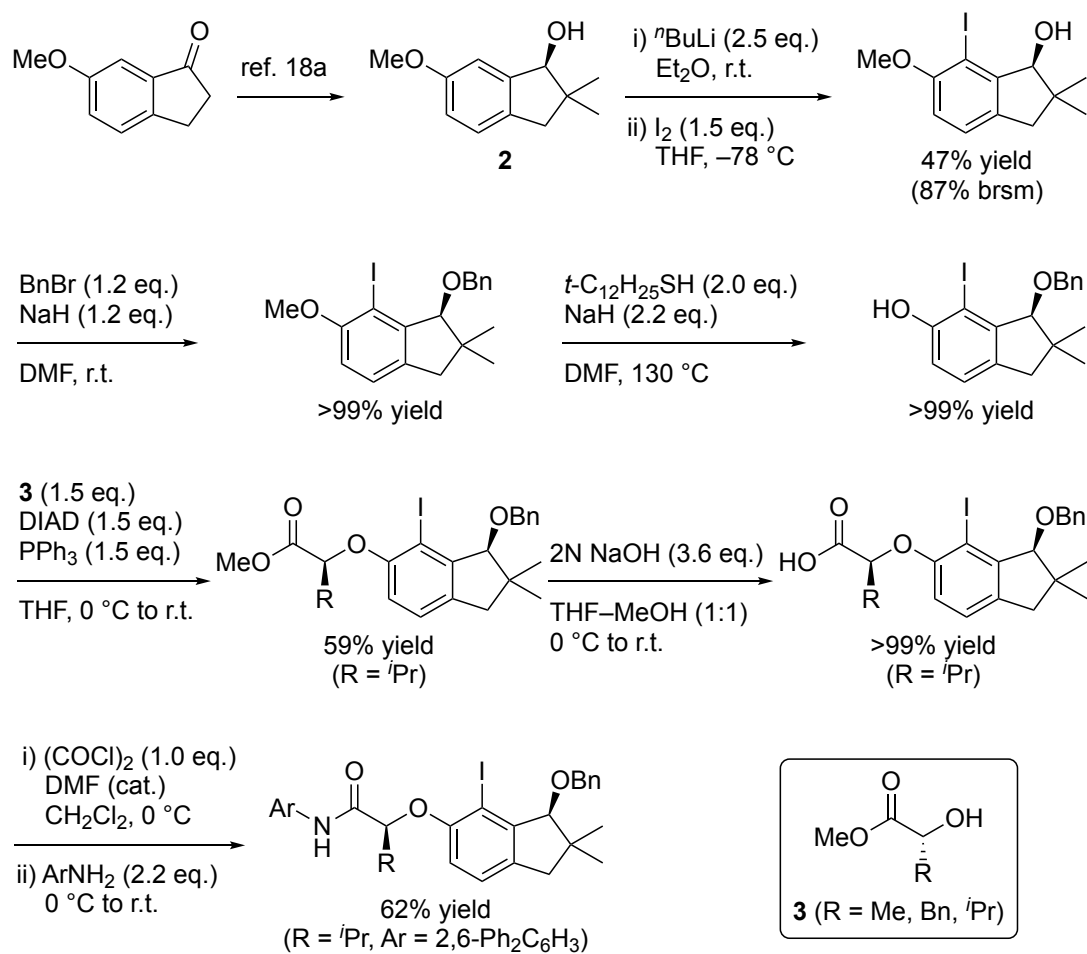
As the next step, the author's attention was turned to the screening of the co-solvent system. The use of organic solvents other than butanone caused a decrease in the product yield and enantioselectivity (entries 6–8). Taking the solubility of catalyst **1a** and substrates into consideration, butanone–H₂O (9 : 1) solvent system was chosen as optimal (entry 9).

Table 3-1 Reaction optimization.^a

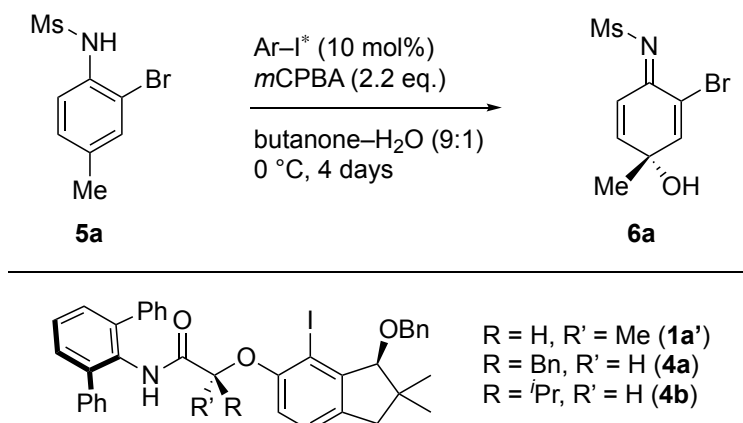
Entry	PG	Solvent	Time (h)	Yield (%) ^b	Ee (%) ^c
1	Ts	butanone–H ₂ O (2:1)	48	83	44
2	Ns		48	<1	-
3	Ms		92	79	52
4	Ac		24	<1	-
5	Bn		24	<1	-
6	Ms	CH ₃ CN–H ₂ O (2:1)	96	81	44
7	Ms	THF–H ₂ O (2:1)	96	16	17
8	Ms	DME–H ₂ O (2:1)	96	54	47
9	Ms	butanone–H ₂ O (9:1)	96	84	51

^aReaction conditions: substrate (0.100 mmol), *m*CPBA (0.220 mmol), and **1a** (0.0100 mmol) in solvent (0.60 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.

The author next fine-tuned the indanol-based catalyst structure toward *N*-mesyl 2-bromo-4-methylaniline **5a**, with focus on the role of the lactamide moiety as the secondary chiral entity.²⁸ The catalyst library used in this study was prepared by following the reported procedure,¹⁹ starting from the enantiopure indanol as shown in Scheme 3-2.^{18a} The use of the diastereomer of **1a** as the catalyst (**1a'**) afforded racemic *p*-quinol imine **6a** (Table 3-2, entry 1), underlying that two chiral centers of the indanol and lactamide work synergistically. Subsequently, the author examined the effects of the amide *N*-aryl group by attaching various 2,6-diaryl 4-substituted anilines which differ sterically and electronically (see Table 3-5 to Table 3-8 for details). However, the enantioselectivities remained in the range of 28 to 51% ee. Therefore, the author shifted his attention to the lactate moiety.²⁹ The use of phenyllactate-derived catalyst **4a** led to slightly higher enantioselectivity, and the even higher selectivity was attained by the use of isopropyl substituted catalyst (**4b**), giving the *p*-quinol imine **6a** in 76% yield and 75% ee (entries 7 and 8).³⁰



Scheme 3-2 Catalyst synthesis

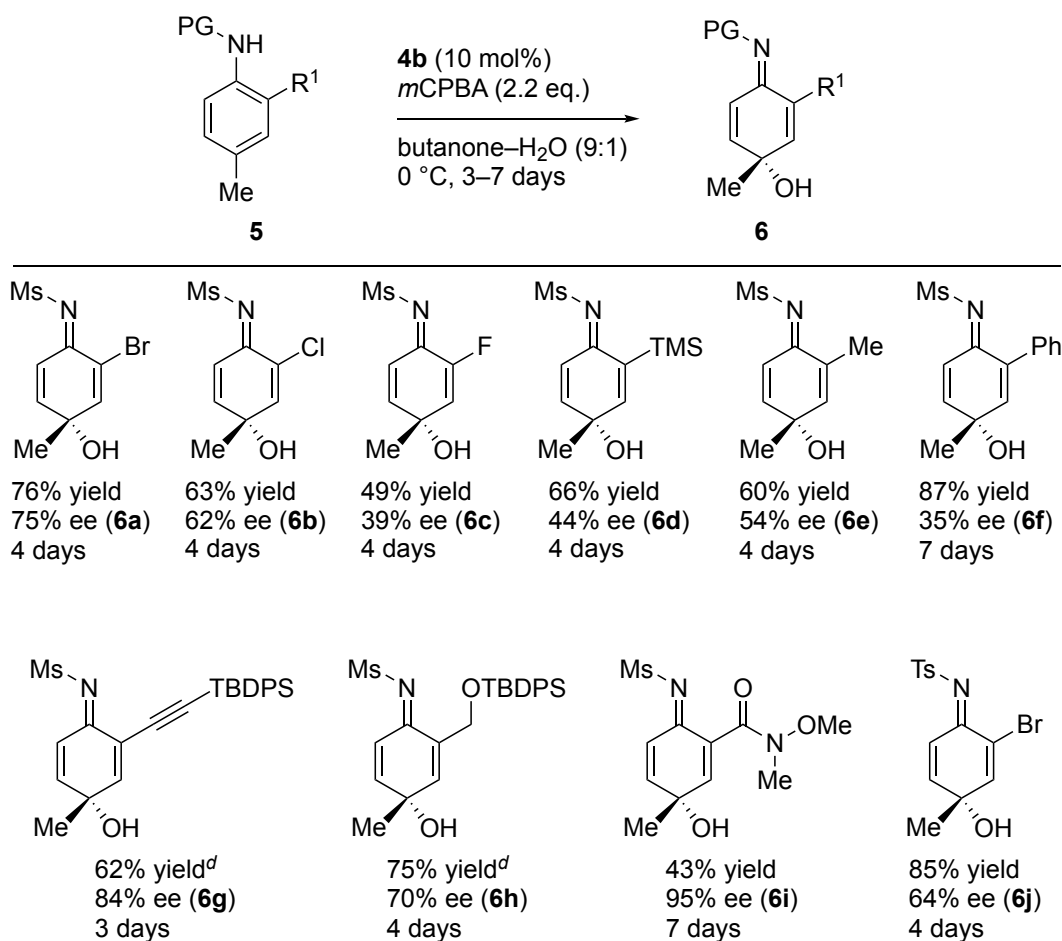
Table 3-2 Catalyst structure optimization^a

Entry	Catalyst	Yield (%) ^b	Ee (%) ^c
1	1a'	88	<1
2	4a	68	67
3	4b	76	75

^aReaction conditions: substrate (0.100 mmol), *m*CPBA (0.220 mmol), and catalyst (0.0100 mmol) in solvent (0.60 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation.

With the optimized reaction conditions in hand, the author evaluated the scope of 4-methyl sulfonanilides with a variety of 2-substituents (Scheme 3-3). 2-Chloro-anilide reacted to give the corresponding *p*-quinol imine **6b** in good yield and moderate enantioselectivity. A silyl group directly attached to the aromatic ring was tolerated to give the product **6d** in moderate yield and selectivity. As for 2-methyl and 2-phenyl anilides, the product **6e** and **6f** were obtained in high yields with 54% ee and 35% ee, respectively. *p*-Quinol imines **6g** and **6h** were obtained in good enantioselectivities by increasing the catalyst loading to 20 mol%. The highest enantioselectivity was observed in the reaction of Weinreb amide **5i** which gave the product **6i** with 95% ee. When the tosyl-protected aniline **5j** was subjected to the optimized conditions, the corresponding dearomatized product **6j** was isolated in high yield with 64% ee (see, Table 3-1, entry 1).

Scheme 3-3 4-Methylsulfonanilides substrate scope.^{a-c}

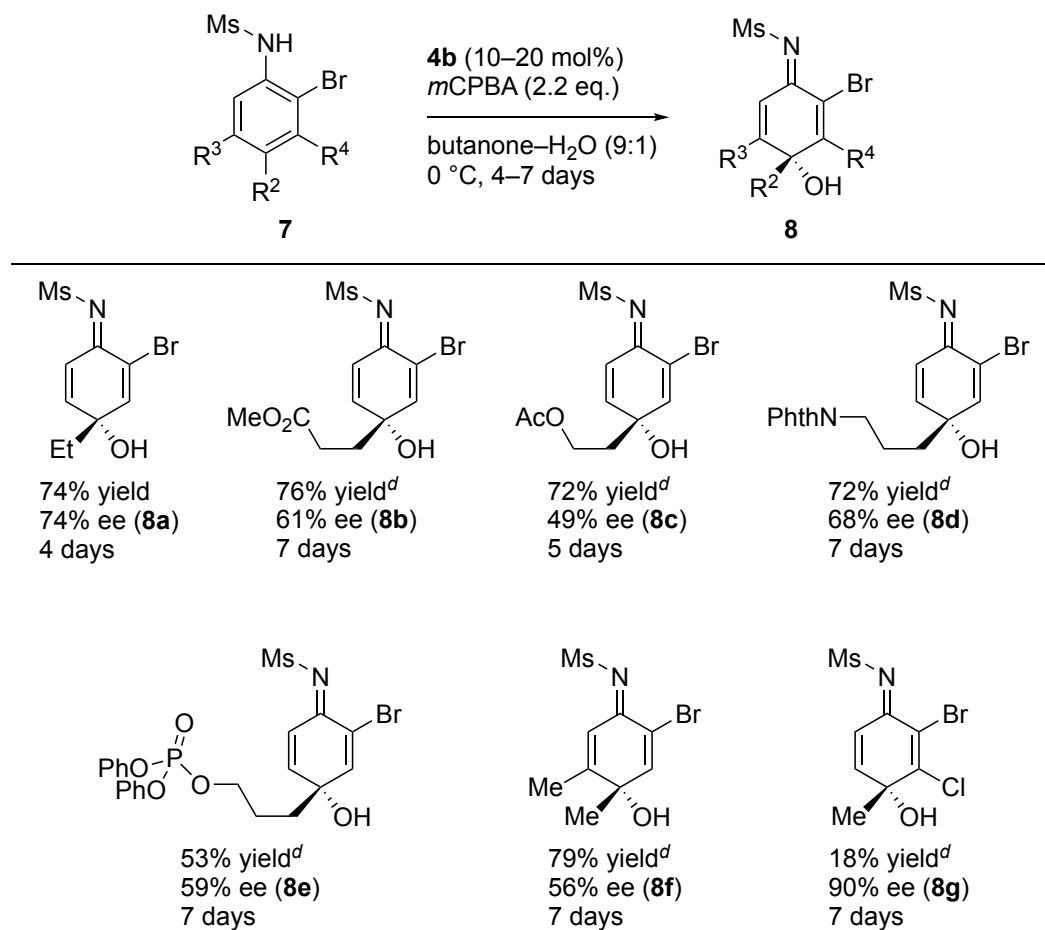


^aReaction conditions: substrate (0.100 mmol), *m*CPBA (0.220 mmol), and **4b** (0.0100 mmol) in solvent (0.60 mL). ^bIsolated yield. ^cEe was determined by chiral HPLC analysis after isolation. ^dPerformed with **4b** (0.0200 mmol).

The author then shifted his focus to the substrate scope of 2-bromoanilides having a different 4-substituent (Scheme 3-4). Ethyl substituted product **8a** was obtained in good yield and enantioselectivity identical to the methyl substituted product **6a**. In contrast, attachment of a methoxycarbonyl and acetoxy functional groups affected the reaction outcomes, giving *p*-quinol imine **8b** and **8c** with 61% ee and 49% ee, respectively. It is of note that the reaction of 4-phenyl-anilide exhibited no enantioselectivity, presumably due to the intervention of a dissociative pathway (Figure 3-2).^{17b, 17c, 31} Pendant functionalities such as *N*-Phthaloyl and phosphate groups were also tolerated to afford **8d** and **8e** with moderate enantioselectivities, respectively. As for trisubstituted

sulfonanilides, 2-bromo-4,5-dimethylsulfoanilide **7f** was converted into *p*-quinol imine **8f** in high yield with moderate enantioselectivity. A chloro substituent at 3-position of the anilide slowed down the reaction dramatically and the target *p*-quinol imine **8g** was obtained in only 18% yield after 7 days, albeit with excellent enantioselectivity.

Scheme 3-4 2-Bromosulfonanilides substrate scope.^{a-c}



^aReaction conditions: substrate (0.100 mmol), *m*CPBA (0.220 mmol), and **4b** (0.0100 mmol) in solvent (0.60 mL). ^bIsolated yield. ^cEe was determined by chiral HPLC analysis after isolation. ^dPerformed with **4b** (0.0200 mmol).

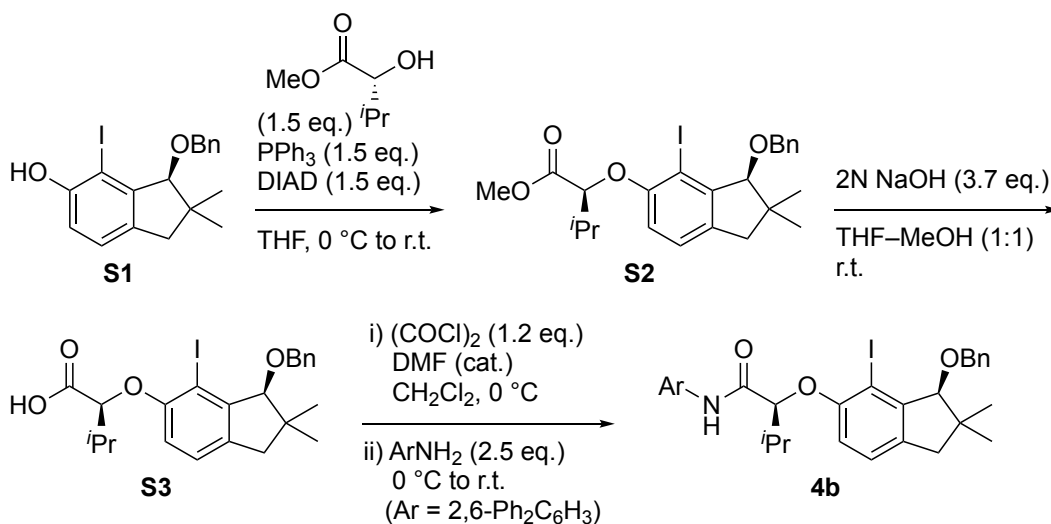
3.4 Conclusion

In conclusion, the author has developed the enantioselective hydrative *para*-dearomatization of sulfonanilides by chiral organoiodine(I/III) catalysis. This reaction was applicable to a variety of sulfonanilides to give the *p*-quinol imines in good yields. Although the observed enantioselectivities vary significantly from 35% to 95% ee depending on the substrates, this study confirmed that the elaboration of the organoiodine catalyst structure paves a way to attain excellent enantioselectivity even in the case of challenging synthetic transformations.

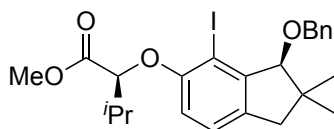
3.5 Experimental section

3.5.1 Catalyst synthesis

3.5.1.1 Preparation of catalyst 4b



Methyl (S)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy)-3-methylbutanoate (S2)

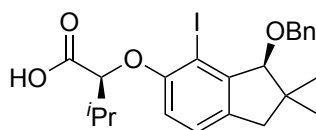


To a stirred solution of **S1**¹⁹ (2.71 mmol, 1.07 g) in THF (10 mL) were sequentially added methyl (*R*)-2-hydroxy-3-methylbutanoate³² (3.56 mmol, 0.470 g) and PPh₃ (4.07 mmol, 1.07 g) at room temperature under argon atmosphere. The solution was cooled down to 0 °C, followed by the addition of diisopropyl azodicarboxylate (DIAD, 4.07 mmol, 0.801 mL). After stirring overnight at 0 °C to room temperature, silica gel was added to the reaction, and all volatiles were removed under reduced pressure, followed by the direct purification by column chromatography (eluent: hexane/AcOEt = 13/1) to afford the title compound as a colorless oil in 59% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.42 (d, *J* = 7.1 Hz, 2H), 7.29–7.32 (m, 2H), 7.23–7.25 (m, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 4.77 (d, *J* = 10.5 Hz, 1H), 4.40 (d, *J* = 5.1 Hz, 1H), 4.36 (s, 1H), 3.75 (s, 3H), 3.06 (d, *J* = 15.3 Hz, 1H), 2.55 (d, *J* = 15.3 Hz, 1H), 2.30–2.38 (m, 1H), 1.36 (s, 3H), 1.17 (d, *J* = 6.8 Hz,

3H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.5, 155.6, 149.3, 138.9, 137.9, 128.4, 128.2, 127.6, 125.4, 112.4, 93.9, 87.9, 82.7, 74.2, 52.1, 46.3, 43.8, 32.1, 28.3, 23.0, 19.2, 17.9; **IR** (neat) 3031, 2959, 1757, 1735, 1461, 1283, 1252, 1068 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{24}\text{H}_{29}\text{O}_4\text{INa}$: m/z 531.1008 ($[\text{M}+\text{Na}]^+$), found: m/z 531.1009 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{20} = +64.8$ ($c = 2.2$, CHCl_3).

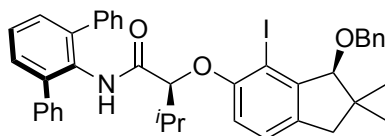
(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-3-methylbutanoic acid (S3)



To a stirred solution of **S2** (1.35 mmol, 0.686 g) in THF (2.5 mL) and MeOH (2.5 mL) was added 2 *N* NaOH aq. (2.5 mL) at 0 °C. After stirring for 5 hours at room temperature, the reaction was quenched with 1*N* HCl aq., extracted with AcOEt, dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was pure enough to be used for next step.

^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, $J = 7.4$ Hz, 2H), 7.31 (m, 2H), 7.25-7.27 (m, 1H), 7.01 (d, $J = 8.2$ Hz, 1H), 6.54 (d, $J = 8.2$ Hz, 1H), 4.93 (d, $J = 10.5$ Hz, 1H), 4.78 (d, $J = 10.2$ Hz, 1H), 4.52 (d, $J = 4.0$ Hz, 1H), 4.36 (s, 1H), 3.06 (d, $J = 15.3$ Hz, 1H), 2.57 (d, $J = 15.3$ Hz, 1H), 2.36-2.42 (m, 1H), 1.36 (s, 3H), 1.20 (d, $J = 6.8$ Hz, 3H), 1.16 (d, $J = 7.1$ Hz, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.5, 155.2, 149.4, 138.7, 138.2, 128.4, 128.3, 127.7, 125.5, 112.4, 93.9, 87.8, 82.0, 74.3, 46.3, 43.8, 32.0, 28.3, 23.0, 19.2, 17.6; **IR** (neat) 2961, 1721, 1460, 1279, 1125, 1101, 1049, 1028 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_4\text{I}$: m/z 493.0881 ($[\text{M}-\text{H}]^-$), found: m/z 493.0881 ($[\text{M}-\text{H}]^-$); **Optical rotation** $[\alpha]_{\text{D}}^{24} = +73.2$ ($c = 1.2$, CHCl_3).

(S)-N-([1,1':3',1''-Terphenyl]-2'-yl)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-3-methylbutanamide (4b)

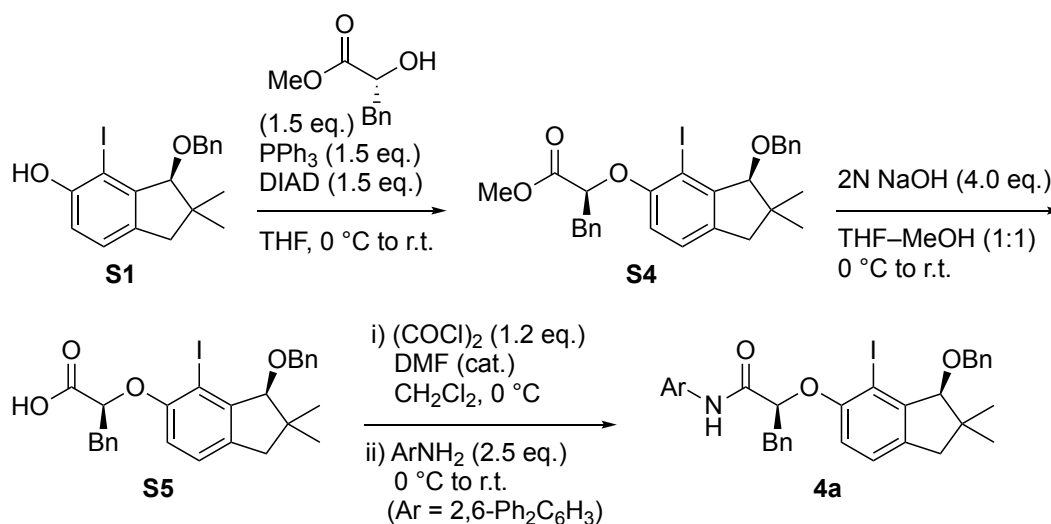


To a stirred solution of **S3** (0.100 mmol, 49.4 mg) in CH_2Cl_2 (3.0 mL) were added a catalytic amount of DMF (1 drop) and $(\text{COCl})_2$ (0.120 mmol, 10.3 μL) at 0 °C under

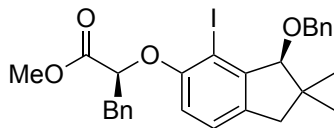
argon atmosphere. After stirring for 20 min at the same temperature, [1,1':3',1''-terphenyl]-2'-amine (0.250 mmol, 61.3 mg) was added. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 N HCl aq., extracted with CH₂Cl₂, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 5/1) to afford the title compound as a colorless solid in 62% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.12 (s, 1H), 7.22-7.41 (m, 18H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.17 (d, *J* = 8.2 Hz, 1H), 4.90 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 10.5 Hz, 1H), 4.34 (s, 1H), 4.10 (d, *J* = 4.0 Hz, 1H), 3.06 (d, *J* = 15.3 Hz, 1H), 2.62 (d, *J* = 15.3 Hz, 1H), 1.93-2.00 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.61 (d, *J* = 6.8 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 169.0, 155.3, 148.9, 140.8, 139.9, 138.6, 138.1, 130.6, 130.1, 129.0, 128.4, 128.3, 128.2, 127.7, 127.4, 127.3, 125.8, 113.2, 93.9, 87.6, 84.8, 74.2, 46.4, 43.8, 31.6, 28.5, 23.0, 19.0, 16.7; **IR (neat)** 3359, 2959, 1687, 1495, 1457, 1270, 1251, 1068 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₄₁H₄₀O₃NINa: *m/z* 744.1951 ([M+Na]⁺), found: *m/z* 744.1949 ([M+Na]⁺); **Optical rotation** [α]_D²⁵ = +41.9 (*c* = 1.1, CHCl₃).

3.5.1.2 Preparation of 4a

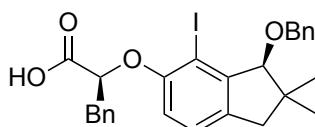


Methyl (S)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-3-phenyl-propanoate (S4)



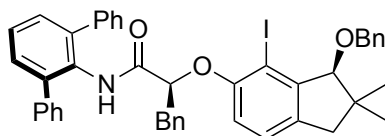
To a stirred solution of **S1** (0.500 mmol, 0.197 g) in THF (3.0 mL) were added PPh_3 (0.750 mmol, 0.197 g), methyl (*R*)-2-hydroxy-3-phenylpropionate (0.750 mmol, 0.135 g) and DIAD (0.750 mmol, 0.148 mL) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, solvent was removed under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 10/1) to afford the title compound as a colorless oil in 79% yield.

(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-3-phenylpropanoic acid (S5)



Prepared by hydrolysis of **S4** with 4.0 equivalents of NaOH in THF/MeOH/H₂O (1/1/1 v/v/v) co-solvent at 0 °C to room temperature. The obtained crude material was pure enough to be used for the next step. Characterization was performed after the next step.

(S)-N-([1,1':3',1''-Terphenyl]-2'-yl)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-3-phenylpropanamide (4a)

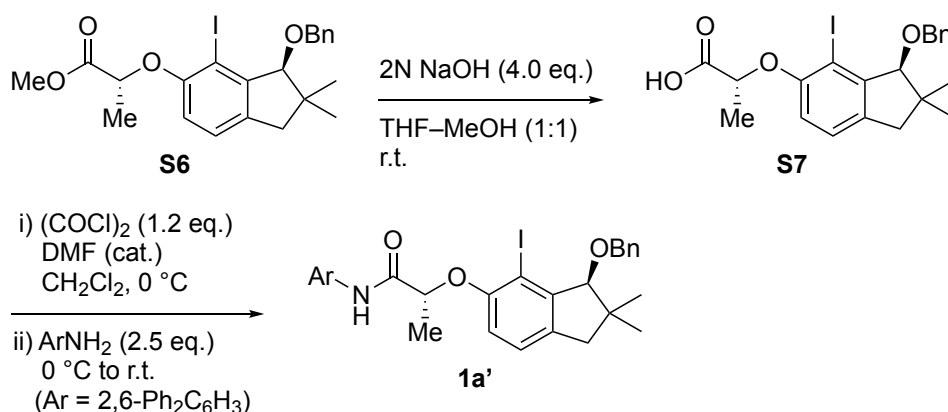


To a stirred solution of **S5** in CH_2Cl_2 (0.03 M) were sequentially added 1.2 equivalent of oxalyl chloride and a catalytic amount of DMF at 0 °C under argon atmosphere. After stirring for 20 min, 2.5 equivalents of 2,6-diphenylaniline were added to the reaction at the same temperature. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 *N* HCl aq., extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent:

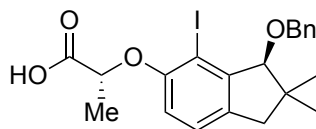
hexane/AcOEt = 5/1) to afford the title compound as a colorless solid in 47% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.19 (s, 1H), 7.25-7.47 (m, 18H), 7.10-7.18 (m, 5H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.02 (d, *J* = 8.2 Hz, 1H), 4.82 (d, *J* = 10.5 Hz, 1H), 4.70 (d, *J* = 10.5 Hz, 1H), 4.47 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.27 (s, 1H), 2.99 (d, *J* = 15.3 Hz, 1H), 2.87 (dd, *J* = 14.3, 3.0 Hz, 1H), 2.65 (dd, *J* = 14.3, 9.2 Hz, 1H), 2.55 (d, *J* = 15.6 Hz, 1H), 1.33 (s, 3H), 1.09 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 169.0, 154.5, 148.7, 140.6, 139.7, 138.6, 138.2, 136.9, 130.5, 130.0, 129.8, 129.0, 128.4, 128.4, 128.3, 128.1, 127.7, 127.7, 127.3, 126.7, 125.7, 113.1, 93.8, 87.6, 81.3, 74.1, 46.3, 43.7, 38.6, 28.4, 22.9; **IR (neat)** 3350, 3060, 3030, 2926, 1496, 1457, 1268, 1251, 1067 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₄₅H₄₀O₃NINa: *m/z* 792.1951 ([M+Na]⁺), found: *m/z* 792.1955 ([M+Na]⁺); **Optical rotation** [α]_D²⁶ = -25.4 (*c* = 3.7, CHCl₃).

3.5.1.3 Preparation of 1a'



(R)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanoic acid (S7)

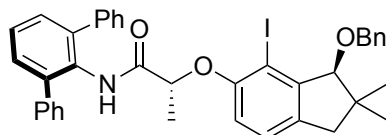


To a stirred solution of methyl (*R*)-2-(((*S*)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1*H*-inden-5yl)oxy)propanoate **S6**¹⁹ (1.63 mmol, 0.783 g) in THF (3.0 mL) and MeOH (3.0 mL), 2 *N* NaOH aq. (3.0 mL) was added at room temperature. After stirring for 60 min, the reaction was quenched with 1 *N* HCl aq., extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was pure enough to be used for next

step.

¹H NMR (500 MHz, CDCl₃) δ 7.35 (d, *J* = 7.1 Hz, 2H), 7.18-7.27 (m, 3H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 7.9 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.71 (d, *J* = 10.8 Hz, 1H), 4.49 (q, *J* = 4.9 Hz, 1H), 4.28 (s, 1H), 2.97 (d, *J* = 15.3 Hz, 1H), 2.47 (d, *J* = 15.3 Hz, 1H), 1.43 (d, *J* = 4.5 Hz, 3H), 1.30 (s, 3H), 0.99 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 177.5, 155.2, 148.8, 139.0, 138.8, 128.3, 128.0, 127.6, 125.8, 117.4, 93.9, 89.9, 76.7, 74.0, 46.3, 43.7, 28.2, 22.9, 18.5; **IR** (neat) 2954, 1713, 1586, 1454, 1271, 1252, 1091, 1052 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₂₁H₂₃O₄INa: *m/z* 489.0539 ([M+Na]⁺), found: *m/z* 489.0539 ([M+Na]⁺); **Optical rotation** [α]_D¹⁴ = +54.1 (*c* = 1.0, CHCl₃).

(*R*)-*N*-([1,1':3',1''-Terphenyl]-2'-yl)-2-(((*S*)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy)propanamide (1a')

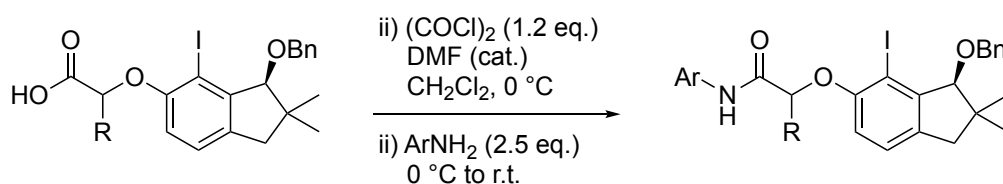


To a stirred solution of **S7** in CH₂Cl₂ (0.03 M) were added 1.2 equivalent of oxalyl chloride and a catalytic amount of DMF at 0 °C under argon atmosphere. After stirring for 20 min, 2.5 equivalents of 2,6-diphenylaniline were added to the reaction at the same temperature. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 *N* HCl aq., extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: CH₂Cl₂ only) to afford the title compound as a colorless solid in 45% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.15 (s, 1H), 7.24-7.47 (m, 18H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.28 (d, *J* = 8.2 Hz, 1H), 4.89 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 10.5 Hz, 1H), 4.36 (q, *J* = 6.7 Hz, 1H), 4.28 (s, 1H), 3.06 (d, *J* = 15.3 Hz, 1H), 2.54 (d, *J* = 15.6 Hz, 1H), 1.36 (s, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.0, 154.2, 149.1, 141.1, 139.7, 138.8, 138.6, 130.7, 130.0, 129.0, 128.4, 128.3, 128.1, 127.8, 127.5, 125.7, 114.0, 93.9, 88.6, 76.5, 74.3, 46.3, 43.8, 28.2, 23.0, 18.0 (*One ¹³C signal is overlapping with others.*); **IR** (neat) 3244, 2955, 2928, 1689, 1497, 1455, 1252, 1068, 1028 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₃₉H₃₆O₃INa: *m/z* 716.1632 ([M+Na]⁺), found: *m/z* 716.1642 ([M+Na]⁺); **Optical rotation** [α]_D²⁷ = +68.5 (*c* = 1.0, CHCl₃).

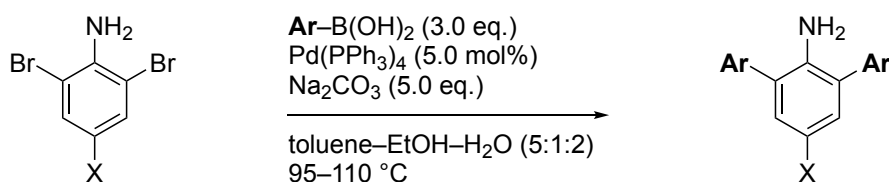
3.5.1.4 Preparation of other catalysts

3.5.1.4.1 General procedure A for synthesis of lactamides



To a stirred solution of substrate carboxylic acid in CH₂Cl₂ (0.03 M) were added 1.2 equivalent of oxalyl chloride and a catalytic amount of DMF at 0 °C under argon atmosphere. After stirring for 20 min, 2.5 equivalents of arylamine were added to the reaction at the same temperature. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1 N HCl aq., extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography.

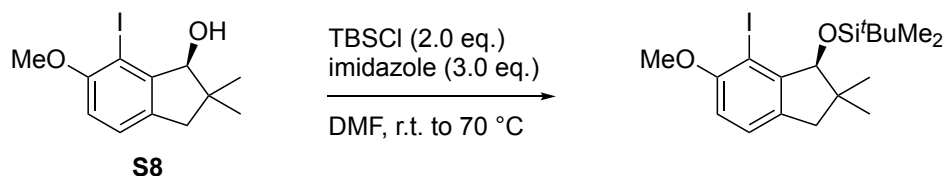
3.5.1.4.2 General procedure B for synthesis of 2,6-diarylanilines



To a stirred solution of 2,6-dibromoarylamine, 3.0 equivalents of ArB(OH)₂, and 5.0 equivalents of Na₂CO₃ in toluene/EtOH/H₂O co-solvent was added 5.0 mol% of Pd(PPh₃)₄ at room temperature under nitrogen atmosphere. After deoxygenated by bubbling nitrogen gas, the mixture was heated up to 95–110 °C and stirred for the indicated time. After cooled down to room temperature and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography.

3.5.1.4.3 Preparation of 7-iodo-6-methoxy-1-siloxyindanols

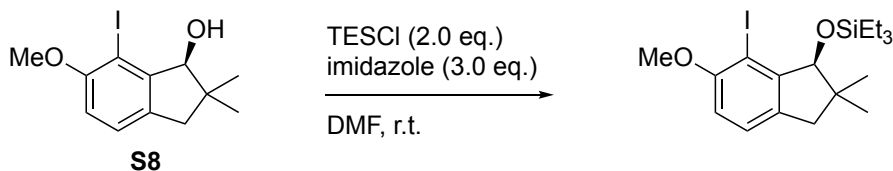
(*S*)-*tert*-Butyl((7-iodo-6-methoxy-2,2-dimethyl-2,3-dihydro-1*H*-inden-1-yl)oxy)dimethylsilane



To a mixture of **S8** (0.200 mmol, 63.6 mg), TBSCl (0.400 mmol, 60.3 mg) and imidazole (0.600 mmol, 40.8 mg) was added anhydrous DMF (1.0 mL) at room temperature under argon atmosphere. After stirring for 15 hours at this temperature, the reaction was heated up to 60 °C and stirred for 7 hours. After that, the reaction was quenched with H₂O at room temperature, and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 99/1 to 30/1) to afford the title compound as a colorless oil in 35% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.05 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 4.50 (s, 1H), 3.86 (s, 3H), 3.08 (d, *J* = 14.7 Hz, 1H), 2.47 (d, *J* = 14.7 Hz, 1H), 1.21 (s, 3H), 0.85 (s, 9H), 0.84 (s, 3H), 0.14 (s, 3H), 0.07 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 156.5, 151.8, 137.9, 125.6, 110.7, 88.5, 86.8, 56.9, 45.3, 45.1, 26.4, 26.2, 23.5, 18.8, -2.5, -3.2; **IR (neat)** 2955, 2928, 2903, 2855, 1460, 1254, 1065, 835 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₈H₂₉O₂INaSi: *m/z* 455.0879 ([M+Na]⁺), found: *m/z* 455.0873 ([M+Na]⁺); **Optical rotation** [α]_D²⁷ = +84.5 (*c* = 1.5, CHCl₃).

(*S*)-Triethyl((7-iodo-6-methoxy-2,2-dimethyl-2,3-dihydro-1*H*-inden-1-yl)oxy)silane



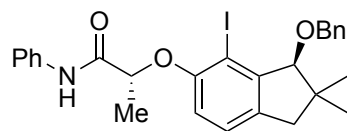
To a stirred solution of **S8** (0.200 mmol, 63.6 mg) and imidazole (0.600 mmol, 40.8 mg) in CH₂Cl₂ (1.0 mL) was added triethylsilyl chloride (0.400 mmol, 67.1 μL) at room temperature under argon atmosphere. After stirring for 60 min at this temperature, the reaction was quenched with H₂O, and extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure.

The residue was purified by column chromatography (eluent: hexane/AcOEt = 40/1) to afford the title compound as a colorless oil in >99% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.05 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 4.51 (s, 1H), 3.86 (s, 3H), 3.06 (d, *J* = 15.0 Hz, 1H), 2.49 (d, *J* = 14.7 Hz, 1H), 1.20 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 3H), 0.73-0.78 (m, 6H); **¹³C NMR** (125 MHz, CDCl₃) δ 156.6, 151.4, 137.5, 125.6, 110.9, 88.4, 86.5, 56.9, 45.5, 44.4, 26.6, 23.2, 7.4, 6.2; **IR (neat)** 3350, 3060, 3030, 2955, 2926, 1496, 1457, 1251, 1067 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₈H₂₉O₂INaSi: *m/z* 455.0879 ([M+Na]⁺), found: *m/z* 455.0874 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +87.6 (*c* = 1.1, CHCl₃).

3.5.1.4.4 Preparation of (*R,S*)-indanol-based lactamides

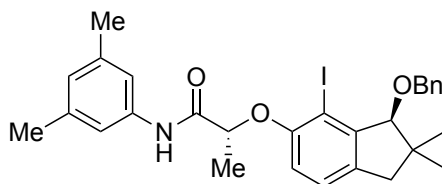
(*R*)-2-(((*S*)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy)-*N*-phenylpropanamide



Prepared according to **the general procedure A** with **S7**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 89/11 to 85/15) to afford the title compound as a colorless oil in 86% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.84 (s, 1H), 7.65 (m, 2H), 7.40-7.42 (m, 2H), 7.24-7.36 (m, 5H), 7.12-7.15 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.84 (q, *J* = 6.7 Hz, 1H), 4.78 (d, *J* = 10.5 Hz, 1H), 4.38 (s, 1H), 3.08 (d, *J* = 15.6 Hz, 1H), 2.60 (d, *J* = 15.6 Hz, 1H), 1.72 (d, *J* = 6.5 Hz, 3H), 1.37 (s, 3H), 1.08 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 169.5, 154.0, 149.4, 139.1, 138.6, 137.5, 129.1, 128.4, 128.1, 127.7, 126.0, 124.7, 120.0, 114.1, 93.8, 88.7, 76.6, 74.1, 46.3, 43.9, 28.3, 22.9, 18.5; **IR (neat)** 3374, 2955, 1693, 1600, 1531, 1467, 1444, 1253 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₇H₂₈O₃NINa: *m/z* 564.1012 ([M+Na]⁺), found: *m/z* 564.1011 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +22.3 (*c* = 3.4, CHCl₃).

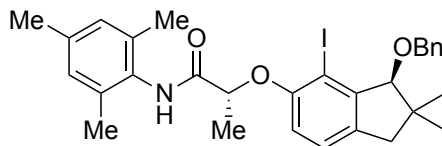
(R)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(3,5-dimethylphenyl)propanamide



Prepared according to **the general procedure A** with **S7**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 89/11 to 85/15) to afford the title compound as a colorless oil in 83% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.69 (s, 1H), 7.41-7.43 (m, 2H), 7.24-7.33 (m, 5H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.78 (s, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.81 (q, *J* = 6.5 Hz, 1H), 4.79 (d, *J* = 10.2 Hz, 1H), 4.38 (s, 1H), 3.08 (d, *J* = 15.3 Hz, 1H), 2.60 (d, *J* = 15.3 Hz, 1H), 2.31 (s, 6H), 1.70 (d, *J* = 6.5 Hz, 3H), 1.38 (s, 3H), 1.08 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 169.4, 154.1, 149.4, 139.1, 138.9, 138.6, 137.2, 128.4, 128.1, 127.7, 126.5, 126.0, 117.7, 114.1, 93.8, 88.8, 76.6, 74.2, 46.3, 43.8, 28.3, 22.9, 21.5, 18.5; **IR (neat)** 3377, 2954, 1690, 1541, 1457, 1252, 1064 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₉H₃₂O₃Na: *m/z* 592.1325 ([M+Na]⁺), found: *m/z* 592.1326 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +20.9 (*c* = 3.3, CHCl₃).

(R)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-mesitylpropanamide



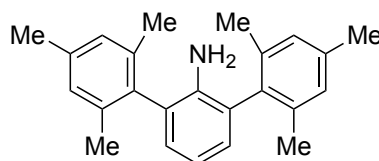
Prepared according to **the general procedure A** with **S7**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 89/11 to 80/20) to afford the title compound as a colorless oil in 74% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.11 (s, 1H), 7.39 (d, *J* = 7.1 Hz, 2H), 7.23-7.30 (m, 3H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 4.92 (q, *J* = 6.8 Hz, 1H), 4.90 (d, *J* = 10.2 Hz, 1H), 4.77 (d, *J* = 10.5 Hz, 1H), 4.37 (s, 1H), 3.09 (d, *J* = 15.3 Hz, 1H), 2.60 (d, *J* = 15.6 Hz, 1H), 2.27 (s, 3H), 2.16 (s, 6H), 1.76 (d, *J* = 6.8 Hz, 3H), 1.37 (s, 3H), 1.07 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.2, 154.2, 149.5, 138.9, 138.7, 137.2, 135.3, 130.3, 129.1, 128.4, 128.1, 127.7, 125.9, 113.9, 93.9, 88.6, 76.5, 74.2, 46.3,

43.9, 28.2, 22.9, 21.0, 18.9, 18.5; **IR** (neat) 3327, 2954, 2924, 2866, 1694, 1498, 1457, 1252, 1088 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₃₀H₃₄O₃Na: *m/z* 606.1481 ([M+Na]⁺), found: *m/z* 606.1483 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +30.1 (*c* = 3.1, CHCl₃).

3.5.1.4.5 Preparation of (*R,R*)-indanol-based lactamides (1)

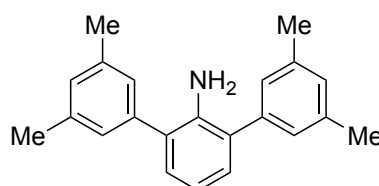
2,2'',4,4'',6,6''-Hexamethyl-[1,1':3',1''-terphenyl]-2'-amine (arylamine 1)



Prepared according to **the general procedure B** with 2,6-dibromoaniline and 2,4,6-trimethylphenylboronic acid (reaction temperature: 100 °C, reaction time: 4 days). The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 70/30 to 50/50) to afford the title compound as a colorless solid in 68% yield.

¹H NMR (500 MHz, CDCl₃) δ 6.97 (s, 4H), 6.90-6.92 (m, 2H), 6.85 (m, 1H), 3.14 (brs, 2H), 2.33 (s, 6H), 2.05 (s, 12H); **¹³C NMR** (125 MHz, CDCl₃) δ 141.1, 137.3, 137.1, 135.8, 129.0, 128.8, 126.2, 118.4, 21.5, 20.4; **IR** (neat) 3474, 3357, 2915, 1603, 1448, 1260 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₂₄H₂₈N: *m/z* 330.2222 ([M+H]⁺), found: *m/z* 330.2217 ([M+H]⁺).

3,3'',5,5''-Tetramethyl-[1,1':3',1''-terphenyl]-2'-amine (arylamine 2)

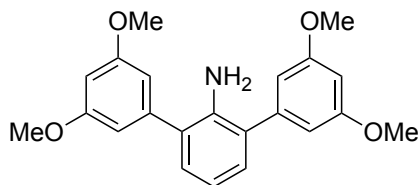


Prepared according to **the general procedure B** with 2,6-dibromoaniline and 3,5-dimethylphenylboronic acid (reaction temperature: 100 °C, reaction time: overnight). The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 4/1) to afford the title compound as a colorless solid in 92% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.12 (s, 4H), 7.08 (d, *J* = 7.4 Hz, 2H), 6.99 (s, 2H), 6.84 (t, *J* = 7.5 Hz, 1H), 3.85 (brs, 2H), 2.36 (s, 12H); **¹³C NMR** (125 MHz, CDCl₃) δ 141.2, 140.3, 138.6, 129.9, 129.2, 128.5, 127.5, 118.4, 21.7; **IR** (neat) 1061, 1455, 905 cm⁻¹;

HRMS (ESI) exact mass calcd. for $C_{22}H_{24}N$: m/z 302.1909 ($[M+H]^+$), found: m/z 302.1902 ($[M+H]^+$).

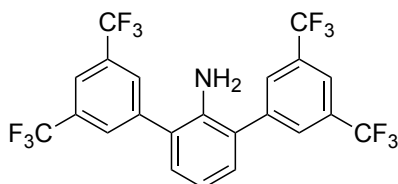
3,3'',5,5''-Tetramethoxy-[1,1':3',1''-terphenyl]-2'-amine (arylamine 3)



Prepared according to **the general procedure B** with 2,6-dibromoaniline and 3,5-dimethoxyphenylboronic acid ($Pd(PPh_3)_4$ (7.5 mol%), reaction temperature: 110 °C, reaction time: overnight). The residue was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 85/15) to afford the title compound as a colorless solid in 94% yield.

1H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, $J = 7.7$ Hz, 2H), 6.84 (t, $J = 7.5$ Hz, 1H), 6.64 (d, $J = 2.3$ Hz, 4H), 6.46 (t, $J = 2.3$ Hz, 2H), 3.98 (brs, 2H), 3.81 (s, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.2, 141.9, 140.9, 129.6, 127.8, 117.8, 107.3, 99.7, 55.5; **IR (neat)** 1590, 1455, 1438, 1411, 1333, 1203, 1151, 1062 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $C_{22}H_{24}O_4N$: m/z 366.1705 ($[M+H]^+$), found: m/z 366.1703 ($[M+H]^+$).

3,3'',5,5''-Tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-amine (arylamine 4)

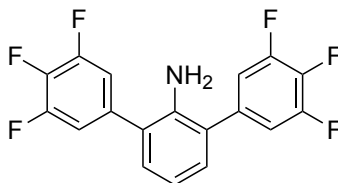


Prepared according to **the general procedure B** with 2,6-dibromoaniline and 3,5-bis(trifluoromethyl)phenylboronic acid ($Pd(PPh_3)_4$ (15 mol%), reaction temperature: 100 °C, reaction time: overnight). The residue was purified by column chromatography (eluent: hexane/ CH_2Cl_2 = 90/10 to 88/12) to afford the title compound as a colorless solid in >99% yield.

1H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 4H), 7.90 (s, 2H), 7.17 (d, $J = 7.4$ Hz, 2H), 6.97 (t, $J = 7.5$ Hz, 1H), 3.69 (brs, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.4 (s), 140.5 (s), 132.6 (q, $J = 273$ Hz), 131.2 (s), 129.7 (s), 125.6 (s), 123.3 (q, $J = 33.4$ Hz), 121.5-121.7 (m), 119.3 (s); **^{19}F NMR** (466 MHz, $CDCl_3$) δ -62.7 (s); **IR (neat)** 1619, 1373, 1274,

1170, 1122, 1105, 900 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{22}\text{H}_{12}\text{NF}_{12}$: m/z 518.0773 ($[\text{M}+\text{H}]^+$), found: m/z 518.0769 ($[\text{M}+\text{H}]^+$).

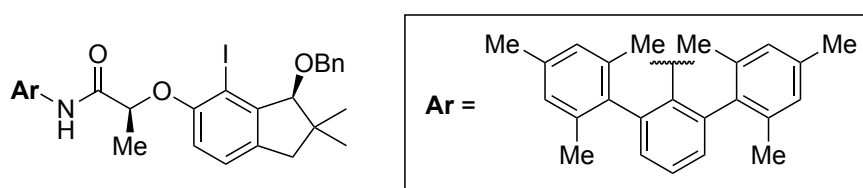
3,3'',4,4'',5,5''-Hexafluoro-[1,1':3',1''-terphenyl]-2'-amine (arylamine 5)



Prepared according to **the general procedure B** with 2,6-dibromoaniline and 3,4,5-trifluorophenylboronic acid ($\text{Pd}(\text{PPh}_3)_4$ (7.5 mol%) was used., reaction temperature: 110 $^{\circ}\text{C}$, reaction time: overnight). The residue was purified by column chromatography (eluent: hexane/ CH_2Cl_2 = 90/10 to 88/12) to afford the title compound as a colorless solid in 91% yield.

^1H NMR (500 MHz, CDCl_3) δ 7.05-7.15 (m, 6H), 6.87 (t, J = 7.5 Hz, 1H), 3.78 (brs, 2H); **^{13}C NMR** (125 MHz, CDCl_3) δ 151.6 (ddd, J = 252, 9.5 3.6 Hz), 140.6 (s), 139.3 (dt, J = 253, 15.5 Hz), 135.4-135.6 (m), 130.5 (s), 125.4 (s), 118.8 (s), 113.6 (dd, J = 16.7, 4.8 Hz); **^{19}F NMR** (466 MHz, CDCl_3) -133.3 to -133.4 (m), -161.4 (tt, J = 21.0, 6.7 Hz); **IR** (neat) 1613, 1522, 1460, 1413, 1352, 1040 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{18}\text{H}_{10}\text{NF}_6$: m/z 354.0712 ($[\text{M}+\text{H}]^+$), found: m/z 354.0700 ($[\text{M}+\text{H}]^+$).

(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(2,2'',4,4'',6,6''-hexamethyl-[1,1':3',1''-terphenyl]-2'-yl)propanamide (1b)

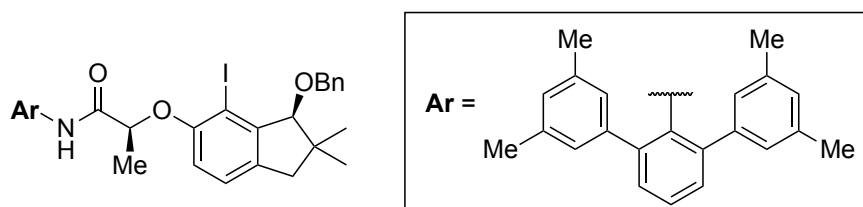


Prepared according to **the general procedure A** with (S)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanoic acid (**S9**) and **arylamine 1**. The residue was purified by column chromatography (eluent: hexane/ AcOEt = 4/1) to afford the title compound as a colorless solid in 88% yield.

^1H NMR (500 MHz, CDCl_3) δ 7.41 (m, 3H), 7.24-7.33 (m, 4H), 7.15 (d, J = 7.7 Hz, 2H), 6.92 (s, 2H), 6.81 (d, J = 8.2 Hz, 1H), 6.77 (s, 2H), 6.06 (d, J = 8.2 Hz, 1H), 4.87 (d, J = 10.2 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.31 (s, 1H), 4.21 (q, J = 6.7 Hz, 1H), 3.04 (d, J

= 15.3 Hz, 1H), 2.58 (d, J = 15.3 Hz, 1H), 2.29 (s, 6H), 2.11 (s, 6H), 1.89 (s, 6H), 1.36 (s, 3H), 1.10 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.8, 154.0, 148.9, 139.5, 138.8, 138.1, 136.7, 136.3, 136.1, 135.7, 132.7, 129.6, 128.4, 128.4, 128.1, 127.8, 127.7, 125.7, 113.2, 93.8, 88.0, 75.6, 74.1, 46.4, 43.9, 28.4, 23.0, 21.3, 20.8, 20.3, 18.0; IR (neat) 3379, 2920, 1698, 1497, 1455, 1251, 1125, 1085, 1069 cm^{-1} ; HRMS (ESI) exact mass calcd. for $\text{C}_{45}\text{H}_{48}\text{O}_3\text{NINa}$: m/z 800.2577 ($[\text{M}+\text{Na}]^+$), found: m/z 800.2577 ($[\text{M}+\text{Na}]^+$); Optical rotation $[\alpha]_{\text{D}}^{26} = +51.7$ (c = 1.0, CHCl_3).

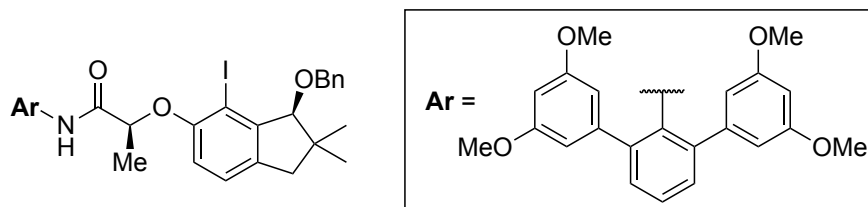
(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(3,3',5,5'-tetramethyl-[1,1':3,1''-terphenyl]-2'-yl)propanamide (1c)



Prepared according to **the general procedure A** with **S9** and **arylamine 2**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 85/15) to afford the title compound as a colorless solid in 95% yield.

^1H NMR (500 MHz, CDCl_3) δ 8.27 (s, 1H), 7.24-7.40 (m, 8H), 7.04 (s, 4H), 6.90 (s, 2H), 6.89 (d, J = 8.4 Hz, 1H), 6.29 (d, J = 8.2 Hz, 1H), 4.86 (d, J = 10.2 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.37 (q, J = 6.7 Hz, 1H), 4.29 (s, 1H), 3.04 (d, J = 15.3 Hz, 1H), 2.56 (d, J = 15.3 Hz, 1H), 2.26 (s, 12H), 1.36 (s, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.0, 154.5, 149.0, 141.3, 139.7, 138.7, 138.5, 137.6, 130.6, 129.7, 129.0, 128.4, 128.2, 127.8, 127.7, 126.9, 125.8, 114.0, 93.9, 88.7, 74.1, 46.4, 43.8, 28.3, 22.9, 21.4, 17.9 (One ^{13}C signal is overlapping with others.); IR (neat) 3385, 2955, 2918, 2865, 1695, 1603, 1497, 1457, 1253, 1090 cm^{-1} ; HRMS (ESI) exact mass calcd. for $\text{C}_{43}\text{H}_{44}\text{O}_3\text{NINa}$: m/z 772.2264 ($[\text{M}+\text{Na}]^+$), found: m/z 772.2260 ($[\text{M}+\text{Na}]^+$); Optical rotation $[\alpha]_{\text{D}}^{25} = +50.6$ (c = 1.1, CHCl_3).

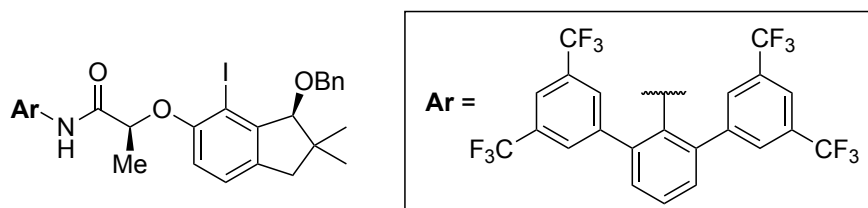
(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(3,3'',5,5''-tetramethoxy-[1,1':3',1''-terphenyl]-2'-yl)propanamide (1d)



Prepared according to **the general procedure A** with **S9** and **arylamine 3**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1) to afford the title compound as a colorless solid in 73% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.17 (s, 1H), 7.37-7.43 (m, 5H), 7.27-7.32 (m, 3H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 4H), 6.41 (t, *J* = 2.3 Hz, 2H), 6.32 (d, *J* = 8.2 Hz, 1H), 4.86 (d, *J* = 10.2 Hz, 1H), 4.73 (d, *J* = 10.2 Hz, 1H), 4.42 (q, *J* = 6.7 Hz, 1H), 4.27 (s, 1H), 3.74 (s, 12H), 3.03 (d, *J* = 15.6 Hz, 1H), 2.56 (d, *J* = 15.6 Hz, 1H), 1.35 (s, 3H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.06 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.5, 160.6, 154.3, 148.9, 141.6, 141.2, 138.7, 138.6, 130.6, 129.9, 128.4, 128.1, 127.7, 125.8, 114.5, 107.0, 100.2, 93.8, 88.8, 77.0, 74.1, 55.5, 46.3, 43.8, 28.3, 22.9, 17.9 (*One ¹³C signal is overlapping with others.*); **IR (neat)** 3369, 2956, 2837, 1690, 1594, 1456, 1204, 1154, 1064 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₄₃H₄₄O₇NINa: *m/z* 836.2055 ([M+Na]⁺), found: *m/z* 836.2051 ([M+Na]⁺); **Optical rotation** [α]_D²⁶ = +32.7 (*c* = 1.1, CHCl₃).

(S)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(3,3'',5,5''-Tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)propanamide (1e)

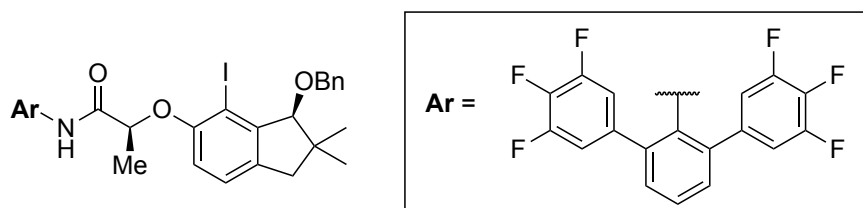


Prepared according to **the general procedure A** with **S9** and **arylamine 4**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 94/6) to afford the title compound as a colorless solid in 58% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.47 (s, 1H), 7.89 (s, 4H), 7.84 (s, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.30 (m, 3H), 6.94 (d, *J* = 7.9 Hz,

1H), 6.38 (d, $J = 8.2$ Hz, 1H), 4.80 (d, $J = 10.5$ Hz, 1H), 4.71 (d, $J = 10.5$ Hz, 1H), 4.44 (q, $J = 6.6$ Hz, 1H), 4.23 (s, 1H), 3.02 (d, $J = 15.6$ Hz, 1H), 2.55 (d, $J = 15.3$ Hz, 1H), 1.34 (s, 1H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.5 (s), 153.4 (s), 149.0 (s), 141.2 (s), 139.0 (s), 138.6 (s), 138.5 (s), 131.9 (q, $J = 34$ Hz), 131.1 (s), 131.0 (s), 129.3 (s), 128.7 (s), 128.4 (s), 128.2 (s), 127.8 (s), 125.8 (s), 123.3 (q, $J = 274$ Hz), 121.7 (s), 113.5 (s), 93.7 (s), 88.2 (s), 75.9 (s), 74.1 (s), 46.2 (s), 43.8 (s), 27.9 (s), 22.8 (s), 17.3 (s); ^{19}F NMR (466 MHz, CDCl_3) δ -62.6 (s); IR (neat) 3351, 2959, 1697, 1528, 1457, 1372, 1276, 1175, 1129 cm^{-1} ; HRMS (ESI) exact mass calcd. for $\text{C}_{43}\text{H}_{32}\text{O}_3\text{NF}_{12}\text{INa}$: m/z 988.1127 ($[\text{M}+\text{Na}]^+$), found: m/z 988.1126 ($[\text{M}+\text{Na}]^+$); Optical rotation $[\alpha]_{\text{D}}^{26} = +58.8$ ($c = 1.1$, CHCl_3).

(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(3,3'',4,4'',5,5''-hexafluoro-[1,1':3',1''-terphenyl]-2'-yl)propanamide (1f)



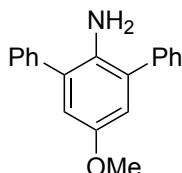
Prepared according to **the general procedure A** with **S9** and **arylamine 5**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 89/11) to afford the title compound as a colorless solid in 79% yield.

^1H NMR (500 MHz, CDCl_3) δ 8.18 (s, 1H), 7.45 (t, $J = 7.7$ Hz, 1H), 7.39 (d, $J = 7.1$ Hz, 2H), 7.35 (d, $J = 7.7$ Hz, 2H), 7.27-7.32 (m, 3H), 7.00 (dd, $J = 7.9$, 7.0 Hz, 4H), 6.99 (d, $J = 8.2$ Hz, 1H), 6.42 (d, $J = 8.2$ Hz, 1H), 4.86 (d, $J = 10.5$ Hz, 1H), 4.74 (d, $J = 10.5$ Hz, 1H), 4.56 (q, $J = 6.8$ Hz, 1H), 4.30 (s, 1H), 3.02 (d, $J = 15.6$ Hz, 1H), 2.60 (d, $J = 15.6$ Hz, 1H), 1.34 (s, 3H), 1.32 (d, $J = 6.8$ Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7 (s), 153.6 (s), 151.0 (ddd, $J = 251$, 9.6, 3.6 Hz), 149.2 (s), 139.5 (dt, $J = 254$, 15.6 Hz), 139.1 (s), 138.5 (s), 138.5 (s), 134.9-135.1 (m), 130.6 (s), 130.6 (s), 128.4 (s), 128.3 (s), 128.2 (s), 127.8 (s), 125.9 (s), 113.5 (s), 113.4 (s), 113.4 (dd, $J = 16.8$, 4.9 Hz), 93.8 (s), 88.0 (s), 76.0 (s), 74.2 (s), 46.3 (s), 44.0 (s), 43.9 (s), 28.1 (s), 23.0 (s), 18.0 (s); ^{19}F NMR (466 MHz, CDCl_3) δ -133.8 (dd, $J = 20.5$, 7.9 Hz), -161.3 (tt, $J = 20.5$, 6.5 Hz); IR (neat) 3287, 2924, 1652, 1528, 1414, 1249, 1082, 1036 cm^{-1} ; HRMS (ESI) exact mass calcd. for $\text{C}_{39}\text{H}_{30}\text{O}_3\text{NF}_6\text{INa}$: m/z 824.1067 ($[\text{M}+\text{Na}]^+$), found: m/z 824.1067

([M+Na]⁺); **Optical rotation** $[\alpha]_{\text{D}}^{26} = +65.8$ ($c = 1.0$, CHCl₃).

3.5.1.4.6 Preparation of (*R,R*)-indanol-based lactamides (2)

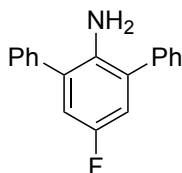
5'-Methoxy-[1,1':3',1''-terphenyl]-2'-amine (arylamine 6)



Prepared according to **the general procedure B** with 2,6-dibromo-4-methoxyaniline and phenylboronic acid (reaction temperature: 95 °C, reaction time: 2 days). The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 67/33) to afford the title compound as a yellowish oil in 97% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.44-7.53 (m, 8H), 7.35-7.38 (m, 2H), 6.76 (s, 2H), 3.79 (s, 3H), 3.54 (brs, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 152.4, 140.0, 134.8, 129.5, 129.3, 129.0, 127.6, 115.7, 56.0; **IR (neat)** 1591, 1464, 1426, 1340, 1201, 1171 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₉H₁₈ON: m/z 276.1388 ([M+H]⁺), found: m/z 276.1383 ([M+H]⁺).

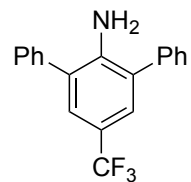
5'-Fluoro-[1,1':3',1''-terphenyl]-2'-amine (arylamine 7)



Prepared according to **the general procedure B** with 2,6-dibromo-4-fluoroaniline and phenylboronic acid (reaction temperature: 95 °C, reaction time: 2 days). The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 3/1) to afford the title compound as a colorless solid in 85% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.45-7.51 (m, 8H), 7.36-7.41 (m, 2H), 6.88 (d, $J = 9.1$ Hz, 2H), 3.67 (brs, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 156.1 (d, $J = 236$ Hz), 139.1 (s), 137.3 (s), 129.4 (s), 129.2 (s), 129.1 (d, $J = 7.2$ Hz), 127.9 (s), 116.2 (d, $J = 22.7$ Hz); **¹⁹F NMR** (466 MHz, CDCl₃) δ -127.7 (t, $J = 8.9$ Hz); **IR (neat)** 1589, 1464, 1426, 1160 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₈H₁₅NF: m/z 264.1183 ([M+H]⁺), found: m/z 264.1181 ([M+H]⁺).

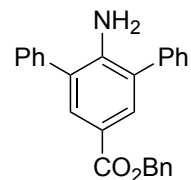
5'-(Trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-amine (arylamine 8)



Prepared according to **the general procedure B** with 2,6-dibromo-4-trifluoromethylaniline and phenylboronic acid (reaction temperature: 95 °C, reaction time: 2 days). The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 3/1) to afford the title compound as a colorless solid in 55% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.46-7.50 (m, 8H), 7.37-7.43 (m, 2H), 7.36 (s, 2H), 4.14 (brs, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 144.1 (s), 138.6 (s), 129.3 (s), 128.1 (s), 127.5 (s), 126.8 (q, *J* = 3.6 Hz), 125.1 (q, *J* = 271 Hz), 119.9 (q, *J* = 33.4 Hz); **¹⁹F NMR** (466 MHz, CDCl₃) δ -61.0 (s); **IR (neat)** 3494, 3395, 1620, 1601, 1355, 1259, 1149, 1106 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₉H₁₅NF₃: *m/z* 314.1157 ([M+H]⁺), found: *m/z* 314.1153 ([M+H]⁺).

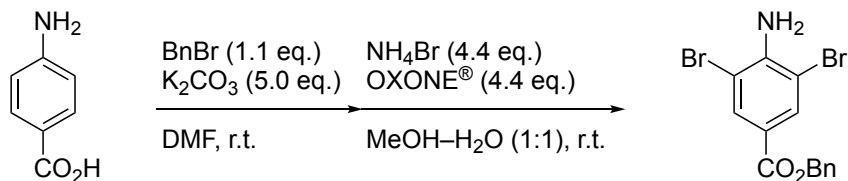
Benzyl 2'-amino-[1,1':3',1''-terphenyl]-5'-carboxylate (arylamine 9)



Prepared according to **the general procedure B** (reaction temperature: 100 °C, reaction time: overnight). The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 70/30 to 50/50) to afford the title compound as a colorless solid in 93% yield.

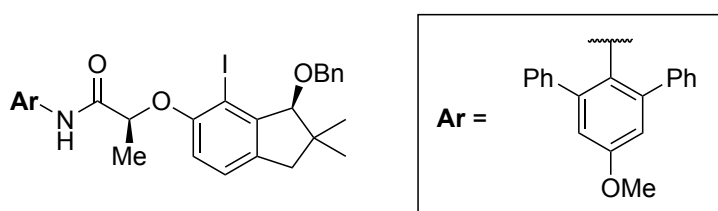
¹H NMR (500 MHz, CDCl₃) δ 7.85 (s, 2H), 7.29-7.53 (m, 15H), 5.33 (s, 2H), 4.28 (s, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 166.8, 145.7, 138.8, 136.8, 131.8, 129.4, 129.3, 128.7, 128.3, 128.2, 127.9, 127.2, 119.4, 66.4; **IR (neat)** 1702, 1611, 1336, 1226, 1107 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₆H₂₂O₂N: *m/z* 380.1645 ([M+H]⁺), found: *m/z* 380.1640 ([M+H]⁺).

Note: 4-Benzyloxycarbonyl-2,6-dibromoaniline was synthesized as follows.



To a stirred solution of 4-aminobenzoic acid (10.0 mmol, 1.37 g) in DMF (50 mL) were added K₂CO₃ (50.0 mmol, 6.91 g) and BnBr (11.0 mmol, 1.31 mL) at room temperature. After stirring for 4 hours at this temperature, the reaction was quenched with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give a crude mixture containing benzyl 4-aminobenzoate. The residue was used for the next step without further purification. To this crude in MeOH (25 mL) and H₂O (25 mL), ammonium bromide (44.0 mmol, 4.31 g) in OXONE® (44.0 mmol, 13.5 g). After stirring for 10 min, the reaction was quenched with saturated Na₂SO₃ aq., filtered through Celite pad, separated, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography to afford the title compound as a colorless solid in 77% yield (over 2 steps). Characterization was performed after the next step.

(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(5'-methoxy-[1,1':3',1''-terphenyl]-2'-yl)propanamide

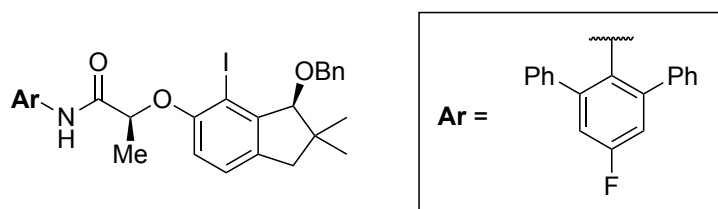


Prepared according to **the general procedure A** with **S9** and **arylamine 6**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1) to afford the title compound as a colorless solid in 79% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.04 (s, 1H), 7.27-7.40 (m, 15H), 6.92 (s, 2H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.29 (d, *J* = 8.2 Hz, 1H), 4.86 (d, *J* = 10.2 Hz, 1H), 4.73 (d, *J* = 10.5 Hz, 1H), 4.38 (q, *J* = 6.7 Hz, 1H), 4.29 (s, 1H), 3.85 (s, 3H), 3.03 (d, *J* = 15.6 Hz, 1H), 2.56 (d, *J* = 15.3 Hz, 1H), 1.35 (s, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.07 (s, 3H); ¹³C NMR (125

MHz, CDCl₃) δ 170.7, 158.5, 154.2, 148.9, 142.6, 139.7, 138.7, 138.5, 129.0, 128.4, 128.3, 128.2, 127.7, 127.5, 125.8, 123.5, 115.3, 114.1, 93.8, 88.7, 76.5, 74.1, 55.7, 46.3, 43.8, 28.3, 22.9, 17.9; **IR** (neat) 3245, 3035, 2956, 1662, 1461, 1347, 1283, 1207, 1055 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₄₀H₃₈O₄Na: m/z 746.1738 ([M+Na]⁺), found: m/z 746.1734 ([M+Na]⁺); **Optical rotation** $[\alpha]_{\text{D}}^{27} = +52.5$ ($c = 1.0$, CHCl₃).

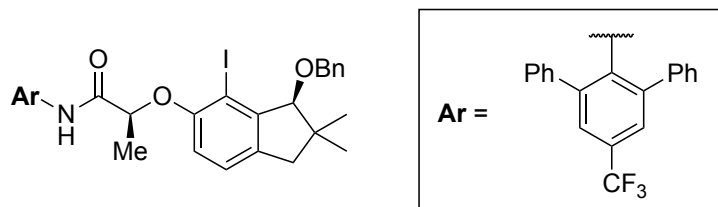
(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(5'-fluoro-[1,1':3',1''-terphenyl]-2'-yl)propanamide



Prepared according to **the general procedure A** with **S9** and **arylamine 7**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1) to afford the title compound as a colorless solid in 48% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.12 (s, 1H), 7.27-7.41 (m, 15H), 7.10 (d, $J = 8.5$ Hz, 2H), 6.91 (d, $J = 7.9$ Hz, 1H), 6.31 (d, $J = 8.2$ Hz, 1H), 4.86 (d, $J = 10.2$ Hz, 1H), 4.74 (d, $J = 10.2$ Hz, 1H), 4.39 (q, $J = 6.7$ Hz, 1H), 4.29 (s, 1H), 3.03 (d, $J = 15.6$ Hz, 1H), 2.57 (d, $J = 15.6$ Hz, 1H), 1.35 (s, 3H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.07 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.4 (s), 161.3 (d, $J = 248$ Hz), 154.1 (s), 149.0 (s), 143.3 (d, $J = 8.3$ Hz), 138.7 (s), 138.6 (d, $J = 2.4$ Hz), 138.6 (s), 128.9 (s), 128.4 (s), 128.1 (s), 127.8 (s), 127.7 (s), 126.7 (d, $J = 2.4$ Hz), 125.7 (s), 116.7 (s), 116.5 (s), 114.1 (s), 93.8 (s), 88.7 (s), 76.4 (s), 74.2 (s), 46.3 (s), 43.8 (s), 28.3 (s), 22.9 (s), 17.8 (s); **¹⁹F NMR** (466 MHz, CDCl₃) δ -114.4 (t, $J = 8.9$ Hz); **IR** (neat) 3243, 3033, 2956, 1663, 1458, 1367, 1283, 1269 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₃₉H₃₅O₃NaF: m/z 734.1538 ([M+Na]⁺), found: m/z 734.1537 ([M+Na]⁺); **Optical rotation** $[\alpha]_{\text{D}}^{27} = +47.8$ ($c = 1.0$, CHCl₃).

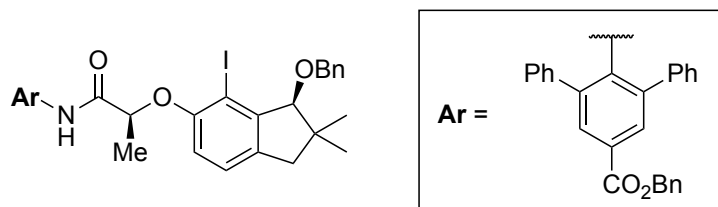
(S)-2-(((S)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-N-(5'-(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)propanamide



Prepared according to **the general procedure A** with **S9** and **arylamine 8**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 86/14 to 75/25) to afford the title compound as a colorless solid in 94% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.31 (s, 1H), 7.63 (s, 2H), 7.28-7.40 (m, 15H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.35 (d, *J* = 8.2 Hz, 1H), 4.86 (d, *J* = 10.5 Hz, 1H), 4.74 (d, *J* = 10.5 Hz, 1H), 4.42 (q, *J* = 6.6 Hz, 1H), 4.29 (s, 1H), 3.04 (d, *J* = 15.3 Hz, 1H), 2.58 (d, *J* = 15.6 Hz, 1H), 1.35 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.08 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.0 (s), 154.0 (s), 149.1 (s), 141.5 (s), 138.7 (s), 138.6 (s), 138.4 (s), 134.1 (s), 129.8 (q, *J* = 33.4 Hz), 128.9 (s), 128.6 (s), 128.4 (s), 128.2 (s), 128.1 (s), 127.8 (s), 126.8 (q, *J* = 3.6 Hz), 125.8 (s), 124.0 (q, *J* = 273 Hz), 114.0 (s), 93.8 (s), 88.6 (s), 77.4 (s), 77.2 (s), 76.9 (s), 76.2 (s), 74.2 (s), 46.3 (s), 43.8 (s), 28.3 (s), 22.9 (s), 17.8 (s); **¹⁹F NMR** (466 MHz, CDCl₃) δ -62.8 (s); **IR (neat)** 3236, 3031, 2956, 1663, 1532, 1457, 1367, 1268, 1128 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₄₀H₃₅O₃NF₃INa: *m/z* 784.1506 ([M+Na]⁺), found: *m/z* 784.1507 ([M+Na]⁺); **Optical rotation** [α]_D²⁷ = +53.4 (*c* = 1.8, CHCl₃).

Benzyl 2'-((S)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanamido)-[1,1':3',1''-terphenyl]-5'-carboxylate (10i)

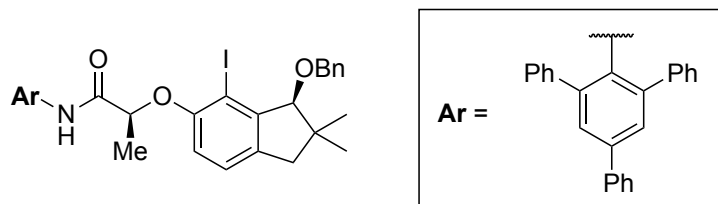


Prepared according to **the general procedure A** with **S9** and **arylamine 9**. The residue was purified by column chromatography (eluent: hexane/AcOEt = 83/17 to 75/25) to afford the title compound as a colorless solid in 89% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.29 (s, 1H), 8.07 (s, 2H), 7.27-7.44 (m, 20H), 6.93 (d, *J*

= 8.2 Hz, 1H), 6.34 (d, J = 8.2 Hz, 1H), 5.38 (s, 2H), 4.86 (d, J = 10.5 Hz, 1H), 4.73 (d, J = 10.5 Hz, 1H), 4.40 (q, J = 6.7 Hz, 1H), 4.28 (s, 1H), 3.04 (d, J = 15.3 Hz, 1H), 2.57 (d, J = 15.6 Hz, 1H), 1.35 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.8, 165.9, 154.0, 149.1, 140.9, 138.9, 138.7, 138.6, 136.0, 135.2, 131.2, 129.2, 129.0, 128.7, 128.5, 128.4, 128.4, 128.2, 127.8, 127.8, 125.8, 114.1, 93.8, 88.7, 76.4, 74.2, 67.1, 46.4, 43.8, 28.3, 23.0, 17.9 (*One ^{13}C signal is overlapping with others.*); **IR** (neat) 3238, 3032, 2956, 1663, 1457, 1235, 1095, 1054 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{47}\text{H}_{42}\text{O}_5\text{NINa}$: m/z 850.2000 ($[\text{M}+\text{Na}]^+$), found: m/z 850.1995 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{27} = +62.6$ (c = 1.0, CHCl_3).

(*S*)-2-(((*S*)-3-(Benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1*H*-inden-5-yl)oxy)-*N*-(5'-phenyl-[1,1':3',1''-terphenyl]-2'-yl)propanamide (10j)

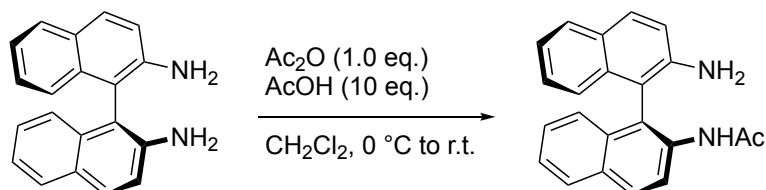


Prepared according to **the general procedure A** with **S9** and 2,4,6-triphenylaniline. The residue was purified by column chromatography (eluent: hexane/AcOEt = 15/1) to afford the title compound as a colorless solid in 58% yield.

^1H NMR (500 MHz, CDCl_3) δ 8.23 (s, 1H), 7.63-7.65 (m, 2H), 7.61 (s, 2H), 7.28-7.46 (m, 18H), 6.93 (d, J = 7.9 Hz, 1H), 6.35 (d, J = 8.2 Hz, 1H), 4.87 (d, J = 10.5 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.43 (q, J = 6.7 Hz, 1H), 4.30 (s, 1H), 3.04 (d, J = 15.6 Hz, 1H), 2.58 (d, J = 15.6 Hz, 1H), 1.36 (s, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.3, 154.2, 149.0, 141.4, 140.7, 140.3, 139.7, 138.7, 138.6, 129.9, 129.1, 129.0, 128.8, 128.4, 128.4, 128.2, 127.8, 127.5, 127.4, 125.8, 114.1, 93.9, 88.7, 76.4, 74.2, 46.4, 43.8, 28.3, 23.0, 17.9 (*One ^{13}C signal is overlapping with others.*); **IR** (neat) 3257, 3027, 2954, 1684, 1664, 1558, 1523, 1463, 1285, 1057 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{45}\text{H}_{40}\text{O}_3\text{NINa}$: m/z 792.1945 ($[\text{M}+\text{Na}]^+$), found: m/z 792.1940 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{27} = +58.7$ (c = 1.3, CHCl_3)

3.5.1.4.7 Preparation of (*R,R,R*)- and (*R,R,S*)-indanol-based BINAM-substituted lactamides

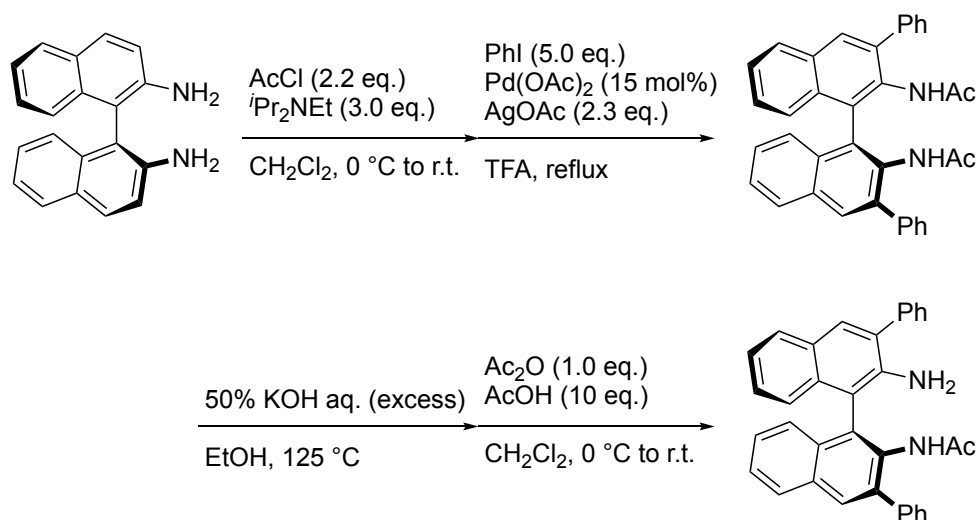
(*S*)-*N*-(2'-Amino-[1,1'-binaphthalen]-2-yl)acetamide



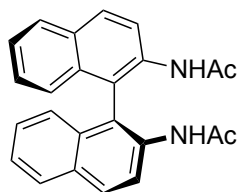
To a stirred solution of (*S*)-[1,1'-binaphthalene]-2,2'-diamine (1.0 mmol, 0.28 g) in CH₂Cl₂ (10 mL) were added AcOH (10 mmol, 0.57 mL) and Ac₂O (1.0 mmol, 95 μ L) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was basified by the addition of 2 *N* NaOH aq. and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1 to 2/1) to afford the title compound as a colorless solid in 66% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.63 (d, *J* = 9.1 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.27-7.28 (m, 2H), 7.19-7.22 (m, 1H), 7.14-7.18 (m, 2H), 7.02 (s, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 3.66 (brs, 2H), 1.86 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 168.8, 142.9, 135.2, 133.7, 132.5, 131.4, 130.5, 129.3, 128.4, 128.3, 128.3, 127.4, 126.9, 125.6, 125.2, 123.7, 122.8, 121.1, 120.7, 118.2, 110.4, 24.8; **IR (neat)** 3350, 3054, 1682, 1619, 1595, 1494, 1425, 1279 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₂H₁₉ON₂: *m/z* 327.1497 ([M+H]⁺), found: *m/z* 327.1492 ([M+H]⁺); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -43.3$ (*c* = 1.0, CHCl₃).

(S)-N-(2'-Amino-3,3'-diphenyl-[1,1'-binaphthalen]-2-yl)acetamide

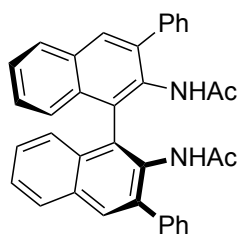


(S)-N,N'-([1,1'-Binaphthalene]-2,2'-diyl)diacetamide



To a stirred solution of (S)-[1,1'-binaphthalene]-2,2'-diamine (5.00 mmol, 1.42 g) in CH₂Cl₂ (30 mL) were added *i*Pr₂NEt (15.0 mmol, 2.61 mL) and AcCl (11.0 mmol, 0.781 mL) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was acidified by the addition of 1 *N* HCl aq. and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1 to 1/2) to afford diacetamide as a colorless solid in >99% yield.

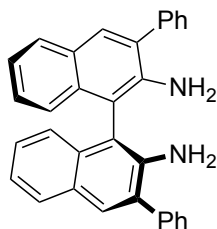
(S)-N,N'-(3,3'-Diphenyl-[1,1'-binaphthalene]-2,2'-diyl)diacetamide



To a stirred solution of diacetamide (1.0 mmol, 0.37 g), AgOAc (2.3 mmol, 0.38 g) and

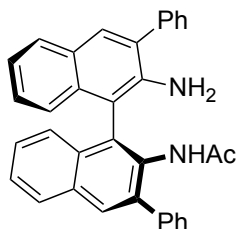
iodobenzene (5.0 mmol, 0.56 mL) in $\text{CF}_3\text{CO}_2\text{H}$ (3.0 mL) was added $\text{Pd}(\text{OAc})_2$ (0.15 mmol, 34 mg) at room temperature under nitrogen atmosphere. After stirring for 14 hours at 75 °C (bath temp.), the reaction was cooled down to room temperature, toluene (10 mL) was added, filtered through Celite pad, and evaporated under reduced pressure. The residue was roughly purified by column chromatography (eluent: hexane/toluene/ Et_2O = 2/1/1 to 0/1/1) to afford the mixture of (*S*)-*N,N'*-(3,3'-diphenyl-[1,1'-binaphthalene]-2,2'-diyl)diacetamide and other byproducts. This mixture was used for the next step without further purification.

(*S*)-3,3'-Diphenyl-[1,1'-binaphthalene]-2,2'-diamine



The hydrolysis of diacetamide with 50% KOH aq. in EtOH afforded the title compound. This crude material was used for the next step without further purification.

(*S*)-*N*-(2'-Amino-3,3'-diphenyl-[1,1'-binaphthalen]-2-yl)acetamide

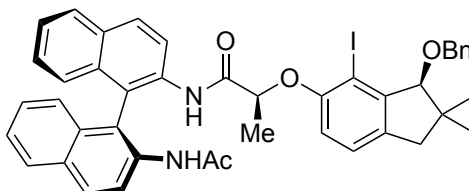


To a stirred solution of the above crude material in CH_2Cl_2 (2.3 mL) were added AcOH (2.3 mmol, 0.13 mL) and Ac_2O (0.23 mmol, 21 μL) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was basified by the addition of 2 *N* NaOH aq. and extracted with CH_2Cl_2 . The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/ AcOEt = 90/10 to 67/33) to afford the title compound as a colorless solid in 18% yield (over 3 steps).

^1H NMR (500 MHz, CDCl_3) δ 8.61 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.83-7.85 (m, 2H), 7.62-7.69 (m, 4H), 7.52-7.57 (m, 4H), 7.43-7.48 (m, 2H), 7.27-7.38 (m, 4H), 7.24-7.25

(m, 1H), 7.15 (s, 1H), 7.01 (d, $J = 8.2$ Hz, 1H), 3.85 (s, 2H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.7, 141.6, 141.0, 140.4, 138.9, 134.8, 133.3, 132.9, 130.7, 130.6, 130.4, 129.8, 129.4, 129.2, 128.4, 128.1, 128.1, 127.6, 127.4, 126.8, 126.7, 125.9, 125.3, 123.8, 123.0, 122.1, 120.4, 110.7, 24.9 (One ^{13}C signal is overlapping with others.); IR (neat) 1700, 1684, 1507, 1497, 1488, 1430, 1367 cm^{-1} ; HRMS (ESI) exact mass calcd. for $\text{C}_{22}\text{H}_{19}\text{ON}_2$: m/z 479.2118 ($[\text{M}+\text{H}]^+$), found: m/z 479.2116 ($[\text{M}+\text{H}]^+$); Optical rotation $[\alpha]_{\text{D}}^{28} = -31.0$ ($c = 0.5$, CHCl_3).

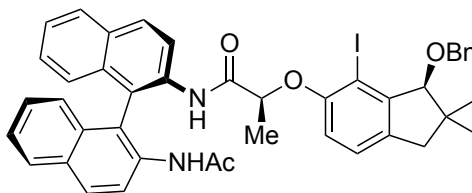
(S)-N-((S)-2'-Acetamido-[1,1'-binaphthalen]-2-yl)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanamide



Prepared according to the general procedure A with S9 and (S)-N-(2'-amino-[1,1'-binaphthalen]-2-yl)acetamide. The residue was purified by column chromatography (eluent: hexane/AcOEt = 50/50) to afford the title compound as a colorless solid in 81% yield.

^1H NMR (500 MHz, CDCl_3) δ 8.39 (d, $J = 9.1$ Hz, 1H), 8.23-8.26 (m, 2H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.97 (d, $J = 8.2$ Hz, 1H), 7.91 (d, $J = 9.1$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.47-7.51 (m, 1H), 7.38-7.40 (m, 3H), 7.23-7.34 (m, 5H), 7.13 (d, $J = 8.2$ Hz, 1H), 7.06 (d, $J = 9.1$ Hz, 1H), 6.97 (s, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 6.32 (d, $J = 7.9$ Hz, 1H), 4.83 (d, $J = 10.2$ Hz, 1H), 4.70 (d, $J = 10.5$ Hz, 1H), 4.55 (q, $J = 6.7$ Hz, 1H), 4.22 (s, 1H), 2.99 (d, $J = 15.3$ Hz, 1H), 2.55 (d, $J = 15.6$ Hz, 1H), 1.77 (s, 3H), 1.33 (s, 3H), 1.31 (d, $J = 6.5$ Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.2, 168.6, 153.7, 149.0, 138.7, 138.7, 135.3, 134.1, 132.6, 132.4, 132.0, 131.3, 130.0, 129.9, 128.6, 128.5, 128.4, 128.2, 127.7, 127.6, 127.3, 126.2, 125.4, 125.4, 125.1, 123.9, 123.3, 121.5, 120.0, 114.0, 93.8, 88.9, 76.3, 74.2, 46.3, 43.8, 28.3, 24.6, 23.0, 18.2 (One ^{13}C signal is overlapping with others.); IR (neat) 3363, 2956, 1688, 1599, 1497, 1455, 1426, 1272, 1251, 1088, 1069 cm^{-1} ; HRMS (ESI) exact mass calcd. for $\text{C}_{43}\text{H}_{39}\text{O}_4\text{N}_2\text{INa}$: m/z 797.1852 ($[\text{M}+\text{Na}]^+$), found: m/z 797.1861 ($[\text{M}+\text{Na}]^+$); Optical rotation $[\alpha]_{\text{D}}^{27} = +19.7$ ($c = 1.2$, CHCl_3).

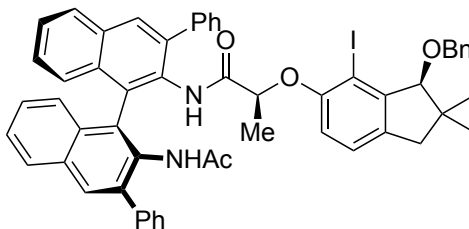
(S)-N-((R)-2'-Acetamido-[1,1'-binaphthalen]-2-yl)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanamide



To a stirred solution of **S9** (0.100 mmol, 46.6 mg) in CH₂Cl₂ (3.0 mL) were added a catalytic amount of DMF (1 drop) and (COCl)₂ (0.120 mmol, 10.3 μL) at 0 °C under argon atmosphere. After stirring for 20 min at this temperature, *i*Pr₂NEt (0.120 mmol, 21.0 μL) and (*R*)-*N*-(2'-amino-[1,1'-binaphthalen]-2-yl)acetamide (0.120 mmol, 39.2 mg) were added. After stirring overnight at 0 °C to room temperature, the reaction was quenched with 1*N* HCl aq., extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 58/42 to 50/50) to afford the title compound as a colorless solid in 45% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J* = 8.8 Hz, 1H), 8.38 (s, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.98-8.00 (m, 2H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.50-7.53 (m, 1H), 7.30-7.39 (m, 7H), 7.19-7.23 (m, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.12 (s, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.44 (d, *J* = 8.2 Hz, 1H), 4.75 (d, *J* = 10.5 Hz, 1H), 4.71 (q, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 10.5 Hz, 1H), 4.15 (s, 1H), 2.98 (d, *J* = 15.3 Hz, 1H), 2.50 (d, *J* = 15.6 Hz, 1H), 1.85 (s, 3H), 1.31 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 171.5, 168.8, 153.4, 149.0, 138.6, 138.6, 135.3, 133.8, 133.1, 132.8, 132.3, 131.3, 130.0, 129.9, 128.5, 128.4, 128.2, 127.8, 127.4, 127.0, 126.4, 125.9, 125.6, 125.4, 125.2, 124.2, 121.4, 120.1, 113.4, 93.6, 88.7, 75.9, 74.0, 46.2, 43.8, 28.2, 24.6, 22.9, 17.9 (*Two ¹³C signals are overlapping with others.*); **IR** (*neat*) 3361, 2957, 1689, 1598, 1499, 1456, 1278, 1252, 1088, 1069 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₄₃H₃₉O₄N₂INa: *m/z* 797.1852 ([M+Na]⁺), found: *m/z* 797.1863 ([M+Na]⁺); **Optical rotation** [α]_D²⁴ = +27.4 (*c* = 0.7, CHCl₃).

(S)-N-((S)-2'-Acetamido-3,3'-diphenyl-[1,1'-binaphthalen]-2-yl)-2-(((S)-3-(benzyloxy)-4-iodo-2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)oxy)propanamide

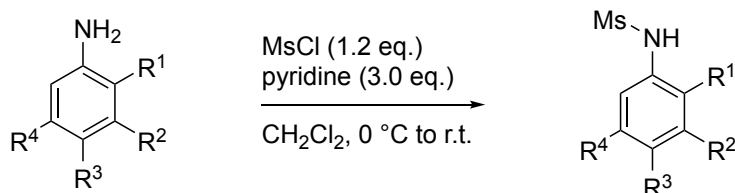


Prepared according to the general procedure A with **S9** and (S)-N-(2'-amino-3,3'-diphenyl-[1,1'-binaphthalen]-2-yl)acetamide. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford title compound as a colorless solid in 93% yield.

¹H NMR (500MHz, CDCl₃) δ 8.22 (m, 2H), 7.90-8.08 (m, 4H), 7.19-7.60 (m, 20H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.07 (d, *J* = 7.9 Hz, 1H), 4.76 (d, *J* = 10.5 Hz, 1H), 4.66 (d, *J* = 10.5 Hz, 1H), 4.21 (q, *J* = 6.7 Hz, 1H), 4.14 (s, 1H), 2.94 (d, *J* = 15.6 Hz, 1H), 2.46 (d, *J* = 15.6 Hz, 1H), 1.85 (s, 3H), 1.29 (s, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 172.3, 169.1, 154.0, 148.9, 141.1, 140.3, 139.3, 138.9, 138.6, 134.9, 133.5, 133.2, 132.5, 131.6, 130.6, 130.4, 129.7, 129.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.4, 127.4, 126.9, 126.6, 126.3, 125.5, 125.3, 124.2, 123.5, 115.2, 93.7, 89.1, 76.7, 74.0, 46.2, 43.8, 28.2, 24.3, 22.9, 17.5 (*Three ¹³C signals are overlapping with others.*); **IR** (neat) 3362, 3060, 2958, 1675, 1591, 1489, 1454, 1370, 1254, 1089, 1069 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₅₅H₄₇O₄N₂INa: *m/z* 949.2478 ([M+Na]⁺), found: *m/z* 949.2487 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = +43.5 (*c* = 1.0, CHCl₃).

3.5.2 Preparation of substrates

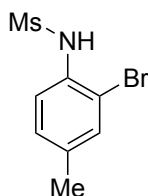
3.5.2.1 General procedure for the mesylation



To a stirred solution of aniline in CH₂Cl₂ were added 3.0 equivalents of pyridine and 1.2 equivalents of MsCl at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was acidified by the addition of 1N HCl aq. and extracted

with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography.

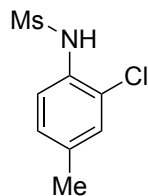
***N*-(2-Bromo-4-methylphenyl)methanesulfonamide (5a)**



Prepared according to the general procedure with 2-bromo-4-methylaniline. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 30/70 to 0/100) to afford the title compound as a colorless solid in 91% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 1.7 Hz, 1H), 7.15 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.63 (brs, 1H), 2.97 (s, 3H), 2.33 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 137.5, 133.3, 132.2, 129.7, 123.6, 116.2, 39.8, 20.7; **IR (neat)** 3263, 1490, 1406, 1379, 1323, 1155, 1046, 977 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₈H₉O₂N⁷⁹BrS: *m/z* 261.9543 ([M-H]⁻), found: *m/z* 261.9542 ([M-H]⁻).

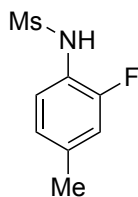
***N*-(2-Chloro-4-methylphenyl)methanesulfonamide (5b)**



Prepared according to the general procedure with 2-chloro-4-methylaniline. The residue was purified by column chromatography (eluent: hexane/AcOEt = 4/1) to afford the title compound as a colorless solid in 91% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.52 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 1.6 Hz, 1H), 7.10 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.62 (brs, 1H), 2.97 (s, 3H), 2.32 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 137.1, 130.9, 130.1, 129.1, 125.6, 123.5, 39.7, 20.8; **IR (neat)** 3262, 1496, 1410, 1385, 1325, 1157, 1058 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₈H₉O₂N³⁵ClS: *m/z* 218.0048 ([M-H]⁻), found: *m/z* 218.0040 ([M-H]⁻).

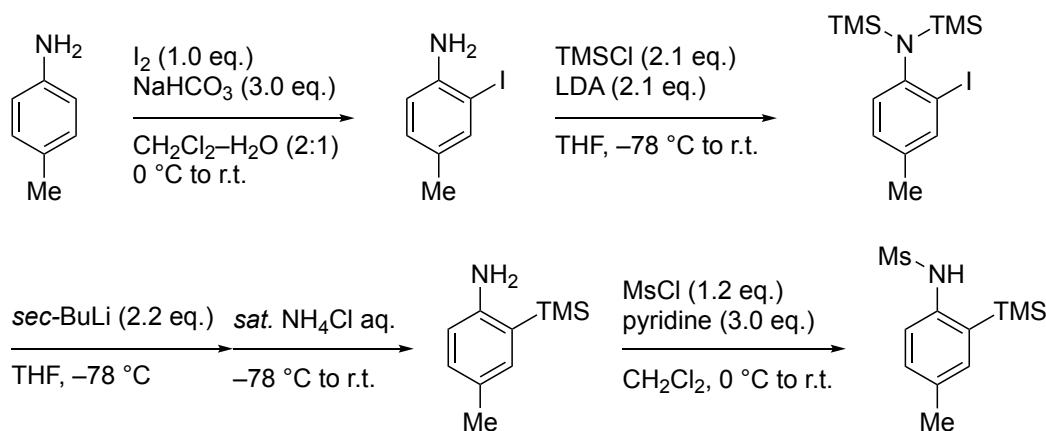
N-(2-Fluoro-4-methylphenyl)methanesulfonamide (**5c**)



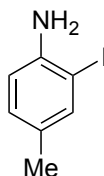
Prepared according to the general procedure with 2-fluoro-4-methylaniline. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1) to afford the title compound as a colorless solid in >99% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.42-7.45 (m, 1H), 6.98 (s, 1H), 6.96 (d, *J* = 4.5 Hz, 1H), 6.34 (brs, 1H), 2.99 (s, 3H), 2.34 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 154.7 (d, *J* = 245 Hz), 137.9 (d, *J* = 7.5 Hz), 125.7 (d, *J* = 3.8 Hz), 124.7 (s), 121.7 (d, *J* = 13.8 Hz), 116.4 (d, *J* = 18.8 Hz), 39.6 (s), 21.0 (s); **¹⁹F NMR** (466 MHz, CDCl₃) δ -129.2 (dd, *J* = 10.7, 8.4 Hz); **IR (neat)** 3251, 1510, 1413, 1324, 1158, 1114 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₈H₉O₂NFS: *m/z* 202.0333 ([M-H]⁻), found: *m/z* 202.0334 ([M-H]⁻).

N-(4-Methyl-2-(trimethylsilyl)phenyl)methanesulfonamide (**5d**)



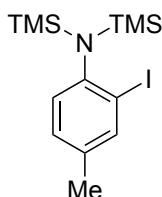
2-Iodo-4-methylaniline



To a stirred solution of 4-methylaniline (15.0 mmol, 1.61 g) in CH₂Cl₂ (60 mL) and H₂O (30 mL) was added NaHCO₃ (45.0 mmol, 3.78 g) at room temperature under argon atmosphere. After stirring for 3 min at this temperature, I₂ (15.0 mmol, 3.81 g) was added

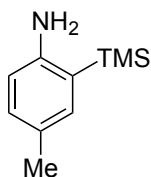
in one portion. After stirring vigorously for 4 days at the same temperature, the reaction was quenched with saturated Na_2SO_3 aq. and extracted with CH_2Cl_2 . The combined layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/ CH_2Cl_2 = 3/1) to afford the title compound as a dark brown liquid in 85% yield.

***N*-(2-Iodo-4-methylphenyl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine³³**



To a stirred solution of 2-iodo-4-methylaniline (5.00 mmol, 1.17 g) in THF (10 mL) was added LDA (5.50 mmol) in THF (3.0 mL) at $-78\text{ }^\circ\text{C}$. After stirring for 10 min at this temperature, TMSCl (5.5 mmol, 0.70 mL) was added. After stirring for 10 min, LDA (5.50 mmol) in THF (3.0 mL) was added at this temperature. After stirring for 20 min, TMSCl (5.5 mmol, 0.70 mL) was added and warmed up to room temperature. After stirring for 50 min at this temperature, the reaction was quenched with saturated NH_4Cl aq., extracted with AcOEt , dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane only) to afford the title compound as a colorless liquid in 79% yield.

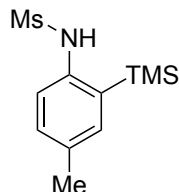
4-Methyl-2-(trimethylsilyl)aniline³³



To a stirred solution of *N*-(2-iodo-4-methylphenyl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (3.95 mmol, 1.49 g) in THF (120 mL) was added *sec*-BuLi (8.7 mmol, 8.6 mL) at $-78\text{ }^\circ\text{C}$ under argon atmosphere. After stirring for 30 min at this temperature, saturated NH_4Cl aq. was added to this reaction. After stirring for 2 hours at $-78\text{ }^\circ\text{C}$ to room temperature, the reaction was extracted with AcOEt , dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/ AcOEt = 90/10) to afford the title compound as

a colorless liquid in 35% yield.

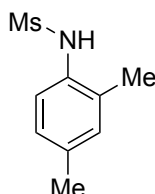
***N*-(4-Methyl-2-(trimethylsilyl)phenyl)methanesulfonamide (5d)**



Prepared according to the general procedure with 4-methyl-2-(trimethylsilyl)aniline. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1) to afford the title compound as a colorless solid in 88% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.40 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 1.7 Hz, 1H), 7.19 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.22 (brs, 1H), 3.03 (s, 3H), 2.33 (s, 3H), 0.38 (s, 9H); **¹³C NMR** (125 MHz, CDCl₃) δ 138.8, 136.3, 135.0, 132.4, 131.4, 121.6, 40.1, 21.0, 0.1; **IR (neat)** 3242, 1476, 1386, 1312, 1263, 1246, 1151, 1139 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₁H₁₈O₂NSSi: *m/z* 256.0833 ([M-H]⁻), found: *m/z* 256.0830 ([M-H]⁻); **Melting point** 79 °C.

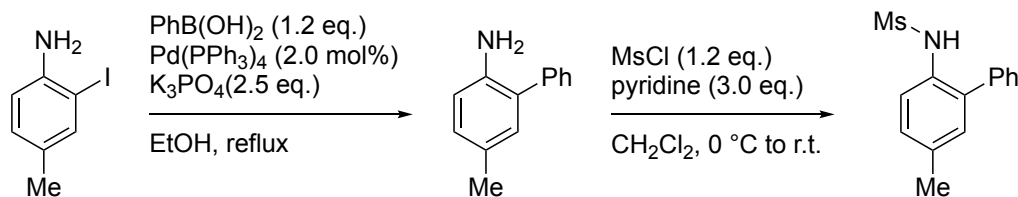
***N*-(2,4-Dimethylphenyl)methanesulfonamide (5e)**



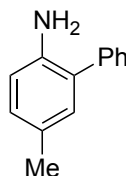
Prepared according to the general procedure with 2,4-dimethylaniline. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1 to 2/1) to afford the title compound as a colorless solid in 75% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.31 (d, *J* = 7.9 Hz, 1H), 7.05 (s, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.02 (brs, 1H), 2.99 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 136.5, 132.0, 132.0, 131.9, 127.8, 124.4, 39.7, 20.9, 18.1; **IR (neat)** 3273, 1501, 1387, 1321, 1151, 1117, 905 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₉H₁₂O₂NS: *m/z* 198.0594 ([M-H]⁻), found: *m/z* 198.0584 ([M-H]⁻).

***N*-(5-Methyl-[1,1'-biphenyl]-2-yl)methanesulfonamide (5f)**

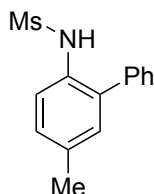


5-Methyl-[1,1'-biphenyl]-2-amine



To a stirred solution of 2-iodo-4-methylaniline (3.0 mmol, 0.70 g) in EtOH (15 mL) were added PhB(OH)_2 (3.6 mmol, 0.44 g), K_3PO_4 (7.5 mmol, 1.6 g) and $\text{Pd(PPh}_3)_4$ (0.060 mmol, 69 mg) at room temperature under argon atmosphere. After stirring overnight at 80 °C (bath temp.), solvent was removed under reduced pressure. The residue was roughly purified by column chromatography (eluent: hexane/AcOEt = 83/17). The mixture was used for the next step without further purification.

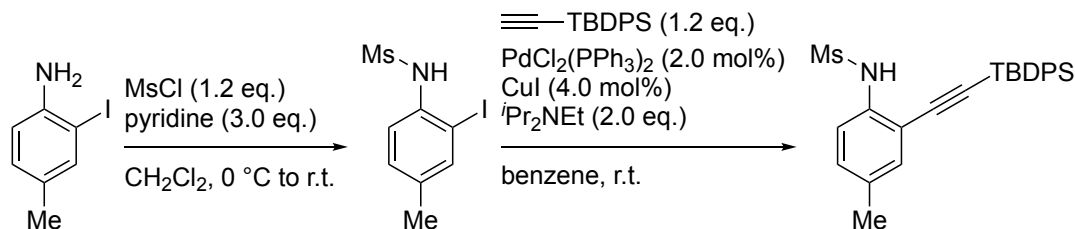
***N*-(5-Methyl-[1,1'-biphenyl]-2-yl)methanesulfonamide (5f)**



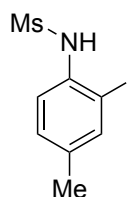
Prepared according to the general procedure with the above mixture. The residue was purified by column chromatography (eluent: hexane/AcOEt = 4/1) to afford the title compound as a colorless solid in 71% yield (over 2 steps).

^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, J = 8.2 Hz, 1H), 7.47-7.50 (m, 2H), 7.41-7.44 (m, 1H), 7.30-7.32 (m, 2H), 7.20 (dd, J = 8.2, 2.0 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.39 (brs, 1H), 2.80 (s, 3H), 2.36 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 137.8, 135.2, 134.1, 131.4, 131.3, 129.6, 129.5, 129.1, 128.4, 121.4, 39.6, 20.9; **IR** (neat) 3281, 1488, 1323, 1152 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{NS}$: m/z 260.0751 ($[\text{M}-\text{H}]^-$), found: m/z 260.0750 ($[\text{M}-\text{H}]^-$).

***N*-(2-((*tert*-Butyldiphenylsilyl)ethynyl)-4-methylphenyl)methane-sulfonamide (5g)**

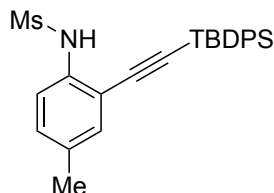


***N*-(2-Iodo-4-methylphenyl)methanesulfonamide**



Prepared according to the general procedure with 2-iodo-4-methylaniline. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 50/50 to 20/80) to afford the title compound as a brown solid in 93% yield. Characterization was performed after the next step.

***N*-(2-((*tert*-Butyldiphenylsilyl)ethynyl)-4-methylphenyl)methanesulfonamide (5g)**

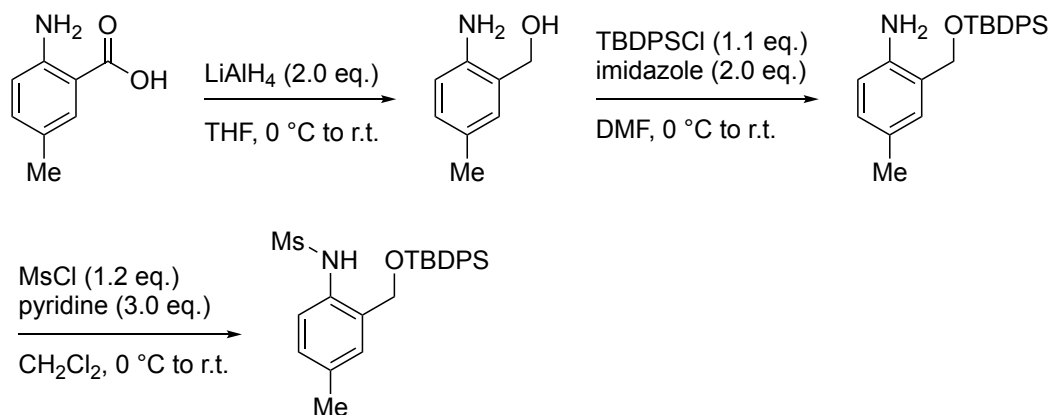


To a stirred solution of *N*-(2-iodo-4-methylphenyl)methane sulfonamide (1.0 mmol, 0.31 g) in benzene (5.0 mL) were added *tert*-butyl(ethynyl)diphenylsilane (1.2 mmol, 0.32 g), *N*-ethyl-diisopropylamine (2.0 mmol, 0.19 mL) and PdCl₂(PPh₃)₂ (0.020 mmol, 14 mg) at room temperature under nitrogen atmosphere. After stirring for 5 min at the same temperature, CuI (0.040 mmol, 7.6 mg) was added to this reaction. After stirring overnight, the reaction was directly passed through Celite, the pad cake was washed with AcOEt and the filtrate was evaporated. The residue was purified by column chromatography (eluent: hexane/AcOEt = 20/1 to 10/1) to afford the title compound in >99% yield as an orange oil.

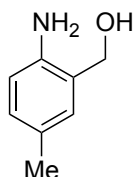
¹H NMR (500 MHz, CDCl₃) δ 7.80 (dd, *J* = 7.7, 1.7 Hz, 4H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.40-7.46 (m, 7H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.93 (s, 1H), 2.89 (s, 3H), 2.34 (s, 3H), 1.17 (s, 9H); **¹³C NMR** (125 MHz, CDCl₃) δ 136.1, 135.6, 135.0, 133.1, 132.6, 131.5, 130.0,

128.2, 120.6, 114.5, 103.7, 97.9, 39.5, 27.3, 20.7, 18.7; **IR (neat)** 3333, 2929, 2892, 2857, 2147, 1494, 1428, 1339, 1157, 1111 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{26}\text{H}_{28}\text{O}_2\text{NSSi}$: m/z 446.1615 ($[\text{M}-\text{H}]^-$), found: m/z 446.1621 ($[\text{M}-\text{H}]^-$).

***N*-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-methylphenyl) methanesulfonamide (5h)**

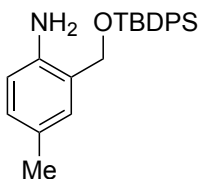


(2-Amino-5-methylphenyl)methanol



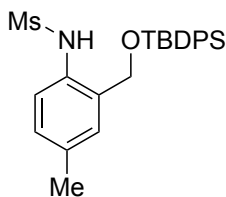
To a stirred solution of 2-amino-5-methylbenzoic acid (3.0 mmol, 0.45 g) in THF (10 mL) was added LiAlH_4 (6.0 mmol, 0.23 g) at 0 °C under argon atmosphere. After stirring for 24 hours at 0 °C to room temperature, the reaction was re-cooled down to 0 °C, followed by the addition of 1 *N* HCl aq. After the addition of saturated NaHCO_3 aq., the reaction was extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 50/50) to afford the title compound in 85% yield.

2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-methylaniline



To a stirred solution of (2-amino-5-methylphenyl)methanol (1.0 mmol, 0.14 g) in DMF (5.0 mL) were added imidazole (2.0 mmol, 0.14 g) and *tert*-butylchlorodiphenylsilane (1.1 mmol, 0.26 mL) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature. The reaction was quenched with H₂O, extracted with AcOEt, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 20/1) to afford the title compound as an orange oil in 81% yield.

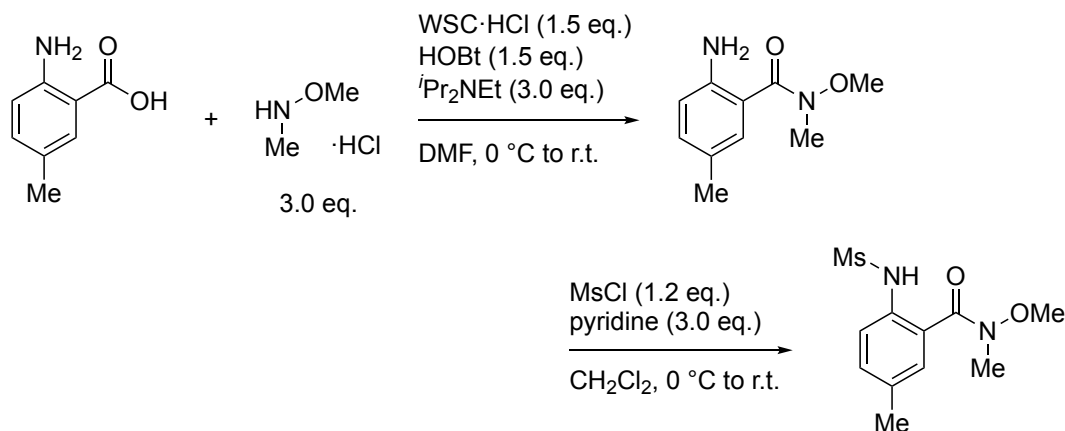
N-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-methylphenyl)methanesulfonamide (5h)



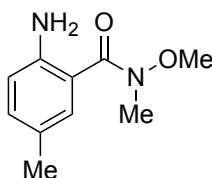
Prepared according to the general procedure with 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-methylaniline. The residue was purified by column chromatography (eluent: hexane/AcOEt = 4/1) to afford the title compound as an orange oil in 98% yield.

¹H NMR (500 MHz, CDCl₃) δ 8.08 (brs, 1H), 7.64-7.66 (m, 4H), 7.37-7.48 (m, 7H), 7.11 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 4.70 (s, 2H), 2.95 (s, 3H), 2.23 (s, 3H), 1.07 (s, 9H); **¹³C NMR** (125 MHz, CDCl₃) δ 135.7, 134.5, 134.3, 132.3, 130.3, 129.7, 129.6, 129.6, 128.1, 120.9, 66.0, 39.9, 26.9, 20.8, 19.3; **IR (neat)** 3270, 2930, 2858, 1501, 1330, 1154, 1113 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₅H₃₀O₃NSSi: *m/z* 452.1721 ([M-H]⁻), found: *m/z* 452.1726 ([M-H]⁻).

***N*-Methoxy-*N*,5-dimethyl-2-(methylsulfonamido)benzamide (5i)**

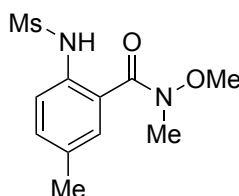


2-Amino-*N*-methoxy-*N*,5-dimethylbenzamide



To a stirred mixture of 2-amino-5-methylbenzoic acid (2.0 mmol, 0.30 g), *N*,*O*-dimethylhydroxylamine hydrochloride (6.0 mmol, 0.59 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.0 mmol, 0.58 g) and 1-hydroxybenzotriazole monohydrate (3.0 mmol, 0.46 g) were added DMF (5.0 mL) and *i*Pr₂NEt (6.0 mmol, 1.1 mL) at 0 °C under argon atmosphere. After stirring for 36 hours at 0 °C to room temperature, the reaction was quenched by the addition of H₂O, extracted with AcOEt, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 1/1) to afford the title compound as a colorless oil in 81% yield. Characterization was performed after the next step.

***N*-Methoxy-*N*,5-dimethyl-2-(methylsulfonamido)benzamide (5i)**

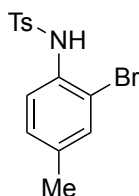


Prepared according to the general procedure with 2-amino-*N*-methoxy-*N*,5-dimethylbenzamide. The residue was purified by column chromatography (eluent:

hexane/AcOEt = 1/1) to afford the title compound as an orange oil in 71% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.94 (brs, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.55 (s, 3H), 3.37 (s, 3H), 2.98 (s, 3H), 2.35 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 168.5, 134.4, 133.2, 132.3, 129.4, 125.3, 122.8, 61.6, 39.8, 33.7, 20.8; **IR (neat)** 3253, 2934, 1633, 1498, 1324, 1152 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₁H₁₅O₄N₂S: *m/z* 271.0758 ([M-H]⁻), found: *m/z* 271.0758 ([M-H]⁻).

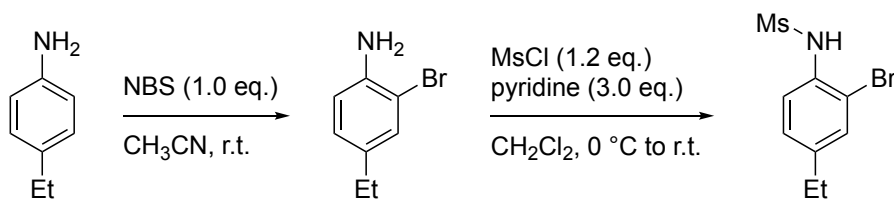
N-(2-Bromo-4-methylphenyl)-4-methylbenzenesulfonamide (**5j**)



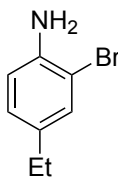
Prepared according to the general procedure with 2-bromo-4-methylaniline and 1.1 equivalents of *p*-toluenesulfonyl chloride instead of methanesulfonyl chloride. The residue was purified by column chromatography (eluent: hexane/CH₂Cl₂ = 100/0 to 30/70) to afford the title compound as a crystalline solid in 99% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.18-7.21 (m, 3H), 7.06 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.83 (brs, 1H), 2.36 (s, 3H), 2.24 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 144.2, 136.8, 136.0, 132.9, 132.1, 129.7, 129.4, 127.4, 123.2, 116.1, 21.7, 20.6; **IR (neat)** 3265, 1491, 1334, 1163 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₄H₁₃O₂N⁷⁹BrS: *m/z* 337.9856 ([M-H]⁻), found: *m/z* 337.9861 ([M-H]⁻).

N-(2-Bromo-4-ethylphenyl)methanesulfonamide (**7a**)



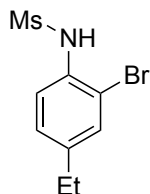
2-Bromo-4-ethylaniline



To a stirred solution of 4-ethylaniline (3.0 mmol, 0.37 mL) in CH₃CN (10 mL) was added

NBS (3.0 mmol, 0.53 g) at room temperature. After stirring for 3 hours at this temperature, the reaction was quenched by the addition of saturated $\text{Na}_2\text{S}_2\text{O}_3$ aq., extracted with AcOEt, dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude material was used for the next step without further purification.

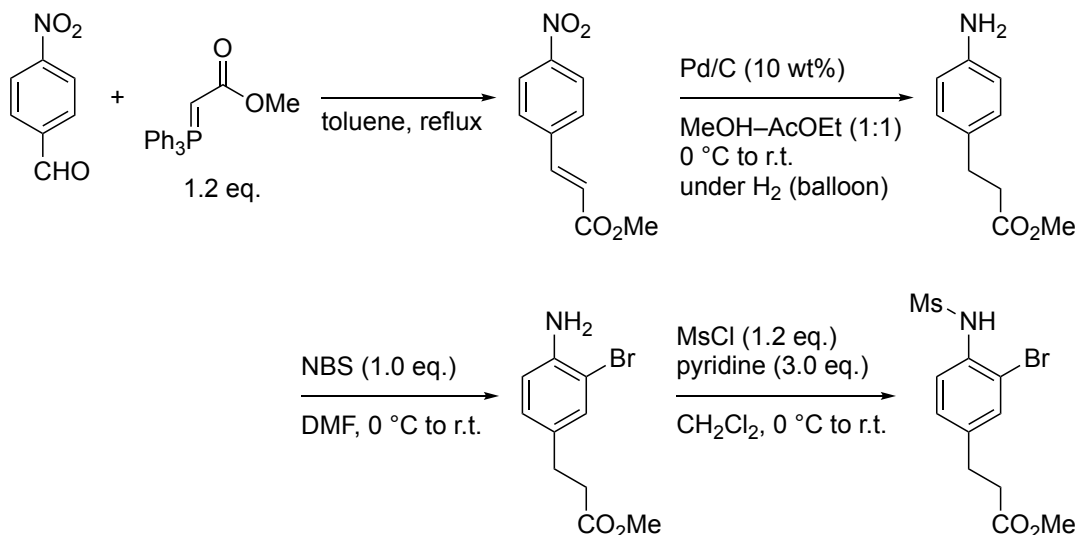
***N*-(2-Bromo-4-ethylphenyl)methanesulfonamide (7a)**

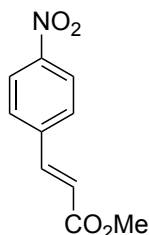


Prepared according to the general procedure with the above crude material. The residue was purified by column chromatography (eluent: hexane/AcOEt = 4/1) to afford the title compound as a colorless solid in 88% yield (over 2 steps).

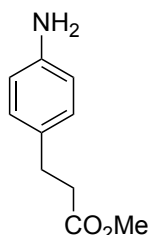
^1H NMR (500 MHz, CDCl_3) δ 7.56 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.63 (brs, 1H), 2.97 (s, 3H), 2.62 (q, J = 7.7 Hz, 2H), 1.23 (t, J = 7.7 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 143.8, 132.3, 132.2, 128.6, 123.8, 116.4, 39.9, 28.1, 15.4; **IR** (neat) 3264, 2966, 2932, 1492, 1383, 1322, 1154, 966 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_9\text{H}_{11}\text{O}_2\text{N}^{79}\text{BrS}$: m/z 275.9699 ($[\text{M}-\text{H}]^-$), found: m/z 275.9700 ($[\text{M}-\text{H}]^-$).

Methyl 3-(3-bromo-4-(methanesulfonamido)phenyl)propanoate (7b)



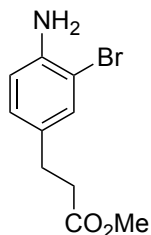
Methyl (*E*)-3-(4-nitrophenyl)acrylate

To a mixture of 4-nitrobenzaldehyde (5.0 mmol, 0.76 g) and methyl (triphenylphosphoranylidene)acetate (6.0 mmol, 2.0 g) was added toluene (25 mL) at room temperature. After stirring overnight at 110 °C, solvent was removed under reduced pressure. To the obtained residue were added silica gel and CH₂Cl₂, evaporated and roughly purified by column chromatography (eluent: hexane/AcOEt = 6/1 to 2/1) to afford the mixture of the title compound and 4-nitrobenzaldehyde. The mixture was used for the next step without further purification.

Methyl 3-(4-aminophenyl)propanoate

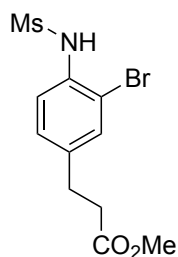
A stirred solution of the above mixture (0.96 g) in MeOH (20 mL) and AcOEt (20 mL) was hydrogenated with Pd/C (96.4 mg) under hydrogen atmosphere overnight at 0 °C to room temperature. After that, the solution was filtered through Celite pad and the pad cake was washed with AcOEt. The combined organic layers were evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 41% yield (over 2 steps).

Methyl 3-(4-amino-3-bromophenyl)propanoate



To a stirred solution of methyl 3-(4-aminophenyl)propanoate (2.1 mmol, 0.37 g) in DMF (5.0 mL) was added NBS (2.1 mmol, 0.36 g) at room temperature under argon atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was quenched with saturated Na₂S₂O₃ aq., extracted with AcOEt, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 6/1 to 3/1) to afford the title compound as a colorless liquid in 82% yield.

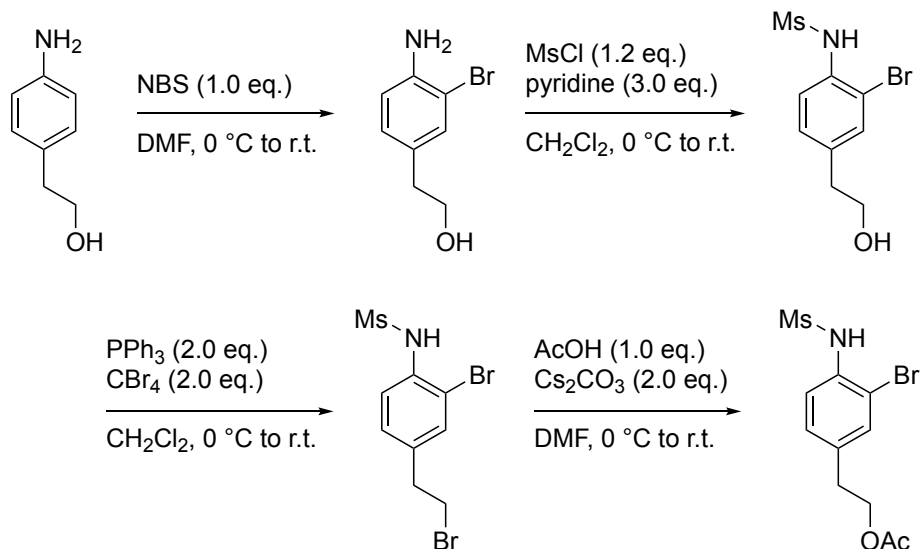
Methyl 3-(3-bromo-4-(methylsulfonamido)phenyl)propanoate (7b)



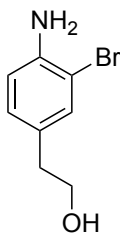
Prepared according to the general procedure with methyl 3-(4-amino-3-bromophenyl)propanoate. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 75% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.66 (brs, 1H), 3.68 (s, 3H), 2.98 (s, 3H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 172.9, 139.9, 133.0, 132.7, 129.0, 123.4, 116.1, 51.9, 40.0, 35.3, 29.9; **IR (neat)** 3260, 1730, 1493, 1327, 1154, 1043 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₁H₁₃O₄NBrS: *m/z* 333.9754 ([M-H]⁻), found: *m/z* 333.9760 ([M-H]⁻).

3-Bromo-4-(methanesulfonamido)phenethyl acetate (7c)

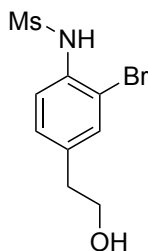


2-(4-Amino-3-bromophenyl)ethan-1-ol



To a stirred solution of 2-(4-aminophenyl)ethan-1-ol (20.0 mmol, 2.74 g) in DMF (50 mL) was added *N*-bromosuccinimide (20.0 mmol, 3.56 g) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was quenched with saturated Na₂S₂O₃ aq., extracted with AcOEt, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 89% yield.

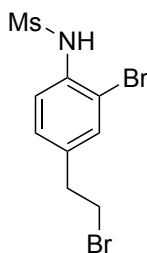
N-(2-Bromo-4-(2-hydroxyethyl)phenyl)methanesulfonamide



Prepared according to the general procedure with 2-(4-amino-3-bromophenyl)ethan-1-ol

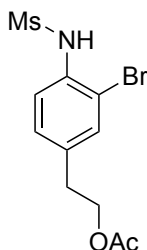
(note: 2.0 equivalents of pyridine were used). The residue was purified by column chromatography (eluent: hexane/AcOEt = 1/1 to 1/2) to afford the title compound as a colorless solid in 60% yield.

***N*-(2-Bromo-4-(2-bromoethyl)phenyl)methanesulfonamide**



To a stirred solution of *N*-(2-bromo-4-(2-hydroxyethyl)phenyl)methane sulfonamide (10.0 mmol, 2.94 g) in CH₂Cl₂ (100 mL) was added PPh₃ (20.0 mmol, 5.24 g) and CBr₄ (20.0 mmol, 6.64 g) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, silica gel was added to the solution, and solvent was removed under reduced pressure, followed by the direct purification by column chromatography (eluent: hexane/AcOEt = 4/1 to 3/1) to afford the title compound as an orange solid in 54% yield.

3-Bromo-4-(methanesulfonamido)phenethyl acetate (7c)

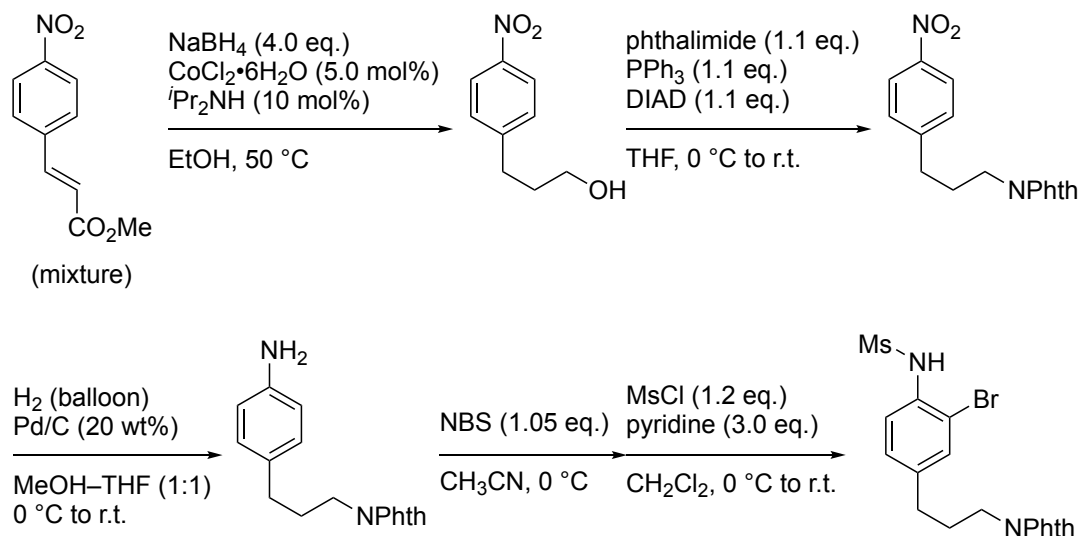


To a stirred solution of *N*-(2-bromo-4-(2-bromoethyl)phenyl)methane sulfonamide (3.00 mmol, 1.07 g) in DMF (10 mL) were added Cs₂CO₃ (6.00 mmol, 1.95 g) and AcOH (3.3 mmol, 0.19 mL) at 0 °C under argon atmosphere. After stirring for 2 days at 0 °C to room temperature, the reaction was quenched with H₂O, and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a yellowish oil in 26% yield.

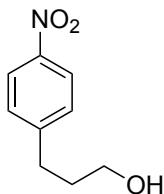
¹H NMR (500 MHz, CDCl₃) δ 7.59 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.69 (brs, 1H), 4.26 (t, *J* = 6.9 Hz, 2H), 3.00 (s, 3H), 2.90 (t, *J*

= 6.8 Hz, 2H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.0, 137.3, 133.4, 133.2, 129.5, 123.5, 116.2, 64.3, 40.1, 34.1, 21.0; IR (neat) 3272, 1734, 1481, 1332, 1157, 1042 cm^{-1} ; HRMS (ESI) exact mass calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_4\text{NBrS}$: m/z 333.9754 ($[\text{M}-\text{H}]^-$), found: m/z 333.9759 ($[\text{M}-\text{H}]^-$).

***N*-(2-Bromo-4-(3-(1,3-dioxoisindolin-2-yl)propyl)phenyl)methanesulfonamide (7d)**

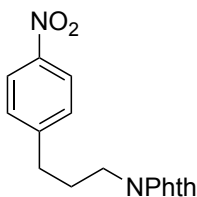


3-(4-Nitrophenyl)propan-1-ol



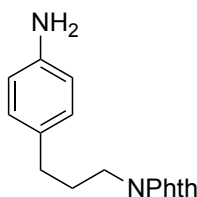
To a stirred solution of the above mixture (see also the preparation of **7b**, 0.21 g) in EtOH (4.0 mL) were added $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.0500 mmol, 11.9 mg), $i\text{Pr}_2\text{NH}$ (0.100 mmol, 14.1 μL) and NaBH_4 (4.0 mmol, 0.15 g) at room temperature. After stirring for 24 hours at 50 $^\circ\text{C}$, the reaction was quenched with H_2O at room temperature, and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 1/1) to afford the title compound as an orange oil.

2-(3-(4-Nitrophenyl)propyl)isoindoline-1,3-dione



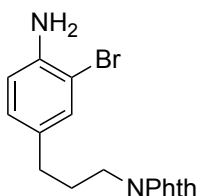
To a stirred solution of 3-(4-nitrophenyl)propan-1-ol (2.0 mmol, 0.36 g) in THF (5.0 mL) were added phthalimide (2.2 mmol, 0.32 g) and PPh_3 (2.2 mmol, 0.58 g) under argon atmosphere at room temperature. The solution was cooled down to 0 °C, followed by the addition of diisopropyl azodicarboxylate (2.2 mmol, 0.43 mL). after stirring overnight at 0 °C to room temperature, the solution was evaporated under reduced pressure. The residue was roughly purified by column chromatography (eluent: hexane/AcOEt = 4/1) to afford the title compound as a colorless solid in 50% yield.

2-(3-(4-Aminophenyl)propyl)isoindoline-1,3-dione



To a stirred solution of 2-(3-(4-nitrophenyl)propyl)isoindoline-1,3-dione (1.0 mmol, 0.16 g) in MeOH (10 mL) and THF (10 mL) was added Pd/C (33 mg) under argon atmosphere at 0 °C. Argon gas was removed under reduced pressure, followed by the refilling of hydrogen gas. After stirring overnight at room temperature, the reaction was filtered through Celite pad, the pad cake was washed with AcOEt and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1 to 2/1) to afford the title compound in 73% yield.

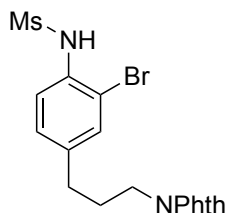
2-(3-(4-Amino-3-bromophenyl)propyl)isoindoline-1,3-dione



To a stirred solution of 2-(3-(4-aminophenyl)propyl)isoindoline-1,3-dione (0.73 mmol, 0.21 g) in MeCN (5.0 mL) was added *N*-bromosuccinimide (0.77 mmol, 0.14 g) at 0 °C.

after stirring for 90 min at 0 °C to room temperature, the reaction was quenched with saturated Na₂S₂O₃ aq., and extracted with AcOEt. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was used for the next step without further purification.

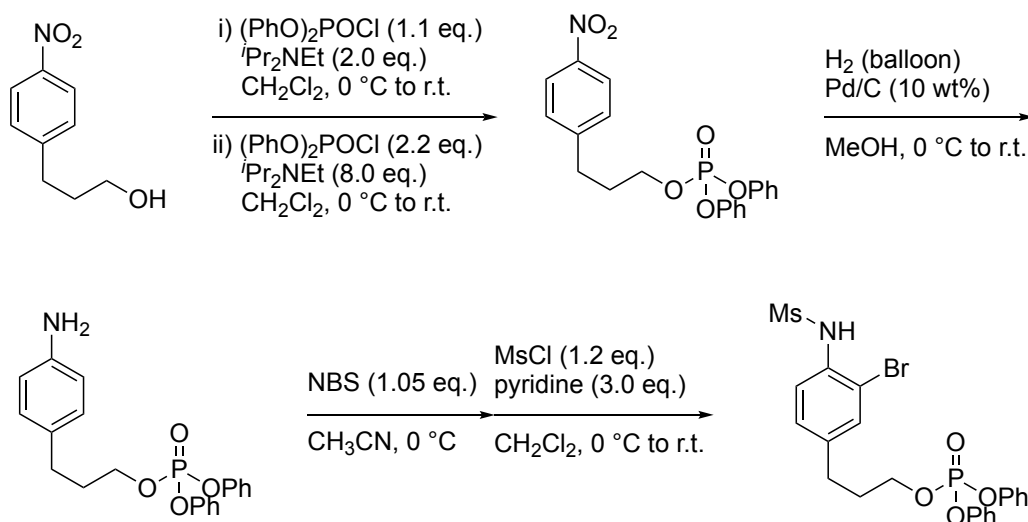
***N*-(2-Bromo-4-(3-(1,3-dioxoisindolin-2-yl)propyl)phenyl)methanesulfonamide (7d)**



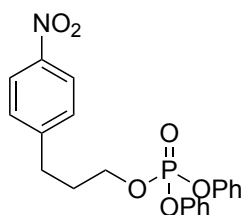
Prepared according to the general procedure with 2-(3-(4-amino-3-bromophenyl)propyl)isoindoline-1,3-dione. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 64% yield (over 2 steps).

¹H NMR (500 MHz, CDCl₃) δ 7.84 (dd, *J* = 5.4, 2.8 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.18 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.61 (brs, 1H), 3.75 (t, *J* = 6.9 Hz, 2H), 2.96 (s, 3H), 2.66 (t, *J* = 7.8 Hz, 2H), 1.99-2.05 (m, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 168.5, 140.5, 134.1, 132.7, 132.6, 132.1, 129.0, 123.3, 123.2, 116.0, 39.9, 37.6, 32.3, 29.6; **IR (neat)** 3265, 2934, 1770, 1705, 1493, 1396, 1331, 1158 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₈H₁₇O₄N₂BrNaS: *m/z* 458.9990 ([M+Na]⁺), found: *m/z* 458.9988 ([M+Na]⁺).

3-(3-Bromo-4-(methylsulfonamido)phenyl)propyl diphenyl phosphate (7e)

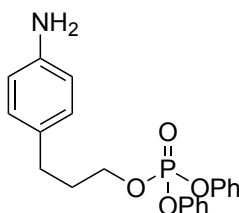


3-(4-Nitrophenyl)propyl diphenyl phosphate



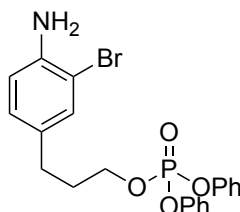
To a stirred solution of 3-(4-nitrophenyl)propan-1-ol (2.0 mmol, 0.36 g) in CH_2Cl_2 (5.0 mL) were added $i\text{Pr}_2\text{NEt}$ (4.0 mmol, 0.70 mL) and diphenyl chlorophosphate (2.2 mmol, 0.38 mL) under argon atmosphere at $0\text{ }^\circ\text{C}$. after stirring overnight at $0\text{ }^\circ\text{C}$ to room temperature, the reaction was quenched with H_2O , and extracted with AcOEt . The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. To this crude material was added CH_2Cl_2 (5.0 mL), $i\text{Pr}_2\text{NEt}$ (16 mmol, 1.4 mL) and diphenyl chlorophosphate (4.4 mmol, 0.76 mL) under argon atmosphere at $0\text{ }^\circ\text{C}$. after stirring for 2 days at $0\text{ }^\circ\text{C}$ to room temperature, the reaction was quenched with H_2O , and extracted with CH_2Cl_2 . The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was roughly purified by column chromatography (eluent: hexane/ AcOEt = 2/1).

3-(4-Aminophenyl)propyl diphenyl phosphate



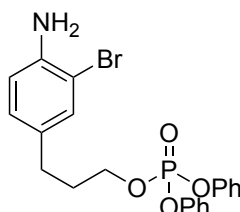
To a stirred solution of 3-(4-nitrophenyl)propyl diphenyl phosphate in MeOH (10 mL) was added Pd/C (90 mg) under argon atmosphere at 0 °C. Argon gas was removed under reduced pressure, followed by the refilling of hydrogen gas. After stirring overnight at room temperature, the reaction was filtered through Celite pad, the pad cake was washed with AcOEt and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 1/1) to afford the title compound in 45% yield (over 2 steps).

3-(4-Amino-3-bromophenyl)propyl diphenyl phosphate



To a stirred solution of 3-(4-aminophenyl)propyl diphenyl phosphate (0.91 mmol, 0.35 g) in MeCN (5.0 mL) was added NBS (0.95 mmol, 0.17 g) at 0 °C. after stirring for 90 min at 0 °C, the reaction was quenched with saturated Na₂S₂O₃ aq., and extracted with AcOEt. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was used for the next step without further purification.

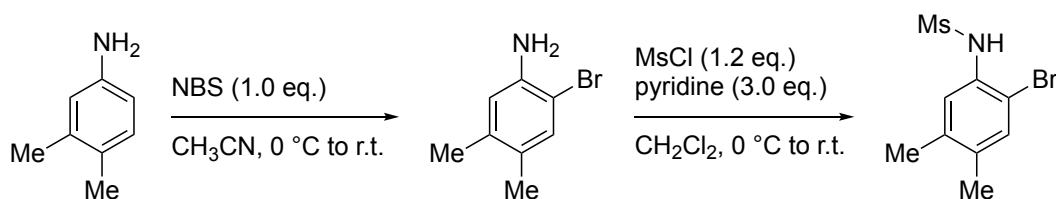
3-(3-Bromo-4-(methylsulfonamido)phenyl)propyl diphenyl phosphate (7e)



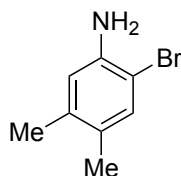
Prepared according to the general procedure with 3-(4-amino-3-bromophenyl)propyl diphenyl phosphate. The residue was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless oil in 81% yield (over 2 steps).

¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, *J* = 8.2 Hz, 1H), 7.34-7.37 (m, 5H), 7.19-7.24 (m, 6H), 7.09 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.66 (s, 1H), 4.24-4.28 (m, 2H), 2.98 (s, 3H), 2.65 (t, *J* = 7.7 Hz, 2H), 1.97-2.02 (m, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 150.6 (d, *J* = 7.2 Hz), 140.1 (s), 132.9 (s), 132.8 (s), 130.0 (s), 129.1 (s), 125.6 (s), 123.5 (s), 120.1 (d, *J* = 4.8 Hz), 116.2 (s), 68.1 (d, *J* = 6.0 Hz), 40.0 (s), 31.5 (d, *J* = 6.0 Hz), 30.7 (s); **IR (neat)** 3153, 1589, 1488, 1331, 1280, 1153 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₂H₂₃O₆NBrNaPS: *m/z* 562.0059 ([M+Na]⁺), found: *m/z* 562.0067 ([M+Na]⁺).

N-(2-Bromo-4,5-dimethylphenyl)methanesulfonamide (7f)

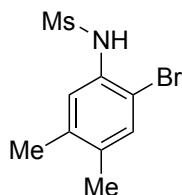


2-Bromo-4,5-dimethylaniline



To a stirred solution of 3,4-dimethylaniline (5.0 mmol, 0.61 g) in MeCN (15 mL) was added NBS (5.0 mmol, 0.89 g) at 0 °C. After stirring for 45 min at room temperature, the reaction was quenched with saturated Na₂S₂O₃ aq., extracted with AcOEt, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 9/1) to afford the inseparable mixture of 2-bromo-4,5-dimethylaniline and 2-bromo-3,4-dimethylaniline (~5:1). The mixture was used for the next step without further purification.

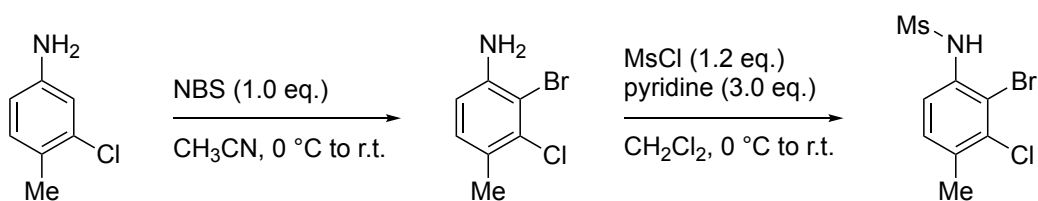
***N*-(2-Bromo-4,5-dimethylphenyl)methanesulfonamide (7f)**



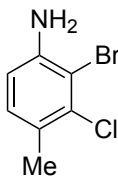
Prepared according to the general procedure with the above mixture. The residue was purified by column chromatography (eluent: hexane/AcOEt = 6/1) to afford the mixture of the title compound and the isomer (~5:1). Pure compound was obtained by recrystallization from CH₂Cl₂ as a colorless solid in 39% yield (over 2 steps).

¹H NMR (500 MHz, CDCl₃) δ 7.42 (s, 1H), 7.34 (s, 1H), 6.56 (brs, 1H), 2.97 (s, 3H), 2.23 (s, 3H), 2.23 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 138.0, 136.4, 133.3, 132.2, 125.0, 113.1, 39.7, 19.7, 19.1; **IR (neat)** 3254, 1487, 1402, 1378, 1365, 1323, 1153 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₉H₁₂O₂N⁷⁹BrNaS: *m/z* 299.9670 ([M+Na]⁺), found: *m/z* 299.9676 ([M+Na]⁺).

***N*-(2-Bromo-3-chloro-4-methylphenyl)methanesulfonamide (7g)**

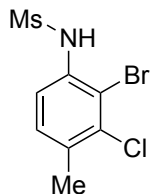


2-Bromo-3-chloro-4-methylaniline



To a stirred solution of 3-chloro-4-methylaniline (5.0 mmol, 0.61 mL) in MeCN (15 mL) was added NBS (5.0 mmol, 0.89 g) at 0 °C under argon atmosphere. After stirring overnight at 0 °C to room temperature, the reaction was quenched with saturated Na₂S₂O₃ aq., extracted with AcOEt, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 9/1) to afford the title compound as a colorless solid in 45% yield.

***N*-(2-Bromo-3-chloro-4-methylphenyl)methanesulfonamide (7g)**

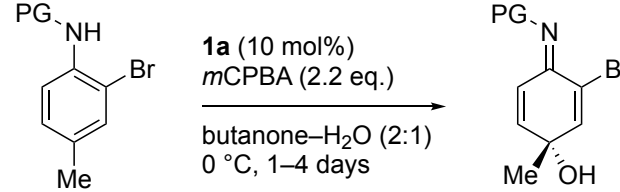
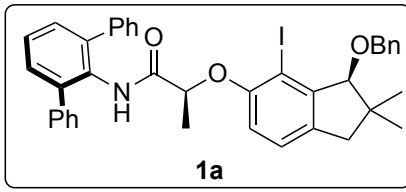


Prepared according to the general procedure with 2-bromo-3-chloro-4-methylaniline. The residue was purified by column chromatography (eluent: hexane/AcOEt = 3/1) to afford the title compound as a colorless solid in 50% yield.

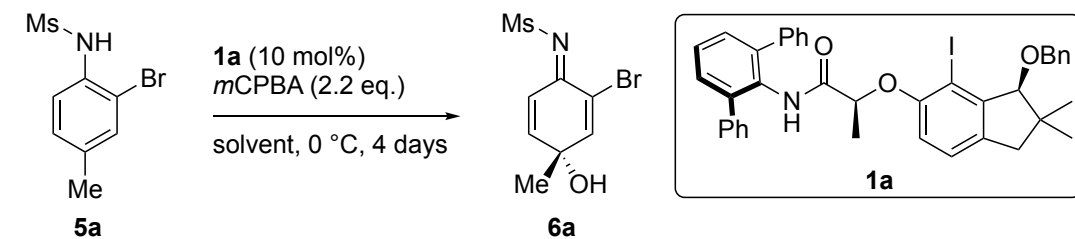
¹H NMR (500 MHz, CDCl₃) δ 7.50 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.78 (brs, 1H), 2.99 (s, 3H), 2.43 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 135.5, 135.3, 134.4, 130.3, 120.7, 117.3, 40.0, 21.3; **IR (neat)** 3266, 1467, 1364, 1320, 1157, 971 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₈H₈O₂N⁷⁹Br³⁵ClS: *m/z* 295.9153 ([M-H]⁻), found: *m/z* 295.9151 ([M-H]⁻).

3.5.3 Optimization of reaction conditions

Table 3-3 Investigation of *N*-protecting groups^a

			
			
Entry	PG	Yield (%) ^b	Ee (%) ^c
1	Ts	83	44
2	Ns	<5	-
3	Ms	79	52
4	4-MeO-C ₆ H ₄ SO ₂	84	40
5	MesSO ₂	84	44
6	Cbz	<5	-
7	Boc	<5	-
8	Ac	<5	-
9	Bz	<5	-
10	Bn	<5	-
11 ^d	Ph ₂ P(=O)	73	13

^aReaction conditions: substrate (0.100 mmol), *m*CPBA (0.220 mmol), and **1a** (0.0100 mmol) in solvent (0.60 mL). ^bNMR yield. ^cEe was determined by chiral HPLC analysis after isolation. ^dRun for 7 days.

Table 3-4 Optimization of solvent system^a

Entry	Solvent	conv. (%) ^b	Yield (%) ^b	Ee (%) ^c
1	butanone–H ₂ O (9:1)	>95	84	51
2	butanone–H ₂ O (2:1)	>95	79	52
3	butanone–H ₂ O (1:2)	>95	81	48
4	CH ₃ CN–H ₂ O (9:1)	>95	84	45
5	CH ₃ CN–H ₂ O (2:1)	>95	81	44
6	CH ₃ CN–H ₂ O (1:2)	>95	65	45
7	THF–H ₂ O (9:1)	39	28	18
8	THF–H ₂ O (2:1)	22	16	17
9	THF–H ₂ O (1:2)	>95	79	16
10	DME–H ₂ O (9:1)	55	36	41
11	DME–H ₂ O (2:1)	80	54	47
12	DME–H ₂ O (1:2)	67	29	41

^aReaction conditions: **5a** (0.100 mmol), *m*CPBA (0.220 mmol), and **1a** (0.0100 mmol) in solvent (0.60 mL). ^bDetermined by ¹H NMR analysis. ^cEe was determined by chiral HPLC analysis after isolation.

Table 3-5 Catalyst screening (i)^a

Cc1ccc(NC(=O)S(=O)(=O)c2ccc(Br)cc2)cc1
 $\xrightarrow[\text{0 } ^\circ\text{C, 4 days}]{\text{Ar-I}^* (10 \text{ mol\%}), \text{mCPBA (2.2 eq.)}, \text{butanone-H}_2\text{O (9:1)}}$
Cc1ccc(NC(=O)S(=O)(=O)c2cc(Br)ccc2)cc1

5a **6a**

Entry	Ar-I*	conv. (%)	Yield (%) ^b	Ee (%) ^c
1	[1]	53	36	-8
2	[2]	49	40	9
3	[3]	48	24	-10
4	[4]	48	27	-16
5	[5]	37	23	-10
6	[6]	31	20	-10
7	1a	>95	84	51

^aReaction conditions: **5a** (0.100 mmol), *m*CPBA (0.220 mmol), and Ar-I* (0.0100 mmol) in solvent (0.60 mL). ^bDetermined by ¹H NMR analysis. ^cEe was determined by chiral HPLC analysis after isolation.

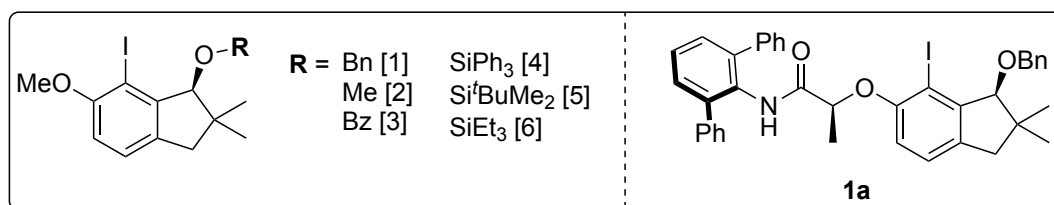
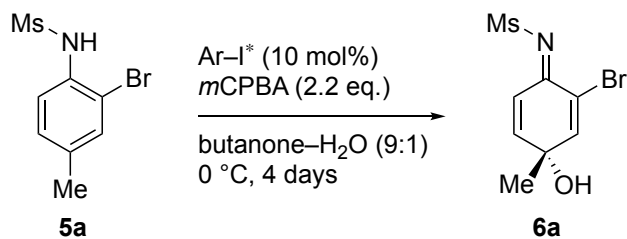


Table 3-6 Catalyst screening (ii)^a

Entry	Ar-I*	Conv. (%)	Yield (%) ^b	Ee (%) ^c
1	[1]	29	26	27
2	[2]	55	43	14
3	[3]	47	43	13
4	[4]	67	64	28
5	1a	>95	84	51
6	[5]	29	29	<1
7	[6]	24	24	4
8	[7]	24	24	2
9	[8]	85	85	-12
10	1a'	88	88	<1

^aReaction conditions: **5a** (0.100 mmol), *m*CPBA (0.220 mmol), and Ar-I* (0.0100 mmol) in solvent (0.60 mL). ^bDetermined by ¹H NMR analysis. ^cEe was determined by chiral HPLC analysis after isolation.

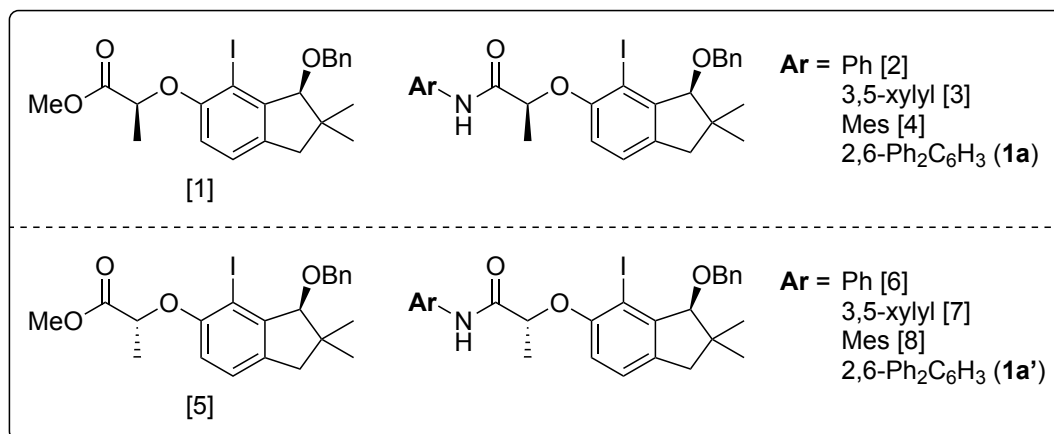
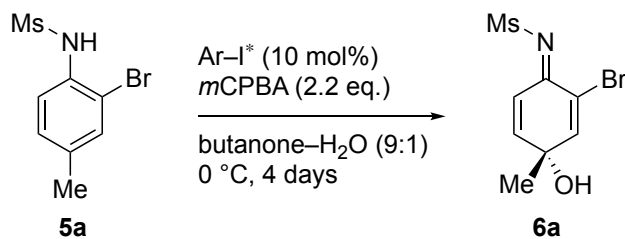


Table 3-7 Catalyst screening (iii)^a



Entry	Ar-I*	Conv. (%)	Yield (%) ^b	Ee (%) ^c
1	1a	>95	84	51
2	[1]	19	10	49
3	[2]	76	67	43
4	[3]	87	74	52
5	[4]	54	30	28
6	[5]	57	33	36

^aReaction conditions: **5a** (0.100 mmol), *m*CPBA (0.220 mmol), and Ar-I* (0.0100 mmol) in solvent (0.60 mL). ^bDetermined by ¹H NMR analysis. ^cEe was determined by chiral HPLC analysis after isolation.

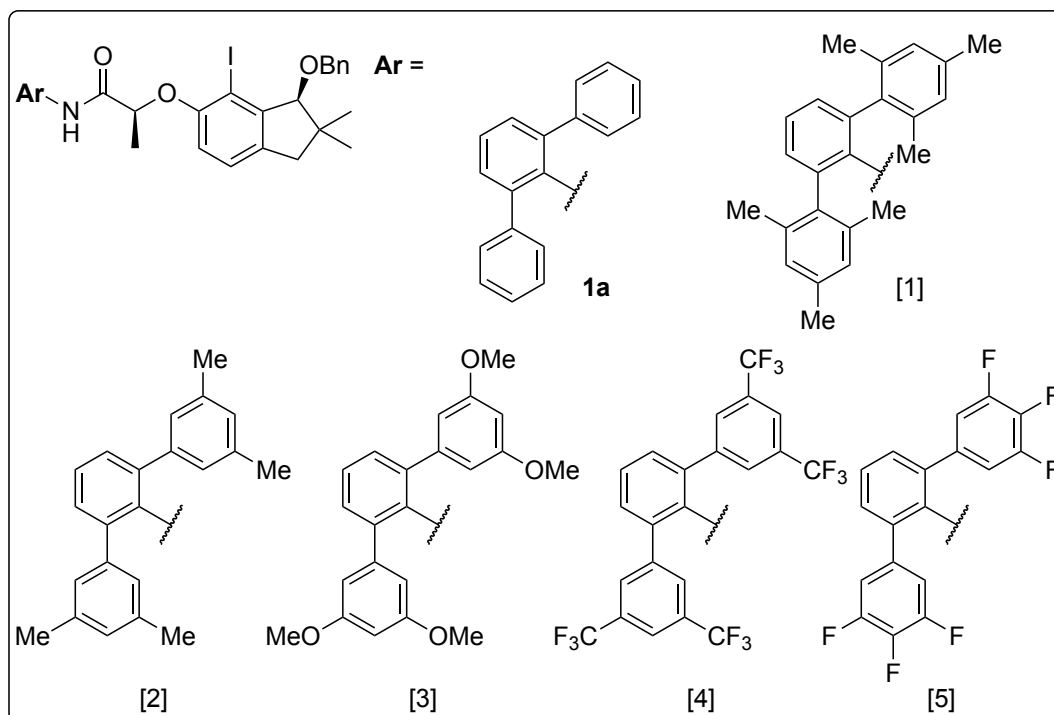
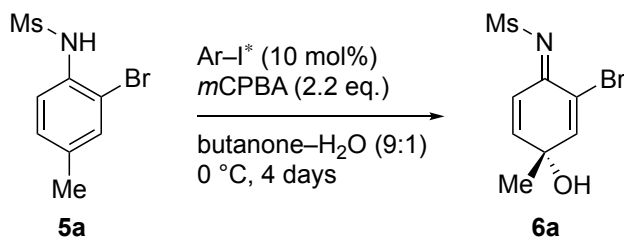
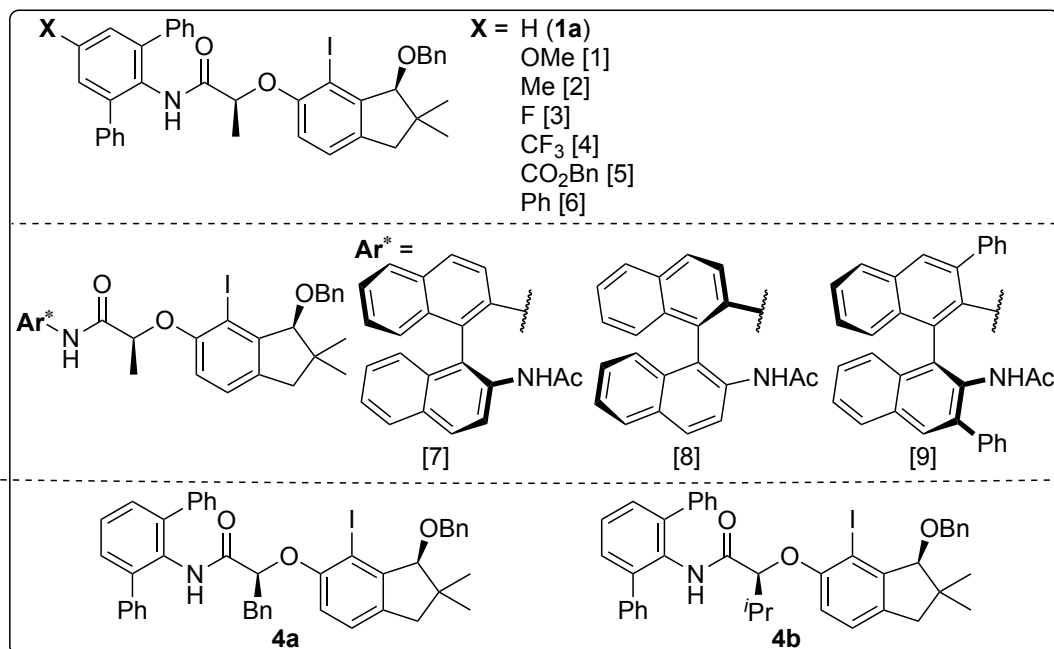


Table 3-8 Catalyst screening (iv)^a

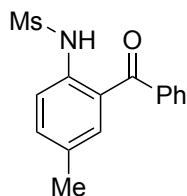
Entry	Ar	Conv. (%)	Yield (%) ^b	Ee (%) ^c
1	1a	>95	84	51
2	[1]	84	62	49
3	[2]	90	71	51
4	[3]	>95	83	50
5	[4]	93	71	51
6	[5]	>95	83	50
7	[6]	77	57	47
8	[7]	74	57	<1
9	[8]	42	41	-19
10	[9]	57	37	50
11	4a	77	68	67
12	4b	>95	76 ^d	75

^aReaction conditions: **5a** (0.100 mmol), *m*CPBA (0.220 mmol), and Ar-I* (0.0100 mmol) in solvent (0.60 mL). ^bDetermined by ¹H NMR analysis. ^cEe was determined by chiral HPLC analysis after isolation. ^dIsolated yield.

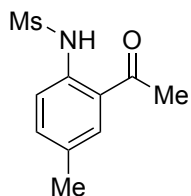


3.5.4 Unsuccessful Substrates

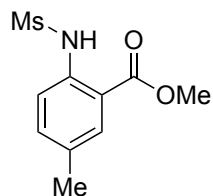
<2-substituents (w/ 10 mol% of **4b**)>



reaction messy
(run at r.t.)

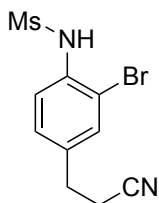


no reaction
(run at r.t.)

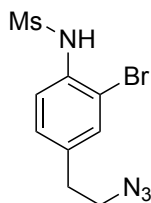


no reaction
(run at r.t.)

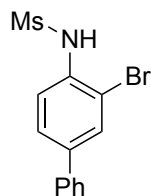
<4-substituents>



low conv.
(w/ 15 mol% of **4b**)

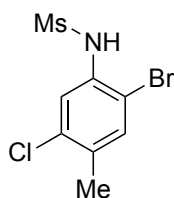


low conv.
(1.1 eq. $\text{PhI}(\text{OAc})_2$)

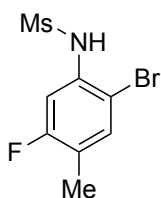


47% yield
<1% ee
(w/ 15 mol% of **4b**)

<5-substituents (w/ 20 mol% of **4b**)>



low conv.



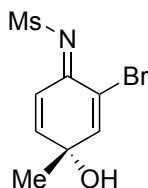
low conv.

Figure 3-2 unsuccessful substrates

3.5.5 General procedure for the enantioselective *para*-hydrative dearomatization

General Procedure: A flask was charged with substrate anilide (0.10 mmol), catalyst **4b** (0.010 mmol, 7.2 mg), butanone (540 μ L) and H₂O (60 μ L). The solution was cooled down to 0 °C. After that, *m*CPBA (*ca.* 70% purity, 0.22 mmol, 49.5 mg) was added to the solution. The reaction was monitored by TLC analysis. After the completion of the reaction, saturated Na₂S₂O₃ aq. (2.0 mL) was added to the reaction mixture and stirred for 5 min at the same temperature, followed by the addition of saturated NaHCO₃ aq. (4.0 mL), H₂O and AcOEt. Two layers were separated, and aqueous layer was extracted with AcOEt. The combined organic layers were washed with saturated NaHCO₃ aq., dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography. Ee was determined by chiral HPLC analysis.

(*R,E*)-*N*-(2-Bromo-4-hydroxy-4-methylcyclohexa-2,5-dien-1-ylidene)methane sulfonamide (6a**)**



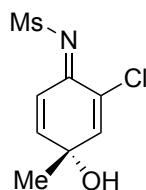
Prepared according to the general procedure with **5a** (0.100 mmol, 26.4 mg) for 4 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 76% yield [75% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.24-7.27 (m, 2H), 6.79 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.25 (s, 3H), 2.14 (s, 1H), 1.49 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 160.4, 152.9, 151.2, 121.3, 119.8, 69.8, 43.3, 26.2; **IR (neat)** 3447, 1643, 1560, 1302, 1135, 1054 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₈H₁₀O₃N⁷⁹BrNaS: *m/z* 301.9462 ([M+Na]⁺), found: *m/z* 301.9461 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = -15.5 (*c* = 2.1, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 13.0 min (minor) and 13.7 min (major)).

The absolute configuration was determined by comparison with the literature,¹⁹ after hydrolysis of **6a** to the corresponding *p*-quinol.

(*R,E*)-*N*-(2-Chloro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-ylidene)methane sulfonamide (6b)

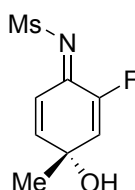


Prepared according to the general procedure with **5b** (0.100 mmol, 22.0 mg) for 4 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 63% yield [62% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 9.9 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.78 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.25 (s, 3H), 2.08 (s, 1H), 1.50 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 160.2, 151.1, 148.2, 130.3, 120.2, 69.1, 43.3, 26.4; **IR (neat)** 3454, 1675, 1648, 1600, 1564, 1304, 1136 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₈H₁₀O₃N³⁵ClNaS: *m/z* 257.9968 ([M+Na]⁺), found: *m/z* 257.9961 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = -9.8 (*c* = 1.5, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL OJ-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 13.0 min (major) and 19.0 min (minor)).

(*R,E*)-*N*-(2-Fluoro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-ylidene)methane sulfonamide (6c)



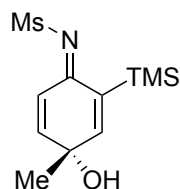
Prepared according to the general procedure with **5c** (0.100 mmol, 20.3 mg) for 4 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 49% yield [39% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.18 (dd, *J* = 9.9, 7.1 Hz, 1H), 6.76 (dd, *J* = 10.2, 2.6 Hz, 1H), 6.40 (dd, *J* = 12.3, 2.4 Hz, 1H), 3.24 (s, 3H), 1.96 (s, 1H), 1.53 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 158.0 (d, *J* = 18.0 Hz), 152.1 (d, *J* = 264.5 Hz), 151.6 (s), 127.2 (d,

$J = 12.0$ Hz), 119.6 (s), 69.2 (d, $J = 8.4$ Hz), 43.2 (s), 26.8 (s); **^{19}F NMR** (466 MHz, CDCl_3) δ -126.6 (m); **IR (neat)** 3459, 1616, 1568, 1305, 1186, 1135, 1093 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_8\text{H}_{10}\text{O}_3\text{NFNaS}$: m/z 242.0263 ($[\text{M}+\text{Na}]^+$), found: m/z 242.0256 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = 0.3$ ($c = 1.1$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL OJ-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 15.0 min (major) and 18.9 min (minor)).

(*R,E*)-*N*-(4-Hydroxy-4-methyl-2-(trimethylsilyl)cyclohexa-2,5-dien-1-ylidene) methanesulfonamide (6d)

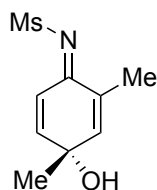


Prepared according to the general procedure with **5d** (0.100 mmol, 25.7 mg) for 4 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless oil in 66% yield [44% ee].

^1H NMR (500 MHz, CDCl_3) δ 7.21 (d, $J = 10.2$ Hz, 1H), 6.96 (d, $J = 2.8$ Hz, 1H), 6.80 (dd, $J = 10.2, 2.8$ Hz, 1H), 3.15 (s, 3H), 1.87 (s, 1H), 1.43 (s, 3H), 0.21 (s, 9H); **^{13}C NMR** (125 MHz, CDCl_3) δ 167.0, 159.3, 151.7, 138.1, 121.6, 66.9, 43.1, 26.5, -1.0; **IR (neat)** 3455, 1642, 1547, 1301, 1247, 1132 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{11}\text{H}_{19}\text{O}_3\text{NNaSSi}$: m/z 296.0753 ($[\text{M}+\text{Na}]^+$), found: m/z 296.0750 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -21.7$ ($c = 1.9$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 13.1 min (minor) and 17.1 min (major)).

(*R,E*)-*N*-(4-Hydroxy-2,4-dimethylcyclohexa-2,5-dien-1-ylidene)methanesulfonamide (6e)

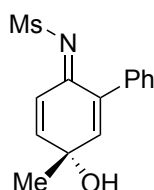


Prepared according to the general procedure with **5e** (0.100 mmol, 19.9 mg) for 4 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 60% yield [54% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.20 (d, *J* = 10.2 Hz, 1H), 6.77 (dd, *J* = 10.1, 2.7 Hz, 1H), 6.61-6.62 (m, 1H), 3.18 (s, 3H), 1.92 (d, *J* = 1.4 Hz, 3H), 1.86 (s, 1H), 1.42 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 165.4, 151.9, 148.0, 132.8, 120.8, 67.4, 43.3, 26.5, 17.3; **IR** (neat) 3447, 1663, 1548, 1297, 1130, 1054 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₉H₁₃O₃NNaS: *m/z* 238.0514 ([M+Na]⁺), found: *m/z* 238.0507 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = -22.3 (*c* = 1.3, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 19.0 min (minor) and 25.2 min (major)).

(*R,E*)-*N*-(5-Hydroxy-5-methyl-[1,1'-biphenyl]-2(5*H*)-ylidene)methanesulfonamide (6f)



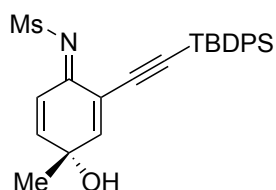
Prepared according to the general procedure with **5f** (0.100 mmol, 26.1 mg) for 7 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1), followed by the purification using PLC (eluent: AcOEt only) to afford the title compound as a colorless solid in 87% yield [35% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.32-7.38 (m, 6H), 6.85 (dd, *J* = 10.2, 2.6 Hz, 1H), 6.80 (d, *J* = 2.8 Hz, 1H), 3.06 (s, 3H), 1.89 (s, 1H), 1.53 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 164.1, 151.2, 149.8, 137.4, 136.0, 129.4, 128.2, 128.0, 121.3, 67.5, 43.2, 26.7; **IR** (neat)

3458, 1554, 1301, 1134 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{14}\text{H}_{15}\text{O}_3\text{NNaS}$: m/z 300.0670 ($[\text{M}+\text{Na}]^+$), found: m/z 300.0665 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -12.0$ ($c = 2.4$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/ i PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 20.5 min (minor) and 27.6 min (major)).

(*R,E*)-*N*-(2-((*tert*-Butyldiphenylsilyl)ethynyl)-4-hydroxy-4-methylcyclohexa-2,5-dien-1-ylidene)methanesulfonamide (6g)

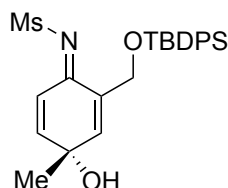


Prepared according to the general procedure with **5g** (0.100 mmol, 44.8 mg) for 3 days (Catalyst **4b** (20.0 mol%, 14.4 mg) was used.). The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 3/1) to afford the title compound as a colorless oil in 62% yield [84% ee].

^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, $J = 7.1$ Hz, 4H), 7.36-7.43 (m, 6H), 7.26 (d, $J = 9.9$ Hz, 1H), 7.18 (d, $J = 2.6$ Hz, 1H), 6.80 (dd, $J = 10.2, 2.8$ Hz, 1H), 3.16 (s, 3H), 1.93 (s, 1H), 1.51 (s, 3H), 1.12 (s, 9H); **^{13}C NMR** (125 MHz, CDCl_3) δ 162.7, 154.5, 150.9, 135.7, 132.8, 129.8, 127.9, 121.8, 120.7, 101.9, 95.5, 67.3, 43.3, 27.1, 26.5, 18.9; **IR** (neat) 3460, 2931, 2857, 1560, 1306, 1111, 1087, 1086 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{26}\text{H}_{29}\text{O}_3\text{NNaSSi}$: m/z 486.1535 ($[\text{M}+\text{Na}]^+$), found: m/z 486.1531 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -14.2$ ($c = 2.9$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/ i PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 7.9 min (minor) and 13.1 min (major)).

(*R,E*)-*N*-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-hydroxy-4-methylcyclohexa-2,5-dien-1-ylidene)methanesulfonamide (6h)

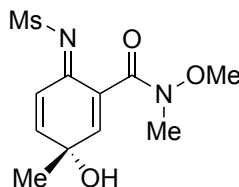


Prepared according to the general procedure with **5h** (0.100 mmol, 45.4 mg) for 4 days (Catalyst **4b** (20.0 mol%, 14.4 mg) was used.). The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 4/1) to afford the title compound as a colorless solid in 75% yield [70% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.66 (m, 4H), 7.38-7.46 (m, 6H), 7.15 (d, *J* = 10.2 Hz, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.78 (dd, *J* = 10.2, 2.8 Hz, 1H), 4.49 (dd, *J* = 16.0, 1.8 Hz, 1H), 4.46 (dd, *J* = 15.9, 2.0 Hz, 1H), 3.02 (s, 3H), 1.93 (s, 1H), 1.44 (s, 3H), 1.10 (s, 9H); **¹³C NMR** (125 MHz, CDCl₃) δ 163.5, 152.0, 146.1, 135.5, 135.0, 133.2, 130.0, 128.0, 120.8, 67.5, 60.5, 43.1, 26.9, 26.4, 19.4; **IR (neat)** 3459, 2931, 2858, 1550, 1305, 1137, 1113 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₂₅H₃₁O₄NNaSSi: *m/z* 492.1641 ([M+Na]⁺), found: *m/z* 492.1635 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = -15.2 (*c* = 3.4, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 17.1 min (minor) and 21.2 min (major)).

(*R,E*)-3-Hydroxy-*N*-methoxy-*N*,3-dimethyl-6-((methylsulfonyl)imino)cyclohexa-1,4-diene-1-carboxamide (6i)



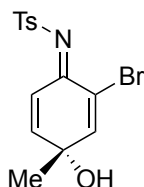
Prepared according to the general procedure with **5i** (0.100 mmol, 27.2 mg) for 7 days. The obtained crude material was purified by column chromatography (eluent: AcOEt only), followed by the further purification using PLC (eluent: AcOEt only) to afford the title compound as a colorless solid in 43% yield [95% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 10.2 Hz, 1H), 6.82 (m, 2H), 3.60 (s, 3H), 3.27

(s, 3H), 3.14 (s, 3H), 2.30 (brs, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.0, 161.53, 152.0, 147.6, 134.3, 120.3, 66.9, 61.8, 43.1, 32.3, 26.6; **IR** (neat) 3369, 2932, 1637, 1558, 1306, 1136 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_5\text{N}_2\text{NaS}$: m/z 311.0678 ($[\text{M}+\text{Na}]^+$), found: m/z 311.0672 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -10.6$ ($c = 0.8$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL OJ-3, hexane/*i*PrOH = 1/1, flow rate = 0.5 mL/min, retention time; 11.0 min (major) and 13.0 min (minor)).

(*R,E*)-*N*-(2-Bromo-4-hydroxy-4-methylcyclohexa-2,5-dien-1-ylidene)-4-methylbenzenesulfonamide (6j)

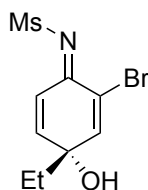


Prepared according to the general procedure with **5j** (0.100 mmol, 34.0 mg) for 4 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 85% yield [64% ee].

^1H NMR (500 MHz, CDCl_3) δ 7.91 (d, $J = 7.9$ Hz, 2H), 7.48 (d, $J = 9.9$ Hz, 1H), 7.34 (d, $J = 8.5$ Hz, 2H), 7.24 (d, $J = 2.6$ Hz, 1H), 6.82 (dd, $J = 9.9$, 2.6 Hz, 1H), 2.44 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 160.0, 152.6, 151.2, 144.0, 138.1, 129.7, 127.2, 121.9, 119.9, 69.8, 26.3, 21.7; **IR** (neat) 3458, 1641, 1596, 1557, 1314, 1303, 1151, 1089 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_3\text{N}^{79}\text{BrNaS}$: m/z 377.9770 ($[\text{M}+\text{Na}]^+$), found: m/z 377.9770 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -4.3$ ($c = 1.0$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 12.8 min (minor) and 15.7 min (major)).

(*R,E*)-*N*-(2-Bromo-4-ethyl-4-hydroxycyclohexa-2,5-dien-1-ylidene)methanesulfonamide (8a)

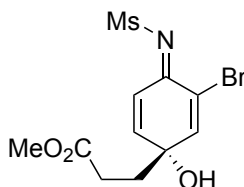


Prepared according to the general procedure with **7a** (0.100 mmol, 27.8 mg) for 4 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 70/30 to 67/33) to afford the title compound as a yellowish oil in 74% yield [74% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.32 (d, *J* = 10.2 Hz, 1H), 7.21 (d, *J* = 2.6 Hz, 1H), 6.74 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.25 (s, 3H), 2.00 (s, 1H), 1.82 (q, *J* = 7.7 Hz, 2H), 0.89 (t, *J* = 7.7 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 160.7, 152.3, 150.4, 122.0, 121.2, 73.1, 43.3, 328, 8.0; **IR** (neat) 3455, 2970, 2935, 1640, 1560, 1304, 1136 cm⁻¹; **HRMS** (ESI) exact mass calcd. for C₉H₁₂O₃N⁷⁹BrNaS: *m/z* 315.9613 ([M+Na]⁺), found: *m/z* 315.9614 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = -9.9 (*c* = 2.2, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 12.9 min (minor) and 14.3 min (major)).

Methyl (*R,E*)-3-(3-bromo-1-hydroxy-4-((methanesulfonyl)imino)cyclohexa-2,5-dien-1-yl)propanoate (8b)



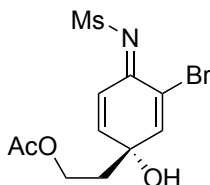
Prepared according to the general procedure with **7b** (0.100 mmol, 33.6 mg) for 7 days. The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless oil in 76% yield [61% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, *J* = 10.2 Hz, 1H), 7.21 (d, *J* = 2.6 Hz, 1H), 6.74 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.69 (s, 3H), 3.25 (s, 3H), 2.77 (brs, 1H), 2.37 (td, *J* = 7.5, 2.3 Hz, 2H), 2.11 (td, *J* = 7.4, 1.6 Hz, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 173.3, 160.3,

151.4, 149.6, 122.3, 121.1, 71.7, 52.3, 43.3, 34.4, 28.6; **IR (neat)** 3446, 1733, 1642, 1561, 1438, 1306, 1138 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_5\text{N}^{79}\text{BrNaS}$: m/z 373.9668 ($[\text{M}+\text{Na}]^+$), found: m/z 373.9670 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -17.4$ ($c = 2.6$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 29.8 min (minor) and 37.9 min (major)).

(*R,E*)-2-(3-Bromo-1-hydroxy-4-((methylsulfonyl)imino)cyclohexa-2,5-dien-1-yl)ethyl acetate (8c)

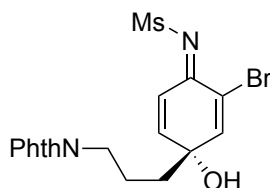


Prepared according to the general procedure with **7c** (0.100 mmol, 33.6 mg) for 5 days (Catalyst **4b** (20.0 mol%, 14.4 mg) was used.). The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 72% yield [49% ee].

^1H NMR (500 MHz, CDCl_3) δ 7.30 (d, $J = 10.2$ Hz, 1H), 7.27 (d, $J = 2.6$ Hz, 1H), 6.79 (dd, $J = 10.2, 2.6$ Hz, 1H), 4.10–4.23 (m, 2H), 3.25 (s, 3H), 2.45 (brs, 1H), 2.08–2.12 (m, 2H), 2.05 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 170.9, 160.2, 151.5, 149.6, 122.0, 120.8, 71.0, 59.3, 43.3, 38.7, 21.0; **IR (neat)** 3446, 1736, 1642, 1561, 1307, 1138, 1068, 1025 cm^{-1} ; **HRMS (ESI)** exact mass calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_5\text{N}^{79}\text{BrNaS}$: m/z 373.9668 ($[\text{M}+\text{Na}]^+$), found: m/z 373.9669 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -13.1$ ($c = 2.5$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 24.3 min (minor) and 35.3 min (major)).

(*R,E*)-*N*-(2-Bromo-4-(3-(1,3-dioxoisindolin-2-yl)propyl)-4-hydroxycyclohexa-2,5-dien-1-ylidene)methanesulfonamide (8d)

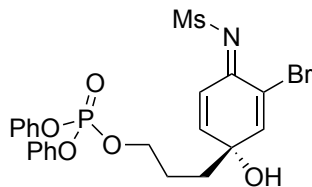


Prepared according to the general procedure with **7d** (0.100 mmol, 43.7 mg) for 7 days (Catalyst **4b** (20.0 mol%, 14.4 mg) was used.). The obtained crude material was purified by column chromatography (eluent: CH₂Cl₂/MeOH = 50/1 to 40/1), followed by further purification by column chromatography (eluent: hexane/AcOEt = 60/40 to 50/50) to afford the title compound as a colorless solid in 72% yield [68% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.85 (q, *J* = 2.8 Hz, 2H), 7.73 (q, *J* = 2.8 Hz, 2H), 7.29 (d, *J* = 10.2 Hz, 1H), 7.22 (d, *J* = 2.6 Hz, 1H), 6.76 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.72 (t, *J* = 6.9 Hz, 2H), 3.23 (s, 3H), 2.29 (s, 1H), 1.69-1.84 (m, 4H); **¹³C NMR** (125 MHz, CDCl₃) δ 168.5, 160.3, 151.8, 150.0, 134.2, 132.0, 123.5, 122.2, 121.0, 72.0, 43.3, 37.7, 36.9, 23.1; **IR (neat)** 3457, 2935, 1771, 1704, 1561, 1307, 1137 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₁₈H₁₇O₅N₂⁷⁹BrNaS: *m/z* 474.9934 ([M+Na]⁺), found: *m/z* 474.9936 ([M+Na]⁺); **Optical rotation** [α]_D²⁵ = -14.9 (*c* = 1.1, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*-PrOH = 1/1, flow rate = 0.75 mL/min, retention time; 27.9 min (major) and 32.2 min (minor)).

(*R,E*)-3-(3-Bromo-1-hydroxy-4-((methylsulfonyl)imino)cyclohexa-2,5-dien-1-yl)propyl diphenyl phosphate (8e)



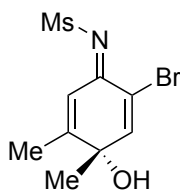
Prepared according to the general procedure with **7e** (0.100 mmol, 54.0 mg) for 7 days (Catalyst **4b** (20.0 mol%, 14.4 mg) was used.). The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 1/1) to afford the title compound as a colorless oil in 53% yield [59% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.34-7.37 (m, 4H), 7.26 (d, *J* = 9.9 Hz, 1H), 7.20-7.22 (m,

6H), 7.13 (d, $J = 2.3$ Hz, 1H), 6.65 (dd, $J = 10.2, 2.6$ Hz, 1H), 4.23-4.26 (m, 2H), 3.25 (s, 3H), 1.67-1.76 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 160.4 (s), 152.0 (s), 150.4 (d, $J = 7.3$ Hz), 150.1 (s), 130.0 (s), 125.7 (s), 121.9 (s), 120.9 (s), 120.1 (d, $J = 4.8$ Hz) 71.8 (s), 68.9 (d, $J = 6.0$ Hz), 43.3 (s), 35.7 (s), 24.6 (d, $J = 7.3$ Hz); **IR** (neat) 3338, 1560, 1310, 1187, 1139, 1023 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_{22}\text{H}_{23}\text{O}_7\text{N}^{79}\text{BrNaPS}$: m/z 578.0008 ($[\text{M}+\text{Na}]^+$), found: m/z 578.0005 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{25} = -2.9$ ($c = 2.9$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AS-3, hexane/ i PrOH = 1/1, flow rate = 0.5 mL/min, retention time; 24.5 min (minor) and 28.7 min (major)).

(*S,E*)-*N*-(2-Bromo-4-hydroxy-4,5-dimethylcyclohexa-2,5-dien-1-ylidene)methane sulfonamide (8f)

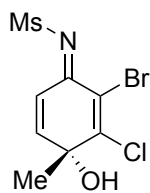


Prepared according to the general procedure with **7f** (0.100 mmol, 27.8 mg) for 7 days (Catalyst **4b** (20.0 mol%, 14.4 mg) was used.). The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound as a colorless solid in 79% yield [56% ee].

^1H NMR (500 MHz, CDCl_3) δ 7.25 (s, 1H), 7.08 (q, $J = 1.3$ Hz, 1H), 3.23 (s, 3H), 2.14 (d, $J = 1.4$ Hz, 3H), 1.91 (brs, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.7, 160.9, 153.2, 121.3, 118.5, 71.7, 43.3, 25.9, 18.7; **IR** (neat) 3447, 1646, 1597, 1558, 1300, 1135 cm^{-1} ; **HRMS** (ESI) exact mass calcd. for $\text{C}_9\text{H}_{12}\text{O}_3\text{N}^{79}\text{BrNaS}$: m/z 315.9619 ($[\text{M}+\text{Na}]^+$), found: m/z 315.9623 ($[\text{M}+\text{Na}]^+$); **Optical rotation** $[\alpha]_{\text{D}}^{28} = -15.0$ ($c = 2.1$, CHCl_3).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/ i PrOH = 2/1, flow rate = 0.2 mL/min, retention time; 21.1 min (minor) and 22.1 min (major)).

(*R,E*)-*N*-(2-Bromo-3-chloro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-ylidene) methanesulfonamide (8g)



Prepared according to the general procedure with **7g** (0.100 mmol, 29.9 mg) for 7 days (Catalyst **4b** (20.0 mol%, 14.4 mg) was used.). The obtained crude material was purified by column chromatography (eluent: hexane/AcOEt = 2/1), PLC (hexane/AcOEt = 2/1), and cosmosil HPLC resolution (eluent: hexane/*i*PrOH = 9/1) to afford the title compound as a colorless solid in 18% yield [90% ee].

¹H NMR (500 MHz, CDCl₃) δ 7.32 (d, *J* = 9.9 Hz, 1H), 6.83 (d, *J* = 9.9 Hz, 1H), 3.25 (s, 3H), 2.47 (brs, 1H), 1.62 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 160.6, 156.9, 149.2, 122.9, 119.5, 71.9, 43.3, 27.4; **IR (neat)** 3445, 1645, 1559, 1307, 1137, 1034 cm⁻¹; **HRMS (ESI)** exact mass calcd. for C₈H₉O₃N⁷⁹Br³⁵ClNaS: *m/z* 335.9067 ([M+Na]⁺), found: *m/z* 335.9067 ([M+Na]⁺); **Optical rotation** [α]_D²⁸ = -9.9 (*c* = 0.5, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 13.5 min (major) and 17.2 min (minor)).

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Chapter 4

An Iridium/Aluminum Cooperative Strategy for the β -C(sp³)-H Borylation of Saturated Cyclic Amines

Despite the widespread success in the functionalization of C(sp²)-H bonds, the deliberate functionalization of C(sp³)-H bonds in a highly site- and stereoselective manner remains a longstanding challenge. Herein, the author reports an iridium/aluminum cooperative catalytic system that enables the β -selective C-H borylation of saturated cyclic amines and lactams. Furthermore, the author has accomplished an enantioselective variant using binaphthol-derived chiral aluminum catalysts to forge C-B bonds with high levels of stereo control. Computational studies suggest that the formation of a Lewis pair with the substrates is crucial to lower the energy of the transition state for the rate-determining reductive elimination step.

4.1 Introduction

Saturated nitrogen-containing heterocycles are indispensable for multiple facets of chemical science, given their prevalence in bioactive organic molecules including pharmaceuticals and natural alkaloids (Figure 4-1 (A)).¹ Despite their importance, the preparation of functionalized cyclic amines still relies largely on conventional multistep reaction sequences that involve the cyclization of pre-functionalized linear precursors (Figure 2-1Figure 4-1 (B), left).² Also, these synthetic strategies cannot be readily adapted, particularly in industrial settings, where the rapid synthesis of numerous analogs is often required. In this regard, it has become apparent that the direct functionalization of a specific C–H bond in the parent framework could offer the opportunity to explore the chemical space more efficiently by facilitating access to a diverse array of analogs (Figure 4-1 (B), right).^{3,4} In contrast to the wealth of synthetic tools available for the functionalization of C–H bonds α to the nitrogen atom,⁵ there is only a limited number of routes that provide direct access to β -functionalized saturated cyclic amines using strategies that rely on directing groups^{5c} or enamine intermediates.⁶ With this limitation in mind, the author sought to develop a distinct catalytic strategy to diversify the periphery of saturated cyclic amines.

From the perspective of molecular diversification, the selective replacement of C–H bonds with C–B bonds should generate a versatile intermediate en route to functionalized cyclic amines, given the ability of organoboron compounds to undergo a variety of indispensable bond-forming reactions.⁷ Over the past two decades, substantial progress has been accomplished in the development of transition-metal catalysts for the borylation of C(sp³)–H bonds.⁸ Surprisingly, however, the β -selective C–H borylation of saturated cyclic amines has remained an elusive transformation, despite a recent surge of reports on C(sp³)–H borylations on a wide range of alkylamines and their derivatives,⁹ while Hartwig and co-workers recently reported a β -selective and non-enantioselective C(sp³)–H borylation of saturated cyclic amines.¹⁰

The author's group has reported transition-metal/Lewis-acid cooperative catalysis as a platform for previously unattainable site-selective C–H functionalization reactions when using transition-metal catalysis alone.¹¹ Employing iridium/aluminum co-catalysis, the *para*-selective C(sp²)–H borylation of (hetero)arenes was previously reported, wherein an aluminum-based Lewis acid, upon complexation with a Lewis-basic

functionality in a substrate, is believed to electronically promote the C–H borylation and simultaneously block the sterically congested *ortho* and *meta* positions (Figure 4-1 (C)).¹² Coupled with the recently reported *meta*-selective (hetero)arene borylation by a bifunctional Lewis-acidic iridium catalyst,¹³ the author speculated whether it would be possible to use this cooperative strategy to accomplish the β -selective C(sp³)–H borylation of saturated cyclic amines. Here, the author reports a cooperative strategy that provides a solution for the site- and enantioselective C(sp³)–H functionalization of saturated cyclic amines

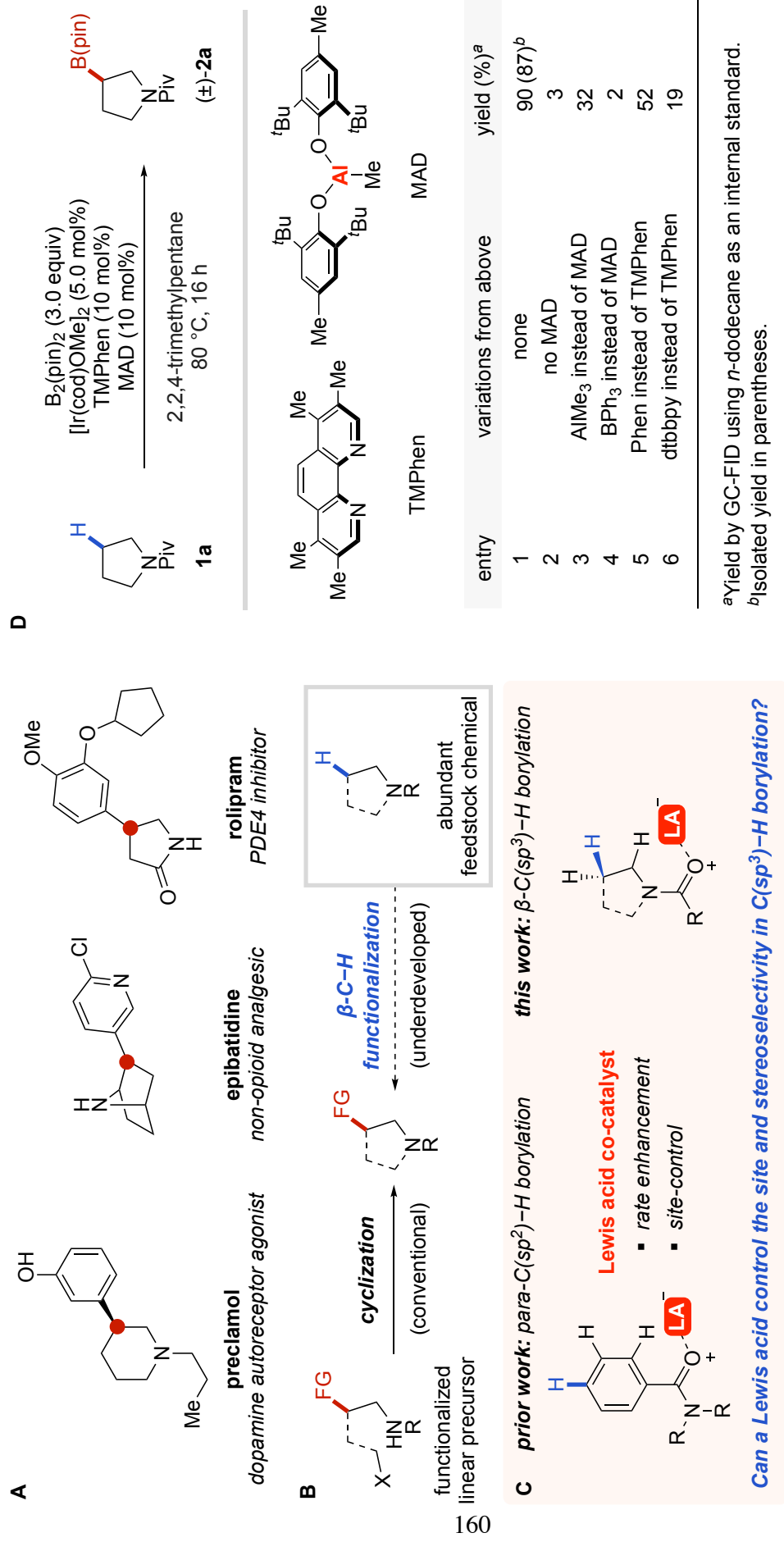


Figure 4-1 (A) Representative bioactive compounds that contain β -functionalized cyclic amines and lactams. (B) In contrast to the wealth of reactions that functionalize C–H bonds α to the nitrogen atom (left), the β -C–H functionalization of saturated cyclic amines remains elusive (right). (C) A blueprint for the cooperative iridium/Lewis acid strategy for site-selective C–H borylations. (D) Optimization studies.

4.2 Results and Discussion

4.2.1 Reaction Development by Ir/Al Catalysis

The author began the investigation by seeking a Lewis-acidic co-catalyst that works in synergy with an iridium catalyst to promote the desired β -C(sp³)-H borylation using *N*-pivaloylpyrrolidine (**1a**) as a model substrate (Figure 4-1 (D)). After an extensive screening of various reaction conditions, which employ [Ir(cod)OMe]₂ (cod = cyclooctadiene), 3,4,7,8-tetramethyl-1,10-phenanthroline (TMPhen), bis(pinacolato)diboron (B₂(pin)₂) as a borylation reagent and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)^{14,15} as a Lewis-acidic co-catalyst. Upon heating to 80 °C in 2,2,4-trimethylpentane, the desired borylation product (**2a**) was obtained in 90% GC yield (87% isolated yield) with complete β -selectivity (entry1). The structure of **2a** was determined unambiguously by a single-crystal X-ray diffraction analysis (Figure 4-26).¹⁶ A control experiment established the importance of the Lewis-acidic co-catalyst, as the formation of borylation products was sluggish in the absence of MAD (entry2). This result validates the author's proposed cooperative strategy (Figure 4-1 (C)), wherein a Lewis-acidic co-catalyst facilitates the C-H borylation, while its dynamic Lewis-pair formation with both the substrate and borylation product, as confirmed by ¹H NMR studies (See P232 for details), allows its catalyst turnover. The use of other Lewis acids in lieu of MAD resulted in a considerably decreased yield of **2a** (entries 3 and 4; see also Table 4-1). A survey of potential ligands revealed that other phenanthroline ligands can deliver **2a** in moderate to good yield, whereas bipyridyl ligands including dtbpy (4,4'-di-*tert*-butyl-2,2'-bipyridyl) are less effective (entries 5 and 6; see also Table 4-2).¹⁷ It should be noted that the choice of the solvent 2,2,4-trimethylpentane is important to prevent solvent C-H borylation.

With the optimized conditions in hand, the author then explored the scope of this β -C-H borylation protocol. As shown in Figure 4-2, a diverse array of cyclic amines proved to be compatible substrates. With respect to ring-sizes, piperidine and azepane underwent the β -C-H borylation to furnish boronate ester **2b** (52%) [alongside diborylation product **3** (23%)] and **2c** (23 %), respectively. Additionally, pyrrolidines and piperidines that bear a variety of substituents including methyl, ethyl, ester, and silyl ether groups at the 2- and 3-positions were well tolerated (**2d–2i**; 32–70 % yield), and excellent

site-selectivity was observed for the C–H borylation at the sterically less demanding β -position relative to the nitrogen atom for all substrates. The observed site-selectivity was tentatively attributed to the steric repulsion between the ligated trisboryliridium complex and the substituents. This β -C–H borylation method is not limited to monocyclic amines; *trans*-decahydroquinoline was found to be a viable substrate to afford **2j** in 69 % with complete site- and diastereoselectivity. Notably, bridged bicyclic amines were also selectively borylated at the β -position relative to the nitrogen atom with complete endo-selectivity (**2k** and **2l**; 61% and 53% yield, respectively), paving the way for the diversified syntheses of epibatidine¹⁸ and tropane alkaloids.¹⁹ It should be noted that the observed selectivity stands in sharp contrast to the amide-directed C–H functionalization of bridged bicyclic compounds that inevitably functionalize the C–H bonds syn to the amide moieties.²⁰ Moreover, this borylation protocol can be further expanded to lactam substrates, which leads to the exclusive formation of β -borylation products **2m** (76%) and **2n** (63%).

Having established a straightforward method to access borylation products that cannot be readily prepared any other way, the author sought to demonstrate their utility as versatile intermediates that can be expediently transformed into a variety of chemical entities (Figure 4-3 (A)). For example, boronate ester **2k** was converted into the corresponding alcohol **4** (70% yield) in a stereospecific manner by treatment with NaBO₃. The structure of **4** was determined unequivocally by a single-crystal X-ray diffraction analysis (Figure 4-35). Alternatively, C–N bond formation can be achieved by the treatment of **2g** with MeONH₂, followed by Boc-protection to generate carbamate **5** as a single diastereomer in 67% yield. The virtue of this C–H borylation methodology becomes evident in the corresponding synthesis of pharmaceutically relevant compounds, given the amenability of organoboron compounds to the formation of C–C bonds.⁷ To test the author's hypothesis, the author selected rolipram, a potent phosphodiesterase-4 inhibitor.²¹ As shown in Figure 4-3 (B), potassium trifluoroborate **6**, which can be prepared on the gram scale from lactam **1m** through the author's developed C–H borylation, was readily coupled with diverse aryl halides to afford *N*-^tBu rolipram (**7a**) and its analogs **7b** and **7c** by using an adaptation of the reported protocol.²² In light of the fact that the synthesis of rolipram still relies on multistep sequences starting from the corresponding benzaldehyde,²³ this C–H borylation technology provides a streamlined synthetic strategy that may have potential in the development of structure-activity relationships.^{3b}

The author next turned his attention to rendering this β -C(sp³)–H borylation process enantioselective. Regardless of the recent progress in C(sp³)–H borylation reactions, only a few should presumably be attributed to the difficulties associated with enantioselective variants have been reported.²⁴ This paucity with decorating planar phenanthrolines, i.e., a privileged class of ligands for iridium-catalyzed C(sp³)–H borylations,^{7,9b} with chiral auxiliaries while maintaining their reactivity. As shown in Figure 4-1 (D), control experiments revealed that a Lewis-acidic aluminum-based co-catalyst is essential for the author's C–H borylation reactions. This result led us to envision that the use of a chiral Lewis-acidic aluminum catalyst instead of achiral MAD could deliver asymmetry without having to touch the structure of the phenanthroline ligand, thereby providing a new alternative to the conventional approach, which relies on chiral ligands bound to the transition metal.²⁵ Toward this end, the author investigated the capability of binaphthol-derived chiral Lewis-acidic aluminum catalysts,²⁶ which can be

prepared in situ from the corresponding binaphthol and trialkylaluminum as confirmed by NMR studies on a stoichiometric reaction,²⁷ to enantioselectively catalyze the C(sp³)-H borylation of *N*-pivaloylpyrrolidine (**1a**). After a brief screening of chiral binaphthols, the author were pleased to find that the combination of **8a** and AlMe₃ promoted the desired borylation with promising levels of enantiomeric excess (Figure 4-3 (C), entry 1). It is worth noting that bulky and lipophilic triisopropylsilyl (TIPS) groups attached to the 6,6'-position of the binaphthol backbone are crucial both in terms of reactivity and selectivity; binaphthol **8b**, which lacks TIPS groups, provided the desired borylation product (**2a**) in diminished yield without enantioinduction (entry 2).²⁸ Screening various trialkylaluminum reagents revealed a trend toward improved enantiomeric ratio with increasing steric demand of the alkyl group (entries 1, 3, and 4).

Finally, switching the 3,3'-substituents to bulkier 4-(1-adamantyl)phenyl groups led to a substantial increase in enantioselectivity, furnishing (*S*)-**2a** in 63% isolated yield with 87.5:12.5 er (entry 5). The examination of the scope of this enantioselective C-H borylation revealed that a wide range of structurally differentiated substrates afford moderate to excellent enantiomeric ratios of the desired β -borylation products (**2b**, **2k**, **2m**, **2n**; 65:35–99:1 er). These results clearly demonstrate that this cooperative strategy based on an achiral iridium/chiral aluminum Lewis acid catalyst system is amenable to asymmetric catalysis. Enantio-enriched borylation products obtained by the author's method can be further transformed. For example, treatment of (*R*)-**2m** (99:1 er) with lithiated furan, followed by a reaction with NBS forged the C-C bond in an enantiospecific manner to afford (*R*)-**9** in 59% yield without decrease of the optical purity by using a reported protocol.²⁹

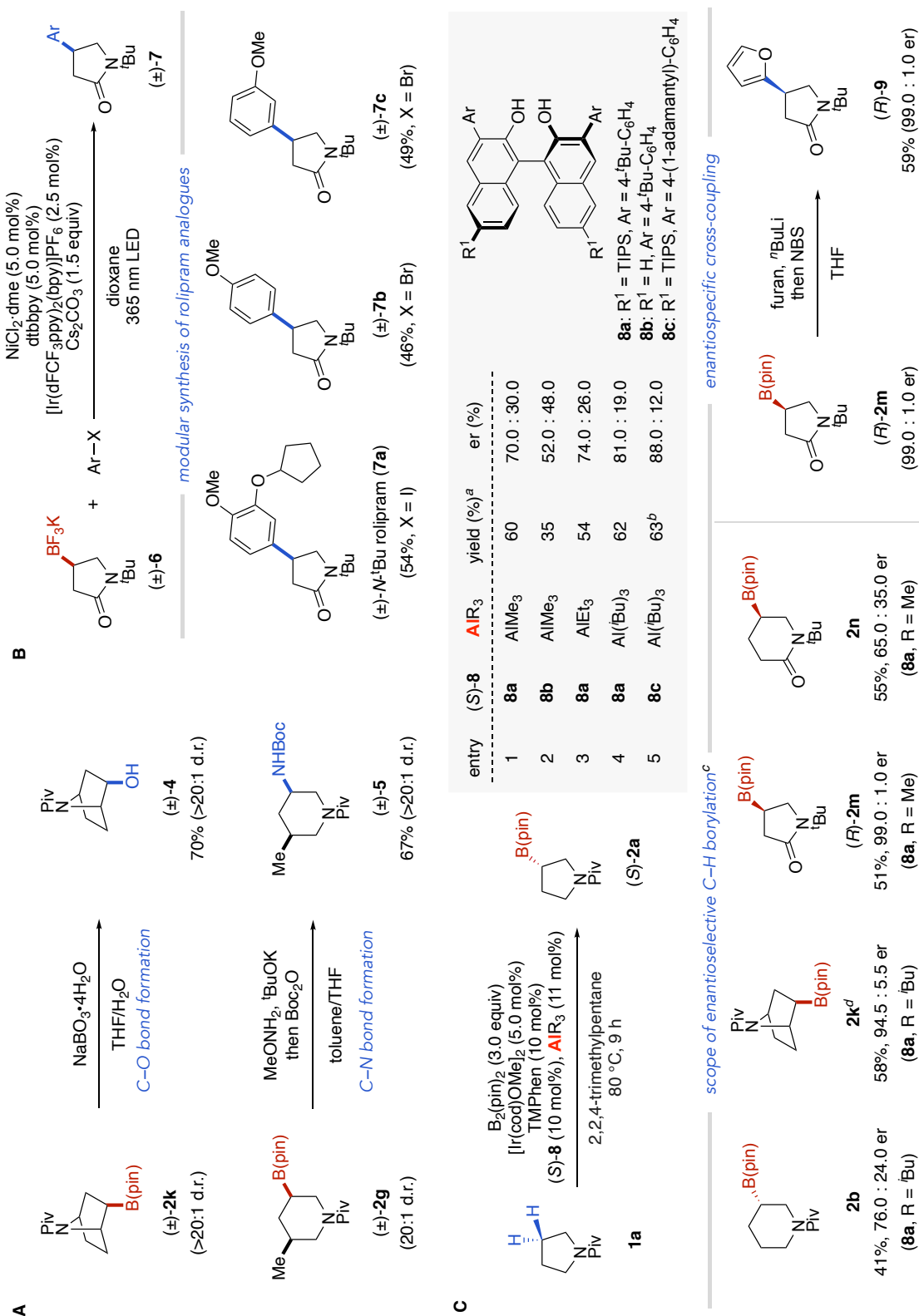


Figure 4-3 (A) Oxidation of borylation products. (B) Modular synthesis of *N*-*t*-Bu rolipram and its analogs. (C) Enantioselective C(sp³)-H borylation enabled by a BINOL-derived chiral aluminum catalyst. ^aNMR yield using triphenylmethane as an internal standard. ^bIsolated yield. ^cEnantioselective C-H borylation reactions were conducted on a 0.30 mmol scale and isolated product yields after purification are shown. ^d7.5 mol% [Ir(cod)OMe]₂ and 15 mol% TMPhen were used.

4.2.2 DFT Calculations

To gain insight into the effect of the Lewis-acidic aluminum co-catalyst and the origins of the β -selectivity, the author conducted density functional theory (DFT) calculations using the borylation of *N*-pivaloylpiperidine (**1b**) as a model reaction (Figure 4-4). For computational efficiency, trimethylaluminum (AlMe_3) and 1,10-phenanthroline (phen) were employed as models for MAD and TMPhen, respectively. On the basis of previous mechanistic investigations by other groups,^{30,31,32} an $\text{Ir}^{\text{III}}/\text{Ir}^{\text{V}}$ catalytic cycle is proposed, in which iridium-trisboryl complex (phen) $\text{Ir}(\text{B}(\text{pin}))_3$ **11** is the active species that undergoes oxidative addition of the C–H bond. As shown in Figure 4-4 (A), the borylation begins with the release of $\text{B}_2(\text{pin})_2$ from the resting state (phen) $\text{Ir}(\text{B}(\text{pin}))_5$ **10** to generate trisboryl complex **11**.³³ As AlMe_3 interacts more strongly with the oxygen atom of **1b** than with that of free $\text{B}_2(\text{pin})_2$ to form the Lewis pair **1b**[Al] (Figure 4-10), the adduct approaches the Ir center of **11** in the oxidative-addition step. Then, the oxidative addition of the β -C–H bond affords Ir^{V} species **13**, followed by reductive elimination of the B–C bond to yield β -borylation product **2b** under concomitant formation of iridium complex **16**. As shown in Figure 4A, the calculated Gibbs energies of activation ($\Delta G^{\ddagger}$) for the C–H oxidative addition ($\beta\text{-TS}_{12/13}[\text{Al}]$) and the B–C reductive elimination ($\beta\text{-TS}_{14/15}[\text{Al}]$) are 28.9 kcal mol⁻¹ and 30.2 kcal mol⁻¹, respectively, indicating that the reductive elimination is the rate-determining step. Intriguingly, the reductive elimination requires a higher $\Delta G^{\ddagger}$ (35.0 kcal mol⁻¹) in the absence of AlMe_3 (Figure 4-11), which clearly underlines its prominent role in accelerating the C–B bond-forming step.

To elucidate the effect of the Lewis-acidic aluminum co-catalyst in the rate-determining reductive elimination, the author carried out a deformation/interaction energy analysis³⁴ by separating each transition state into two moieties (frag-a and frag-b) (Figure 4-4 (C)).³⁵ The analysis clearly shows that the difference in energy between $\beta\text{-TS}_{14/15}$ and $\beta\text{-TS}_{14/15}[\text{Al}]$ should be attributed to the difference in interaction energy (E_{int}) between frag-a and frag-b; the calculated E_{int} in $\beta\text{-TS}_{14/15}$ and $\beta\text{-TS}_{14/15}[\text{Al}]$ are –99.2 kcal mol⁻¹ and –90.5 kcal mol⁻¹, respectively (Figure 4-4 (B)). To decipher the difference in E_{int} , the author focused on the Ir–C $^{\beta}$ interactions, as (i) E_{int} depends on the Ir–C $^{\beta}$ and Ir–B interactions in the transition state, and (ii) the Ir–B interaction does not differ very much regardless of the presence or absence of AlMe_3 (Figure 4-12). On this basis, coupled with

the recent theoretical study on C(sp³)–H borylation of cyclic ethers, which has demonstrated that the Ir–C bond energy increases with decreasing C(sp³)-valence orbital energy,³⁵ the author separated the Ir–C^β bonds in a homolytic manner to evaluate the effect of the aluminum Lewis acid on the C(sp³)-valence orbital energy. The author's results suggest that the Ir–C^β bond is stronger in the presence than in the absence of the aluminum Lewis acid (Figure 4-13). As shown in Figure 4-4 (C), coordination of AlMe₃ lowers the C(sp³)-valence orbital energy by 0.70 eV (–8.36 eV in β-TS_{14/15} vs –9.06 eV in β-TS_{14/15}[Al]). Given that the covalent bond energy increases with the increasing energy difference between two valence orbitals,³⁵ the lower energy of β-TS_{14/15}[Al] relative to that of β-TS_{14/15} probably arises from the low energy C(sp³)-orbital in the presence of the aluminum Lewis acid (Figure 4-14). Considering these results in their entirety, the author concluded that the Lewis-acidic co-catalyst stabilizes the C(sp³)-valence orbital via an inductive effect, thereby leading to a stronger Ir–C^β bond, which is responsible for the higher (more attractive) E_{int} in the reductive-elimination step (see Figure 4-15).

The author next sought to understand the origins of the β-selectivity. As shown in Figure 4-4 (B), the calculated Gibbs energies of activation for the reductive elimination at both the α- and γ-positions were found to be higher in energy than that of β-position (α-TS_{14/15}[Al]: 55.0 kcal mol^{–1}; γ-TS_{14/15}[Al]: 34.8 kcal mol^{–1}). Likewise, a deformation/interaction analysis showed that less negative (less attractive) E_{int} in α-TS_{14/15}[Al] and γ-TS_{14/15}[Al] should be responsible for the larger $\Delta G^{\ddagger}$. In the former case, the C^α(sp³)-orbital should exist at higher energy due to its antibonding overlap with the lone-pair orbital of the nitrogen atom (Figure 4-17), whereas in the latter case, the higher energy of the C^γ(sp³) orbital arises from its anti-bonding overlap with the C^α–C^β σ-bonding molecular orbital (Figure 4-17).

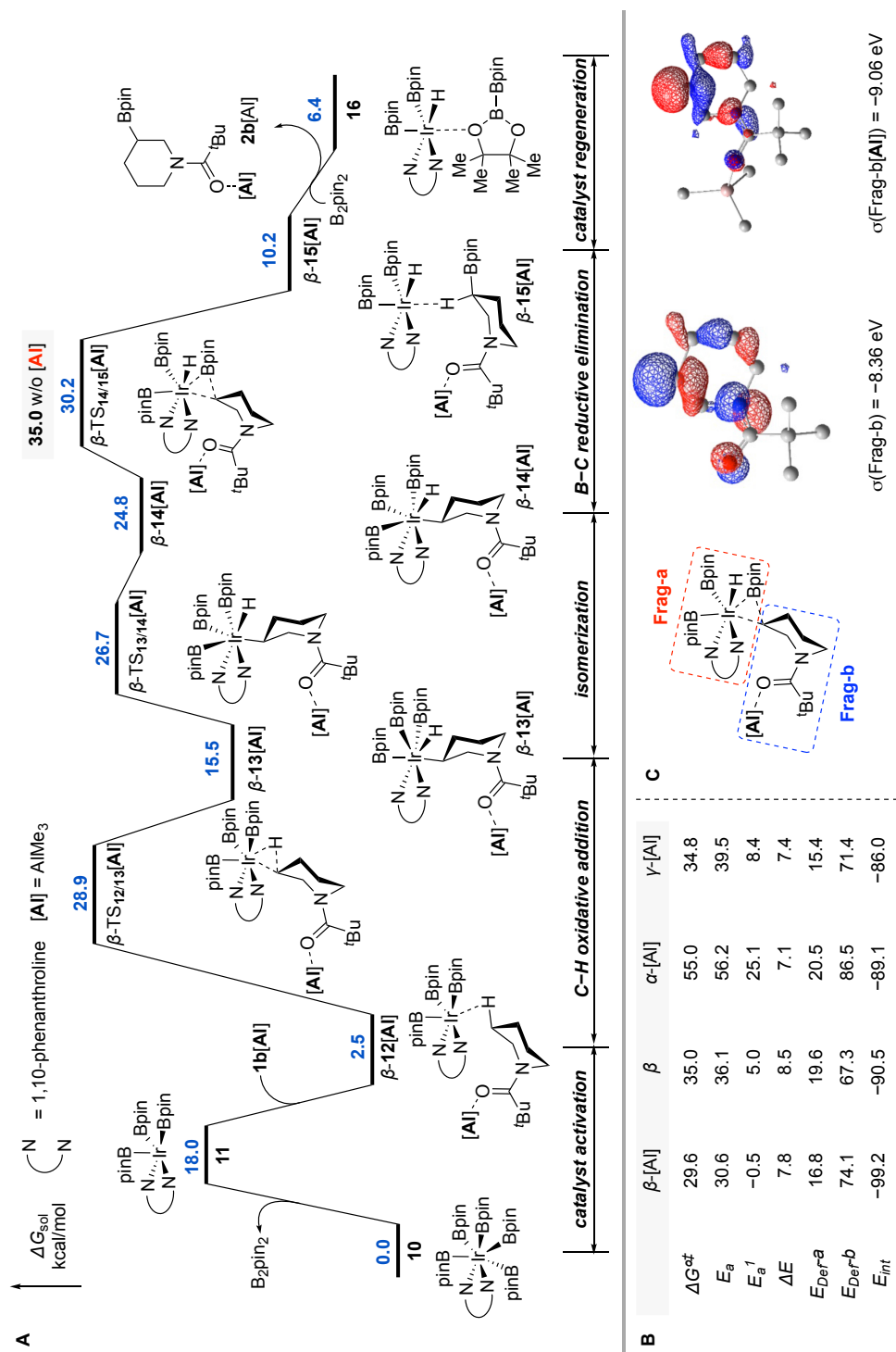


Figure 4-4 Computational investigations. (A) Calculated Gibbs energy profile (in kcal/mol) of the iridium(III)-catalyzed C(sp³)-H borylation of **1b** in the presence of AlMe₃. (B) The Gibbs energies of the activation for the formation of the C-B bond ($\Delta G^\ddagger$), activation barrier in potential energy (E_a and E_a') are given relative to **10** and **11**, respectively), the reaction energy (ΔE) defined by eq. (5) in the Supplementary Materials, deformation energies (E_{Def-a} and E_{Def-b}) of frag-a and frag-b, interaction energy (E_{int}) between frag-a and frag-b in the TS of the reductive elimination of B-C bond. (C) Separation of β -TS_{14/15} into frag-a and frag-b and their valence orbital energies (eV) in the absence/presence of AlMe₃

4.3 Conclusion

In summary, the author have demonstrated that the use of a Lewis-acidic Al-based co-catalyst facilitates the otherwise sluggish reductive elimination step in Ir-catalyzed C–H borylation reactions, which allows the site- and stereoselective functionalization of saturated cyclic amines. The author anticipate that this cooperative strategy will find widespread applications in the realm of C–H functionalization, which may ultimately unlock unprecedented retrosynthetic strategies.

4.4 Experimental section

4.4.1 Chemicals related to chapters 4 and 5 in the Thesis

All substrates for borylation reaction: unless otherwise noted, purified by silica-gel column chromatography, followed by distillation over CaH_2 under vacuum and stored in a nitrogen-filled glovebox at room temperature (if liquid) or purified by silica-gel column chromatography and stored in a nitrogen-filled glovebox at room temperature (if solid);

All BINOL derivatives for asymmetric borylation: prepared according to modified literature procedures, purified by silica-gel column chromatography, and stored in a nitrogen-filled glovebox at room temperature;

Bis(pinacolato)diboron ($\text{B}_2(\text{pin})_2$): purchased from Oakwood Chemical, ChemICHIBA, or BLD Pharmatech, recrystallized from hot hexane, and stored in a nitrogen-filled glovebox at room temperature;

$[\text{Ir}(\text{cod})\text{OMe}]_2$: prepared from $\text{IrCl}_3 \cdot n\text{H}_2\text{O}$ according to modified literature procedure and stored in a nitrogen-filled glovebox at -35°C ;

3,4,7,8-Tetramethyl-1,10-phenanthroline (TMPhen): purchased from Sigma-Aldrich or TCI, stored in a nitrogen-filled glovebox, and used as received;

Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD): prepared from 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) and AlMe_3 and stored in a nitrogen-filled glovebox at -35°C ;

AlMe_3 (1.4 M in hexanes): purchased from TCI, stored in a nitrogen-filled glovebox at -35°C , and used as received;

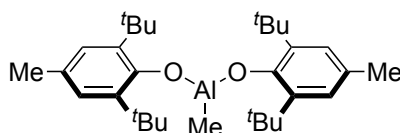
AlEt_3 (1.0 M in hexanes): purchased from TCI, stored in a nitrogen-filled glovebox at -35°C , and used as received;

Al^iBu_3 (0.55 M in hexanes): purchased from TCI, stored in a nitrogen-filled glovebox at -35°C , and used as received;

2,2,4-Trimethylpentane (isooctane): purchased from nacalai tesque, distilled over CaH_2 under argon atmosphere, and stored in a nitrogen-filled glovebox at room temperature with $\text{MS4}\text{\AA}$.

4.4.2 Catalyst Synthesis

Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)³⁶



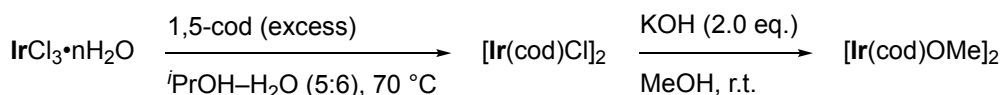
In a nitrogen-filled glovebox, to a flame-dried round-bottomed flask containing BHT (45.5 mmol, 10.0 g) in anhydrous hexane (60 mL) was slowly added AlMe₃ (1.4 M in hexanes, 24.0 mmol, 17.1 mL) at room temperature (over 10 min) with vigorous stirring (**Caution:** gas bubbles vigorously). After stirring for 60 min at this temperature, all volatiles were removed under reduced pressure. Purification by single trituration with hexane afforded the pure title compound in 54% yield (12.9 mmol, 6.21 g) as a colorless solid.

(**Note:** If this compound is not still pure after single trituration, several washes with hexane give the pure product (confirmed by ¹H NMR analysis). The contamination of BHT dramatically decreases the yield of the borylation products (data not shown)).

¹H NMR (400 MHz, benzene-*d*₆) δ 7.18 (s, 4H), 2.30 (s, 6H), 1.59 (s, 36H), -0.26 (s, 3H);

¹³C NMR (101 MHz, benzene-*d*₆) δ 152.8, 138.6, 128.2, 126.3, 35.1, 32.0, 21.5, -9.0.

(1,5-Cyclooctadiene)(μ-methoxy)iridium(I) dimer [Ir(cod)OMe]₂³⁷



[step 1: preparation of [Ir(cod)Cl]₂]

To a 250 mL Schlenk flask containing IrCl₃·*n*H₂O (55 wt%Ir, 14.3 mmol based on iridium, 5.00 g) were sequentially added 1,5-cyclooctadiene (81.5 mmol, 10.0 mL), *i*PrOH (25 mL), and H₂O (30 mL) under argon atmosphere at room temperature (**Note:** 1,5-cyclooctadiene was purchased from Sigma-Aldrich (“purified by redistillation” grade) and solvents were thoroughly deoxygenated by argon bubbling for 30 min just before use). After stirring for 21 hours at 70 °C, the resulting suspension was filtered through filter paper and the resulting red solid was washed with cold MeOH (150 mL, thoroughly deoxygenated by argon bubbling for 30 min just before use). Drying under high vacuum at room temperature for 19 h under dark afforded the title compound in 71% yield (5.08 mmol, 3.41 g) as a bright red solid.

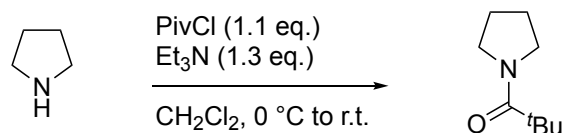
[step 2: preparation of $[\text{Ir}(\text{cod})\text{OMe}]_2$]

To a 250 mL Schlenk flask containing MeOH (200 mL) was thoroughly deoxygenated by argon bubbling, followed by the addition of $[\text{Ir}(\text{cod})\text{Cl}]_2$ (9.47 mmol, 6.36 g) and KOH (18.9 mmol, 1.06 g) at room temperature. After stirring for 16 hours at this temperature, deoxygenated H_2O (50 mL) was added and filtered through filter paper. The resulting yellow solid was washed with deoxygenated H_2O (150 mL) and thoroughly dried under reduced pressure at 80 °C for 12 hours in a desiccator, followed by backfilling with argon gas. The resulting yellow solid was taken into a nitrogen-filled glovebox. The solid was recrystallized from hot CH_2Cl_2 (then stored at -35 °C) to afford the analytically pure title compound in 82% yield (7.77 mmol, 5.15 g) as a bright yellow solid, which was stored in a nitrogen-filled glovebox at -35 °C.

^1H NMR (400 MHz, CDCl_3) δ 3.60-3.48 (m, 8H), 3.23 (s, 6H), 2.28-2.15 (m, 8H), 1.42-1.28 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 56.3, 54.2, 31.4.

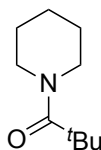
4.4.3 Substrate Synthesis

General procedure: Preparation of *N*-pivaloyl cyclic amine



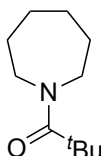
A 200 mL round-bottomed flask was charged with a solution of pyrrolidine (20.0 mmol, 1.42 g) and Et₃N (26.0 mmol, 2.62 mL) in CH_2Cl_2 (100 mL) and cooled to 0 °C. Pivaloyl chloride (22.0 mmol, 2.71 mL) was added dropwise over 5 min and the resulting mixture was warmed to room temperature. After 12 hours, the reaction mixture was quenched with 3 M HCl aq. (10 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (10 mL $\times$ 2). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 50/50) to provide 2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one (**1a**) in 89% yield (17.8 mmol, 2.76 g) as a colorless oil. Spectral data were in full agreement with the reported literature values.³⁸

2,2-Dimethyl-1-(piperidin-1-yl)propan-1-one (1b)



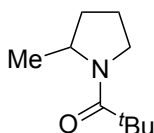
Prepared following the general procedure using piperidine. Purification by MPLC (eluent: hexane/AcOEt = 100/0 to 60/40) afforded the title compound in 81% yield (8.09 mmol, 1.37 g) as a colorless oil. Spectral data were in full agreement with the reported literature values.³⁹

1-(Azepan-1-yl)-2,2-dimethylpropan-1-one (1c)



Prepared following the general procedure using azepane. Purification by MPLC (eluent: hexane/AcOEt = 100/0 to 60/40) afforded the title compound in 74% yield (14.8 mmol, 2.71 g) as a colorless oil. Spectral data were in full agreement with the reported literature values.⁴⁰

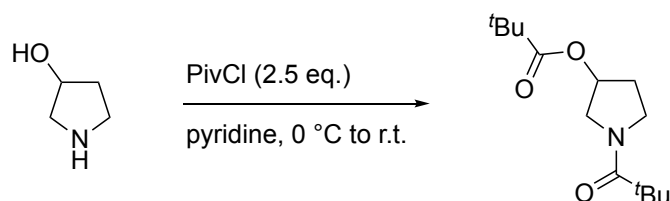
(±)-2,2-Dimethyl-1-(2-methylpyrrolidin-1-yl)propan-1-one (1d)



Prepared following the general procedure using 2-methylpyrrolidine (5.00 mmol, 426 mg). Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 60/40) afforded the title compound in 85% yield (4.25 mmol, 719 mg) as a colorless oil.

R_f: 0.55 (eluent: hexane/AcOEt = 4/1, KMnO₄); **¹H NMR** (400 MHz, CDCl₃): δ 4.25 (br, 1H), 3.67-3.61 (m, 1H), 3.56-3.50 (m, 1H), 2.01-1.87 (m, 2H), 1.86-1.76 (m, 1H), 1.47 (br, 1H), 1.24 (s, 9H), 1.16 (d, *J* = 6.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ 176.1, 54.6, 47.5, 39.2, 31.2, 27.7, 25.3, 19.8; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₉NNaO: *m/z* 192.1359 ([M+Na]⁺), found: *m/z* 192.1356 ([M+Na]⁺).

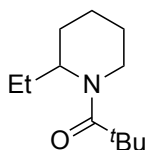
(±)-1-Pivaloylpyrrolidin-3-yl pivalate (1e)



A 100 mL round-bottomed flask was charged with a solution of pyrrolidin-3-ol (5.00 mmol, 436 mg) in pyridine (10 mL) and cooled to 0 °C. Pivaloyl chloride (12.5 mmol, 1.54 mL) was added dropwise over 5 min and the resulting mixture was warmed to room temperature. After 15 hours, the reaction mixture was quenched with 3 M HCl aq. (50 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 60/40) to provide the title compound in 81% yield (4.03 mmol, 1.03 g) as a colorless solid.

R_f: 0.25 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point**: 61-62 °C; **¹H NMR** (400 MHz, CDCl₃): δ 5.26 (br, 1H), 3.71-3.67 (m, 3H), 3.66-3.59 (m, 1H), 2.04 (br, 2H), 1.25 (s, 9H), 1.17 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 178.0, 176.7, 53.3, 45.8, 38.9, 38.7, 27.4, 27.0 (*Two ¹³C signals were not detected due to peak broadening, which could be attributed to amide rotation*); **HRMS (ESI)** exact mass calcd. for C₁₄H₂₅NNaO₃: *m/z* 278.1727 ([M+Na]⁺), found: *m/z* 278.1727 ([M+Na]⁺).

(±)-1-(2-Ethylpiperidin-1-yl)-2,2-dimethylpropan-1-one (1f)

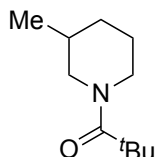


Prepared following the general procedure, using 2-ethylpiperidine (5.00 mmol, 566 mg). Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 60/40) afforded the title compound in 91% yield (4.55 mmol, 897 mg) as a colorless oil.

R_f: 0.75 (eluent: hexane/AcOEt = 4/1, KMnO₄); **¹H NMR** (400 MHz, benzene-*d*₆): δ 4.67 (br, 1H), 3.83 (br, 1H), 2.55 (t, *J* = 12.6 Hz, 1H), 1.52-1.10 (m, 8H), 1.21 (s, 9H), 0.75 (t, *J* = 7.6 Hz, 3H); **¹³C NMR** (101 MHz, C₆D₆): δ 175.4, 50.9, 40.8, 38.9, 28.8, 28.0, 26.4,

22.6, 19.4, 10.8; **HRMS (ESI)** exact mass calcd. for $C_{12}H_{23}NNaO$: m/z 220.1672 ($[M+Na]^+$), found: m/z 220.1671 ($[M+Na]^+$).

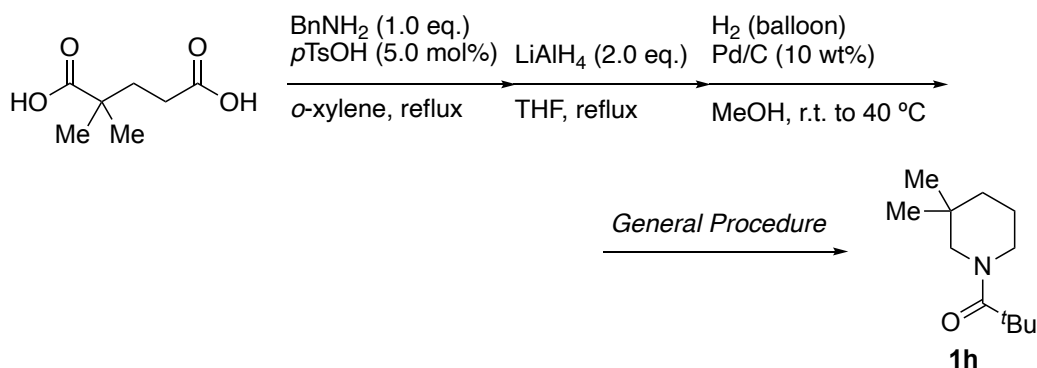
(±)-2,2-Dimethyl-1-(3-methylpiperidin-1-yl)propan-1-one (1g)



Prepared following the general procedure, using 3-methylpiperidine (5.00 mmol, 496 mg). Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 60/40) afforded the title compound in 88% yield (4.40 mmol, 807 mg) as a colorless oil.

R_f: 0.75 (eluent: hexane/AcOEt = 4/1, $KMnO_4$); **¹H NMR** (400 MHz, $CDCl_3$): δ 4.30 (d, J = 12.5 Hz, 1H), 4.23 (d, J = 12.5 Hz, 1H), 2.71 (t, J = 11.9 Hz, 1H), 2.39 (t, J = 11.9 Hz, 1H), 1.83-1.79 (m, 1H), 1.69-1.62 (m, 1H), 1.60-1.38 (m, 2H), 1.25 (s, 9H), 1.10 (dq, J = 12.5, 6.4 Hz, 1H), 0.88 (d, J = 6.4 Hz, 3H); **¹³C NMR** (101 MHz, $CDCl_3$): δ 176.1, 52.7, 45.9, 38.9, 33.5, 31.7, 28.6, 25.8, 19.2; **HRMS (ESI)** exact mass calcd. for $C_{11}H_{21}NNaO$: m/z 206.1515 ($[M+Na]^+$), found: m/z 206.1513 ($[M+Na]^+$).

1-(3-Azabicyclo[3.1.0]hexan-3-yl)-2,2-dimethylpropan-1-one (1h)

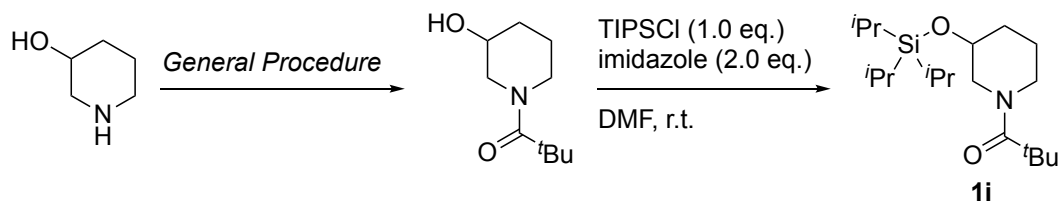


To a 300 mL round-bottomed flask containing a solution of 2,2-dimethylglutaric acid (100 mmol, 16.0 g) in *o*-xylene (96 mL) was added *p*-TsOH·H₂O (5.00 mmol, 0.950 g.) at room temperature. The resulting mixture was heated to reflux. Then benzylamine (100 mmol, 10.9 mL) was slowly added under reflux. After stirring for 12 hours, the mixture was cooled to room temperature. After the addition of saturated NaHCO₃ aq., the two layers were separated, and the organic phase was acidified by the addition of 1 M HCl aq. After

the collection of the organic phase, *o*-xylene was evaporated under vacuum (conditions: 3 torr at 75 °C) and directly used for the next step without further purification. To a 500 mL round-bottomed flask containing a solution of the resulting crude mixture in THF (150 mL), was slowly added a suspension of LiAlH₄ (200 mL, 7.59 g) in THF (200 mL) under gentle reflux. The resulting mixture was stirred for 16 hours. After the very slow addition of 1 M NaOH aq. under reflux, the mixture was heated for 1 hour. After filtration, followed by the addition of AcOEt and brine, the two layers were separated. The aqueous was extracted with AcOEt. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was used for the next step without purification. To a 300 mL round-bottomed flask containing a solution of the crude *N*-benzyl amine in MeOH (140 mL) was added 10% Pd/C (2.00 g) under argon atmosphere at room temperature. The flask was carefully evacuated and backfilled with hydrogen gas three times. After 22 hours at 40 °C, the flask was evacuated and backfilled with argon three times. The mixture was purified through Celite pad, and the pad cake was washed with AcOEt. After the concentration under reduced pressure, the crude mixture was roughly purified by vacuum distillation and used for the next step without further purification. To a 100 mL round-bottomed flask containing the roughly purified amine in CH₂Cl₂ (30 mL) were added triethylamine (44.2 mmol, 6.16 mL) and pivaloyl chloride (26.5 mmol, 3.23 mL) at room temperature. After 12 hours at this temperature, the reaction mixture was quenched with 1 M HCl aq. and the two layers were separated. The aqueous phase was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (eluent: hexane/AcOEt = 6/1) followed by vacuum distillation to afford the title compound in 7% yield (7.45 mmol, 1.47 g over 4 steps) as a colorless oil.

R_f: 0.48 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde) **¹H NMR** (400 MHz, CDCl₃) δ 3.58-3.48 (m, 2H), 3.26 (s, 2H), 1.64-1.55 (m, 2H), 1.42-1.36 (m, 2H), 1.28 (s, 9H), 0.91 (s, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.5, 55.3, 46.5, 38.8, 38.1, 31.3, 28.5, 26.0, 22.3; **HRMS (ESI)** exact mass calcd. for C₁₂H₂₃ONNa: *m/z* 220.1672 ([M+Na]⁺), found: *m/z* 220.1674 ([M+Na]⁺).

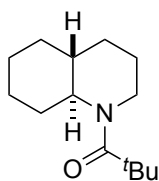
(±)-2,2-Dimethyl-1-(3-((triisopropylsilyl)oxy)piperidin-1-yl)propan-1-one (1i)



Following the general procedure, 3-hydroxypiperidine (5.00 mmol, 506 mg) was reacted with pivaloyl chloride (5.5 mmol, 0.68 mL). The crude residue was used in the next step without further purification. To a 100 mL round-bottomed flask containing a solution of the crude alcohol in DMF (10 mL) was added sequentially imidazole (10.0 mmol, 681 mg) and triisopropylsilyl chloride (5.00 mmol, 1.06 mL) at room temperature. The resulting mixture was stirred for 12 hours. After the addition of H_2O (10 mL), the aqueous phase was extracted with Et_2O (10 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: hexane/AcOEt = 90/10 to 80/20) to provide the title compound in 59% yield (2.96 mmol, 1.01 g over 2 steps) as a colorless oil.

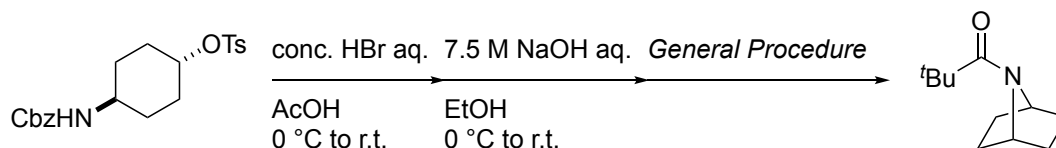
R_f: 0.55 (eluent: hexane/AcOEt = 9/1, KMnO_4); **¹H NMR** (400 MHz, CDCl_3): δ 4.24 (d, J = 12.8 Hz, 1H), 4.09 (d, J = 12.8 Hz, 1H), 3.71 (tt, J = 8.9, 4.1 Hz, 1H), 2.89 (t, J = 11.4 Hz, 1H), 2.82 (dd, J = 12.2, 9.2 Hz, 1H), 2.04–2.00 (m, 1H), 1.78–1.74 (m, 1H), 1.54–1.36 (m, 2H), 1.28 (s, 9H), 1.06 (s, 21H); **¹³C NMR** (101 MHz, CDCl_3): δ 176.5, 67.5, 52.4, 45.7, 38.9, 34.7, 28.6, 23.8, 18.2, 12.4; **HRMS (ESI)** exact mass calcd. for $\text{C}_{19}\text{H}_{39}\text{NNaO}_2\text{Si}$: m/z 362.2642 ($[\text{M}+\text{Na}]^+$), found: m/z 362.2644 ($[\text{M}+\text{Na}]^+$).

(±)-trans-2,2-Dimethyl-1-(octahydroquinolin-1(2H)-yl)propan-1-one (1j)



Prepared following the general procedure using *trans*-decahydroquinoline. Purification by MPLC (eluent: hexane/AcOEt = 100/0 to 80/20) afforded the title compound in 77% yield (7.70 mmol, 1.72 g) as a colorless solid. Spectral data were in full agreement with the reported literature values.⁴⁰

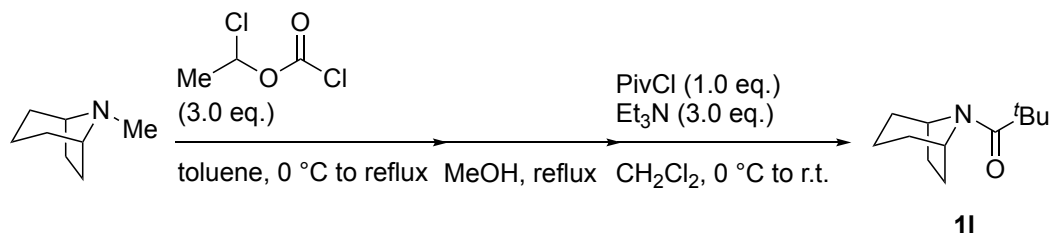
1-(7-Azabicyclo[2.2.1]heptan-7-yl)-2,2-dimethylpropan-1-one (1k)



To a 200 mL round-bottomed flask containing a solution of *trans*-4-(benzyloxycarbonylamino)cyclohexyl 4-methylbenzenesulfonate⁴¹ (16.8 mmol, 6.78 g) in AcOH (40 mL) was added 47% HBr aq. (5.0 mL) at 0 °C and the resulting mixture was warmed to room temperature. After 2 hours, the solvent was removed under reduced pressure. The resulting residue was washed with Et₂O to give a white powder, which was used in the next step without further purification. To a 200 mL round-bottomed flask containing a solution of the crude amine hydrobromide salt in EtOH (40 mL) and H₂O (5.0 mL) was added 7.5 M NaOH aq. (20 mL) at 0 °C and the resulting mixture was warmed to room temperature. After 15 hours, the solution was cooled to 0 °C and acidified by the addition of conc. HCl aq. (15 mL) and all volatiles were removed under reduced pressure. The crude residue was dissolved in 5 M NaOH aq. (50 mL) and extracted with Et₂O (20 mL × 5). The combined organic layers were dried over Na₂SO₄ and acidified by the addition of HCl (10 mL, 1.0 M in Et₂O) and concentrated under reduced pressure to afford a beige solid, which was used in the next step without further purification. To a 200 mL round-bottomed flask containing a suspension of the crude amine hydrochloride salt in CH₂Cl₂ (40 mL) was added sequentially Et₃N (50.4 mmol, 7.02 mL) and pivaloyl chloride (16.8 mmol, 2.07 mL) at 0 °C and the resulting mixture was warmed to room temperature. After 5 h, the reaction mixture was quenched with 3 M HCl aq. (10 mL) and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (10 mL × 2). The combined organic layers were washed with brine (5.0 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by MPLC (eluent: hexane/AcOEt = 95/5 to 70/30) to provide the title compound in 41% yield (6.90 mmol, 1.25 g over 3 steps) as a colorless solid.

R_f: 0.50 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point**: 73-75 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.60 (br, 2H), 1.77 (br d, *J* = 6.2 Hz, 4H), 1.45 (br d, *J* = 6.2 Hz, 4H), 1.22 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 174.7, 55.5, 39.4, 29.7, 28.1; **HRMS (ESI)** exact mass calcd. for C₁₁H₁₉NNaO: *m/z* 204.1359 ([M+Na]⁺), found: *m/z* 204.1356 ([M+Na]⁺).

1-(8-Azabicyclo[3.2.1]octan-8-yl)-2,2-dimethylpropan-1-one (11)



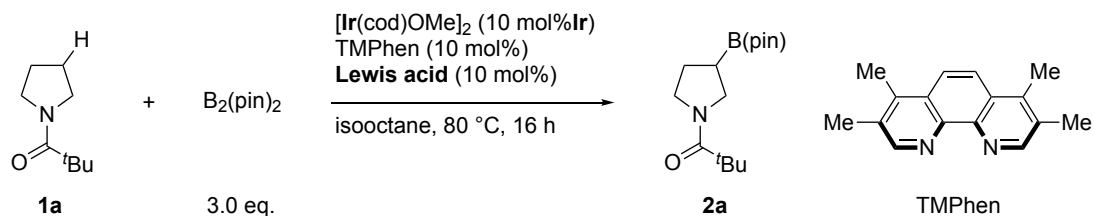
To a 100 mL round-bottomed flask containing a solution of tropane (8.00 mmol, 1.00 g) in toluene (20 mL) was added 1-chloroethyl chloroformate (24.0 mmol, 2.62 mL) at 0 °C and the resulting mixture was heated to reflux. After 12 hours, the solvent was removed under reduced pressure. The resulting residue was dissolved in MeOH (30 mL) and the resulting solution was refluxed. After 15 hours, the solvent was removed under reduced pressure. The resulting residue was dissolved in CH₂Cl₂ (20 mL) and cooled to 0 °C. To the stirred mixture was added sequentially Et₃N (24 mmol, 5.7 mL) and pivaloyl chloride (8.0 mmol, 0.97 mL) and the resulting mixture was warmed to room temperature. After 12 hours, the reaction mixture was quenched with 3 M HCl aq. (5.0 mL) and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (10 mL × 2). The combined organic layers were washed with brine (5.0 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by MPLC (eluent: hexane/AcOEt = 95/5 to 70/30) to provide the title compound in 86% yield (6.86 mmol, 1.34 g, over 3 steps) as a colorless solid.

R_f: 0.50 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting Point**: 94-95 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.60 (br, 2H), 1.88 (br, 2H), 1.78-1.70 (m, 5H), 1.58 (br, 1H), 1.50-1.47 (m, 2H), 1.24 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 173.7, 54.2, 39.1, 31.7, 28.3, 27.6, 17.1; **HRMS (ESI)** exact mass calcd. for C₁₂H₂₁NNaO: *m/z* 218.1515 ([M+Na]⁺), found: *m/z* 218.1516 ([M+Na]⁺).

4.4.4 Racemic β -C(sp³)-H Borylation of Cyclic Amines

4.4.4.1 Optimization Studies

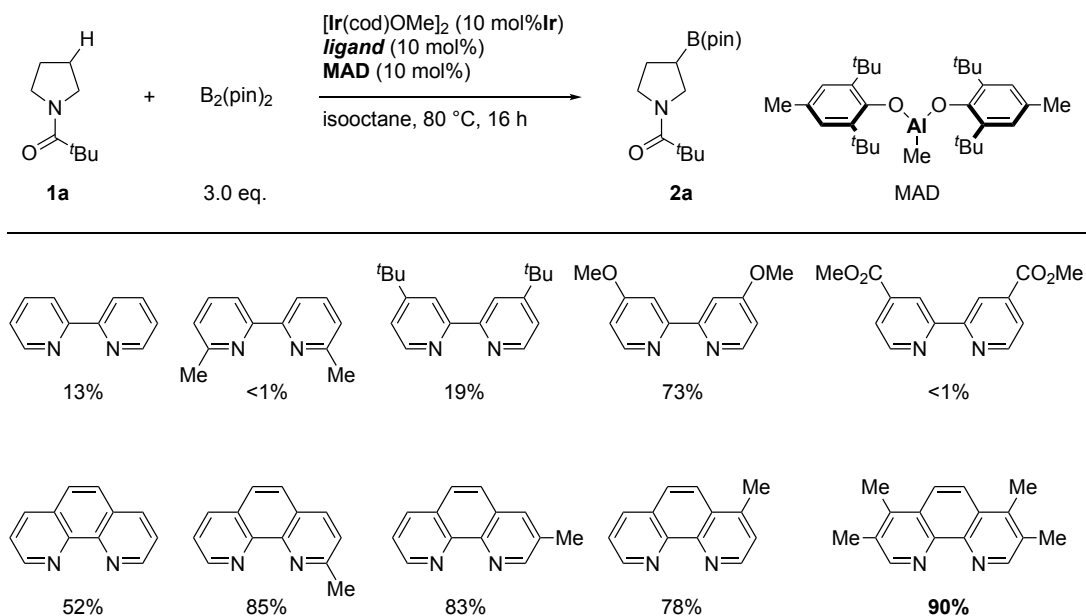
Table 4-1 Survey of Lewis acids for β -C(sp³)-H borylation of *N*-pivaloyl pyrrolidine^a



Entry	Lewis acid	Yield (%) ^b
1	none	3
2	MAD	90
3	AlMe ₃	32
4	AlPh ₃	<1
5	Me ₂ AlCl	32
6	BPh ₃	2
7	BEt ₃	3

^aReaction conditions: **1a** (0.20 mmol), B₂(pin)₂ (0.30 mmol), [Ir(cod)OMe]₂ (0.010 mmol), TMPhen (0.020 mmol), Lewis acid (0.020 mmol), isooctane (1.0 mL). ^bYields determined by GC-FID with *n*-dodecane as internal standard.

Table 4-2 Survey of *N,N*-ligands for β -C(*sp*³)-H borylation of *N*-pivaloyl pyrrolidine^{a,b}



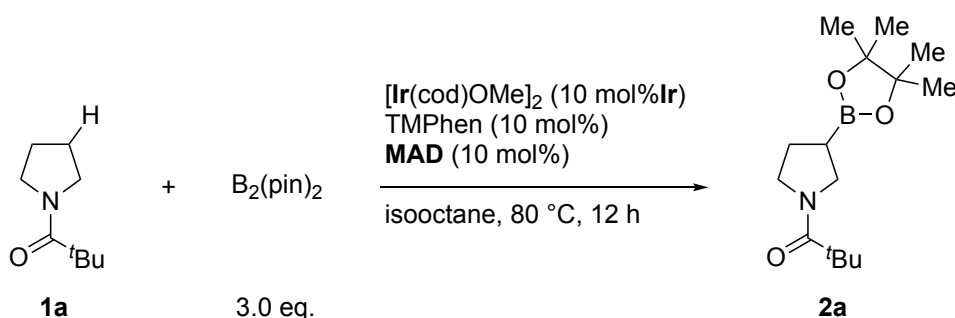
^aReaction conditions: **1a** (0.20 mmol), $B_2(pin)_2$ (0.30 mmol), $[Ir(cod)OMe]_2$ (0.010 mmol), ligand (0.020 mmol), MAD (0.020 mmol), isooctane (1.0 mL). ^bYields determined by GC-FID with *n*-dodecane as internal standard.

4.4.4.2 Characterization data for borylation products

Notes: Borylation products are unstable on silica gel. Column chromatography should be done very quickly (<10 min) to prevent the decomposition of the product.

If pinacol still remains after column chromatography, it can be removed under high vacuum in a desiccator at 80 °C.

Typical Procedure: β -C–H Borylation of Cyclic Amines

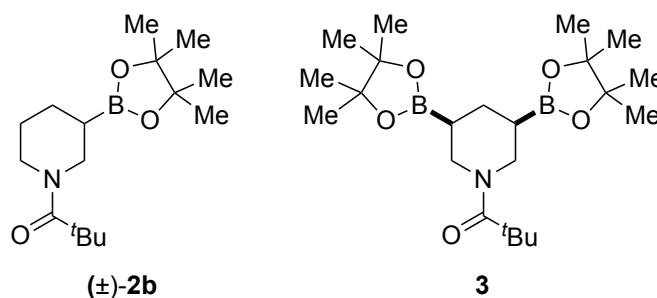


(±)-2,2-Dimethyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl)propan-1-one (2a): In a N_2 -filled glove box, a 15 mL vial equipped with a stir bar was charged with $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), $B_2(\text{pin})_2$ (3.00 mmol, 762 mg), TMPhen (0.100 mmol, 23.6 mg) and isooctane (2.5 mL). The vial was sealed with a Teflon-lined cap and moved to a preheated metal heating block (70 °C). The reaction mixture was then stirred at 70 °C for 30 min, after which the color of the mixture turned deep green. Upon cooling to room temperature, **1a** (1.00 mmol, 155 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (2.5 mL) were added sequentially. The reaction vessel was then sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 80 °C. After 12 hours, the reaction mixture was cooled to room temperature and volatiles were removed under reduced pressure. The crude residue was purified by column chromatography (eluent: hexane/AcOEt = 95/5 to 60/40) to afford the title compound in 87% yield (0.868 mmol, 244 mg) as a tan solid. Recrystallization from a saturated hexane solution at room temperature afforded single crystals suitable for X-ray crystallographic analysis.

R_f: 0.70 (eluent: hexane/AcOEt = 1/1, KMnO_4); **Melting point:** 78–80 °C; **^1H NMR** (400 MHz, CDCl_3): δ 3.73 (t, J = 9.5 Hz, 1H), 3.64 (br, 1H), 3.48–3.31 (m, 2H), 1.98 (br, 1H), 1.83–1.73 (m, 1H), 1.56 (br, 1H), 1.24 (s, 9H), 1.23 (s, 12H); **^{13}C NMR** (101 MHz, CDCl_3): δ 176.3, 83.6, 49.7, 48.6, 38.9, 29.7, 27.5, 25.5, 24.7; **HRMS (ESI)** exact mass

calcd. for $C_{15}H_{29}BNO_3$: m/z 282.2235 ($[M+H]^+$), found: m/z 282.2229 ($[M+H]^+$).

(±)-2,2-Dimethyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-yl)propan-1-one (2b) and **cis-1-(3,5-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-yl)-2,2-dimethylpropan-1-one (3)**



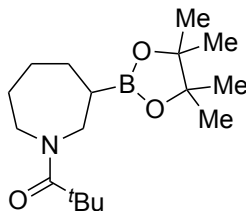
Following the typical procedure, the reaction was conducted with **1b** (1.00 mmol, 169 mg), $[Ir(cod)OMe]_2$ (0.0500 mmol, 33.1 mg), $B_2(pin)_2$ (3.00 mmol, 762 mg), TMPhen (0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 100 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30) afforded a beige solid (251 mg) consisting of 69:31 inseparable mixture of **2b** (52%) and **3** (23%). For characterization purposes, borylation products were separated by recycling gel permeation chromatography (eluent: $CHCl_3$ only) to provide analytically pure samples **2b** (115 mg, 39%) as a colorless solid and **3** (63.2 mg, 15%) as an off-white solid.

(±)-2,2-Dimethyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-yl)propan-1-one (2b)

Recrystallization from a saturated hexane solution at room temperature afforded single crystals suitable for X-ray crystallographic analysis.

R_f: 0.40 (eluent: hexane/AcOEt = 4/1, $KMnO_4$); **Melting point**: 86-89 °C; **¹H NMR** (400 MHz, $CDCl_3$): δ 4.26-4.20 (m, 2H), 2.92 (t, J = 12.0 Hz, 1H), 2.83 (t, J = 12.0 Hz, 1H), 1.87-1.81 (m, 1H), 1.67-1.62 (m, 1H), 1.49-1.40 (m, 2H), 1.25 (s, 9H), 1.21 (s, 12H), 1.16-1.09 (m, 1H); **¹³C NMR** (101 MHz, $CDCl_3$): δ 176.3, 83.6, 47.6, 46.5, 39.1, 28.9, 26.9, 26.7, 25.2, 25.1; **HRMS (ESI)** exact mass calcd. for $C_{16}H_{31}BNO_3$: m/z 296.2392 ($[M+H]^+$), found: m/z 296.2384 ($[M+H]^+$).

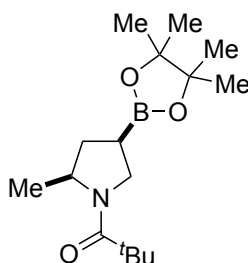
(±)-2,2-Dimethyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azepan-1-yl)propan-1-one (2c)



Following the typical procedure, the reaction was conducted with **1c** (1.00 mmol, 183 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen (0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 120 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30) followed by recycling gel permeation chromatography (eluent: CHCl₃ only) afforded the title compound in 23% yield (0.230 mmol, 71.1 mg) as a pale yellow solid. Recrystallization from a saturated hexane solution at room temperature afforded single crystals suitable for X-ray crystallographic analysis.

R_f: 0.25 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point**: 95-96 °C; **¹H NMR** (400 MHz, C₆D₆): δ 3.93 (dd, *J* = 14.1, 4.0 Hz, 1H), 3.47 (dd, *J* = 14.1, 9.1 Hz, 1H), 3.38-3.32 (m, 2H), 1.91-1.85 (m, 1H), 1.68-1.40 (m, 5H), 1.32-1.21 (m, 1H), 1.27 (s, 9H), 1.07 (s, 6H), 1.06 (s, 6H); **¹³C NMR** (101 MHz, C₆D₆): δ 175.8, 83.1, 49.9, 48.7, 39.1, 28.9, 28.7, 24.9(2) (Two ¹³C signals were not detected due to peak broadening); **HRMS (ESI)** exact mass calcd. for C₁₇H₃₂BNNaO₃: *m/z* 332.2367 ([M+Na]⁺), found: *m/z* 332.2368 ([M+Na]⁺).

(±)-cis-2,2-Dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl)propan-1-one (2d)



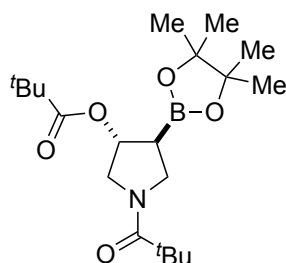
Following the typical procedure, the reaction was conducted with **1d** (1.00 mmol, 169 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen

(0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 100 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30) afforded the title compound in 53% yield (0.532 mmol, 157 mg, 95:5 dr) as a beige solid.

Note: The major diastereomer was assigned as *cis* by X-ray crystallographic analysis. A small sample was further purified by recycling gel permeation chromatography (eluent: CHCl₃ only) to provide an analytically pure *cis*-**2d** as a white solid, which was recrystallized from a saturated hexane solution at room temperature to afford single crystals suitable for X-ray crystallographic analysis.

R_f: 0.20 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point:** 114-115 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.01 (hept, *J* = 6.7 Hz, 1H), 3.92 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.32 (t, *J* = 10.5 Hz, 1H), 2.21 (dt, *J* = 13.1, 6.7 Hz, 1H), 1.50-1.34 (m, 2H), 1.25 (s, 12H), 1.24 (s, 9H), 1.21 (d, *J* = 6.7 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ 176.3, 83.7, 55.4, 49.8, 39.1, 35.0, 27.8, 24.9(2), 20.4; **HRMS (ESI)** exact mass calcd. for C₁₆H₃₁BNO₃: *m/z* 296.2392 ([M+H]⁺), found: *m/z* 296.2385 ([M+H]⁺).

(±)-*trans*-1-Pivaloyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-3-yl pivalate (2e)



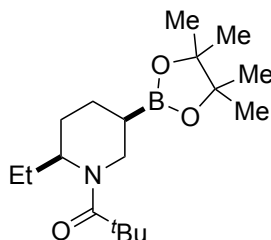
Following the typical procedure, the reaction was conducted with **1e** (1.00 mmol, 255 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen (0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 120 °C for 12 hours. The crude residue was purified by column chromatography (eluent: hexane/AcOEt = 95/5 to 60/40) followed by recycling gel permeation chromatography (eluent: CHCl₃ only) to afford the title compound in 32% yield (0.320 mmol, 122 mg, >95:5 dr) as an off-white solid.

Note: The relative stereochemistry was assigned as *trans* by X-ray crystallographic analysis. Recrystallization from a saturated heptane solution at room temperature afforded

single crystals.

R_f: 0.35 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point**: 91-92 °C; **¹H NMR** (400 MHz, benzene-*d*₆): δ 5.54 (br, 1H), 3.94 (br 2H), 3.73 (br 2H), 1.75 (br, 1H), 1.22 (s, 9H), 1.10 (s, 9H), 0.94 (s, 6H), 0.94 (s, 6H); **¹³C NMR** (101 MHz, benzene-*d*₆): δ 177.4, 175.5, 83.9, 53.8, 48.1, 38.9, 38.7, 27.7, 27.1, 24.7, 24.6 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **HRMS (ESI)** exact mass calcd. for C₂₀H₃₆BNNaO₅: *m/z* 404.2579 ([M+Na]⁺), found: *m/z* 404.2578 ([M+Na]⁺).

(±)-cis-1-(2-Ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-yl)-2,2-dimethylpropan-1-one (2f)

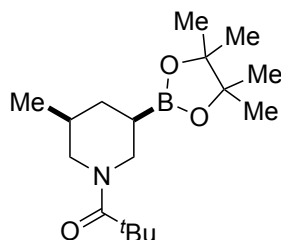


Following the typical procedure, the reaction was conducted with **1f** (1.00 mmol, 197 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen (0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 100 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30) afforded the title compound in 70% yield (0.699 mmol, 226 mg, >95:5 dr) as an off-white solid.

Note: The relative stereochemistry was assigned as *cis* by X-ray crystallographic analysis. Recrystallization from a saturated heptane solution at room temperature afforded single crystals.

R_f: 0.20 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point**: 90-91 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.54 (br, 1H), 3.96 (br, 1H), 2.83 (br, 1H), 1.54-1.40 (m, 6H), 1.16 (s, 9H), 1.12 (s, 12H), 1.00-0.92 (m, 1H), 0.72 (t, *J* = 7.3 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ 176.2, 83.1, 50.1, 42.3, 38.8, 28.5, 24.7, 24.6, 22.7, 22.3, 20.8, 10.5; **HRMS (ESI)** exact mass calcd. for C₁₈H₃₄BNNaO₃: *m/z* 346.2524 ([M+Na]⁺), found: *m/z* 346.2524 ([M+Na]⁺).

(±)-*cis*-2,2-Dimethyl-1-(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-yl)propan-1-one (2g)

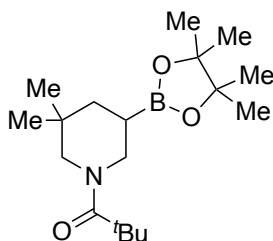


Following the typical procedure, the reaction was conducted with **1g** (1.00 mmol, 183 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen (0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 100 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30) afforded the title compound in 66% yield (0.660 mmol, 204 mg, 95:5 dr) as a beige solid.

Note: The major diastereomer was assigned as *cis* by X-ray crystallographic analysis. Recrystallization from a saturated heptane solution at room temperature afforded single crystals.

R_f: 0.35 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point:** 116-117 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.43 (d, *J* = 13.7 Hz, 1H), 4.36 (d, *J* = 13.7 Hz, 1H), 2.61 (t, *J* = 12.6 Hz, 1H), 2.23 (t, *J* = 12.6 Hz, 1H), 1.90 (d, *J* = 12.6 Hz, 1H), 1.70-1.66 (m, 1H), 1.58-1.45 (m, 1H), 1.26 (s, 9H), 1.22 (s, 12H), 1.17-1.01 (m, 1H), 0.87 (d, *J* = 6.9 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ 175.9, 83.4, 52.7, 47.0, 38.9, 35.2, 32.4, 28.6, 24.9, 24.8, 19.4; **HRMS (ESI)** exact mass calcd. for C₁₇H₃₃BNO₃: *m/z* 310.2548 ([M+H]⁺), found: *m/z* 310.2542 ([M+H]⁺).

(±)-1-(3,3-Dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-yl)-2,2-dimethylpropan-1-one (2h)



Following the typical procedure, the reaction was conducted with **1h** (1.00 mmol, 197 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen

(0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 100 °C for 16 hours. Purification by column chromatography (eluent: hexane/AcOEt = 100/0 to 83/17) afforded the title compound in 36% yield (0.359 mmol, 116 mg) as an off-white solid.

Note: β -selectivity was confirmed by ^1H - ^1H COSY NMR analysis (Figure 4-5).

R_f: 0.25 (eluent: hexane/AcOEt = 6/1, *p*-anisaldehyde); **Melting point:** 142 °C (decomp.); **^1H NMR** (400 MHz, CDCl_3) δ 4.32 (d, J = 14.2 Hz, 1H), 4.21 (d, J = 12.8 Hz, 1H), 2.73 (*virt* dd, J = 14.2, 12.8 Hz, 1H), 2.30 (d, J = 12.8 Hz, 1H), 1.54 (d, J = 12.8 Hz, 1H), 1.44-1.37 (m, 1H), 1.28 (s, 9H), 1.31-1.26 (m, 1H), 1.23 (s, 12H), 0.92 (s, 3H), 0.88 (s, 3H); **^{13}C NMR** (101 MHz, CDCl_3) δ 176.4, 83.4, 55.3, 47.8, 39.9, 38.9, 31.3, 29.1, 28.7, 25.1, 24.9, 24.8, 23.0; **HRMS (ESI)** exact mass calcd. for $\text{C}_{18}\text{H}_{34}\text{BNNaO}_3$: m/z 346.2524 ($[\text{M}+\text{Na}]^+$), found: m/z 346.2532 ($[\text{M}+\text{Na}]^+$).

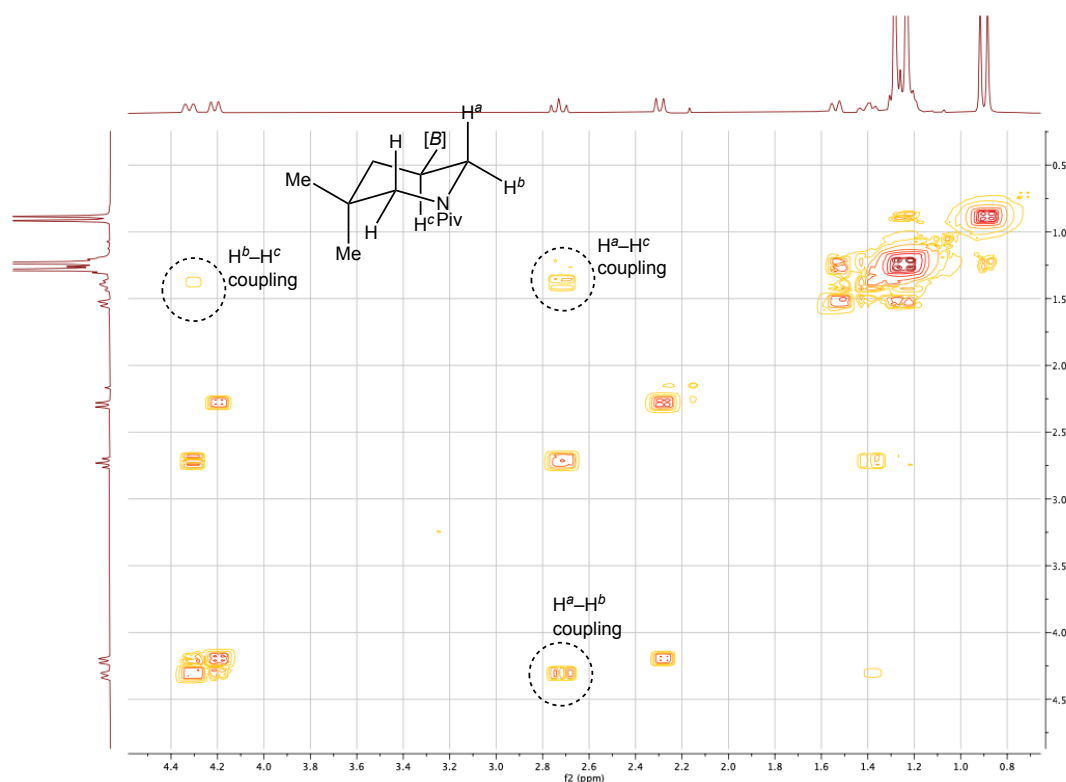
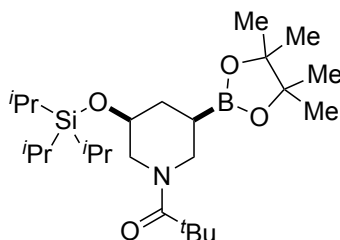


Figure 4-5 ^1H - ^1H COSY analysis of **2h**

(±)-cis-2,2-Dimethyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)oxy)piperidin-1-yl)propan-1-one (2i)

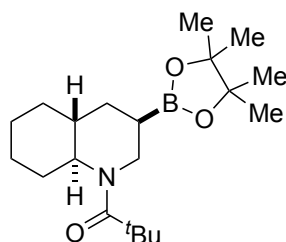


Following the typical procedure, the reaction was conducted with **1i** (1.00 mmol, 341 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen (0.100 mmol, 23.6 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 100 °C for 24 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 80/20) afforded the title compound in 38% yield (0.381 mmol, 178 mg, >95:5 dr) as an off-white solid.

Note: The relative stereochemistry was assigned as *cis* on the analogy of **2g**.

R_f: 0.40 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point:** 77-78 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.57 (d, *J* = 11.5 Hz, 1H), 4.32 (d, *J* = 13.4 Hz, 1H), 3.62 (tt, *J* = 10.0, 4.7 Hz, 1H), 2.64 (t, *J* = 13.4 Hz, 1H), 2.41 (t, *J* = 11.5 Hz, 1H), 2.12 (d, *J* = 13.0 Hz, 1H), 1.42-1.32 (m, 1H), 1.27 (s, 9H), 1.23 (s, 12H), 1.16-1.11 (m, 1H), 1.06 (s, 21H); **¹³C NMR** (101 MHz, CDCl₃): δ 176.2, 83.5, 68.2, 52.5, 46.8, 38.9, 36.2, 28.6, 24.9, 24.8, 18.2, 12.4; **HRMS (ESI)** exact mass calcd. for C₂₅H₅₀BNNaO₄Si: *m/z* 490.3494 ([M+Na]⁺), found: *m/z* 490.3498 ([M+Na]⁺).

(±)-2,2-Dimethyl-1-((3*R,4*aR**,8*aS**)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octahydroquinolin-1(2*H*)-yl)propan-1-one (2j)**

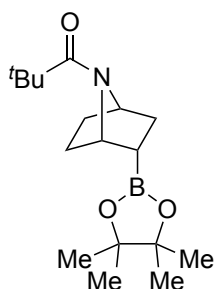


Following the typical procedure, the reaction was conducted with **1j** (1.00 mmol, 224 mg), [Ir(cod)OMe]₂ (0.0750 mmol, 49.7 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen (0.150 mmol, 35.4 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 110 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30)

afforded the title compound in 69% yield (0.690 mmol, 241 mg, >95:5 dr) as a beige solid. **Note:** The relative stereochemistry was assigned by X-ray crystallographic analysis. Recrystallization from a saturated hexane solution at room temperature afforded single crystals.

R_f: 0.45 (eluent: hexane/AcOEt = 4/1, KMnO₄); **Melting point:** 171-172 °C; **¹H NMR** (400 MHz, CDCl₃): δ 3.81 (dd, *J* = 13.7, 6.2 Hz, 1H), 3.46 (td, *J* = 11.1, 2.9 Hz, 1H), 3.22 (t, *J* = 13.7 Hz, 1H), 2.08 (dd, *J* = 12.1, 3.4 Hz, 1H), 1.70-1.67 (m, 3H), 1.59-1.36 (m, 4H), 1.32-1.26 (m, 2H), 1.24 (s, 9H), 1.23 (s, 12H), 1.08-0.99 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃): δ 176.8, 83.5, 61.5, 40.9, 38.8, 37.6, 33.3, 30.1, 28.5, 27.4, 26.5, 25.5, 24.9, 19.9; **HRMS (ESI)** exact mass calcd. for C₂₀H₃₇BNO₃: *m/z* 350.2861 ([M+H]⁺), found: *m/z* 350.2854 ([M+H]⁺).

(±)-2,2-Dimethyl-1-((1*S,2*S**,4*R**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azabicyclo[2.2.1]heptan-7-yl)propan-1-one (2k)**



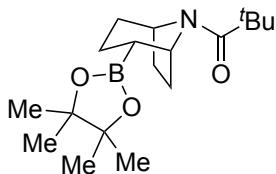
Following the typical procedure, the reaction was conducted with **1k** (1.00 mmol, 181 mg), [Ir(cod)OMe]₂ (0.0750 mmol, 49.7 mg), B₂(pin)₂ (3.00 mmol, 762 mg), TMPhen (0.150 mmol, 35.4 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 110 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30) afforded the title compound in 61% yield (0.609 mmol, 187 mg, >95:5 dr) as a pale-yellow viscous oil.

Note: The relative stereochemistry was assigned as *endo* by X-ray crystallographic analysis of the corresponding alcohol **4**.

R_f: 0.20 (eluent: hexane/AcOEt = 4/1, KMnO₄); **¹H NMR** (400 MHz, CDCl₃): δ 4.51 (br, 1H), 4.46 (br, 1H), 1.80-1.73 (m, 1H), 1.58 (br, 1H), 1.48-1.36 (m, 3H), 1.30-1.23 (m, 1H), 1.10 (s, 12H), 1.07 (s, 9H), 1.03-1.01 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃): δ 173.9, 83.3, 77.4, 57.5, 55.4, 39.0, 31.7, 29.2, 27.8, 24.6 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **HRMS (ESI)** exact mass

calcd. for $C_{17}H_{30}BNNaO_3$: m/z 330.2211 ($[M+Na]^+$), found: m/z 330.2210 ($[M+Na]^+$).

(±)-2,2-Dimethyl-1-((1*R,2*R**,5*R**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]octan-8-yl)propan-1-one (2l)**

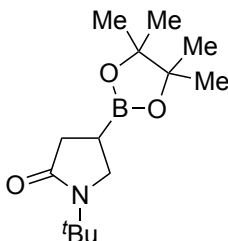


Following the typical procedure, the reaction was conducted with **1l** (1.00 mmol, 195 mg), $[Ir(cod)OMe]_2$ (0.0750 mmol, 49.7 mg), $B_2(pin)_2$ (3.00 mmol, 762 mg), TMPhen (0.150 mmol, 35.4 mg), MAD (0.100 mmol, 48.1 mg) and isooctane (5.0 mL) at 110 °C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 95/5 to 70/30) afforded the title compound in 53% yield (0.529 mmol, 170 mg, >95:5 dr) as an off-white solid.

Note: The relative stereochemistry was assigned by X-ray crystallographic analysis. Recrystallization from a saturated hexane solution at room temperature afforded single crystals.

R_f: 0.15 (eluent: hexane/AcOEt = 4/1, $KMnO_4$); **Melting point:** 114-115 °C; **¹H NMR** (400 MHz, $CDCl_3$): δ 4.59 (br, 2H), 1.82 (br, 2H), 1.73-1.63 (m, 5H), 1.49-1.37 (m, 2H), 1.21 (s, 9H), 1.17 (s, 12H); **¹³C NMR** (101 MHz, $CDCl_3$): δ 173.3, 83.2, 55.7, 54.0, 39.0, 31.9, 28.2, 27.3, 24.8, 24.7, 18.7 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **HRMS (ESI)** exact mass calcd. for $C_{18}H_{32}BNNaO_3$: m/z 344.2367 ($[M+Na]^+$), found: m/z 344.2367 ($[M+Na]^+$).

(±)-1-(tert-Butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (2m)

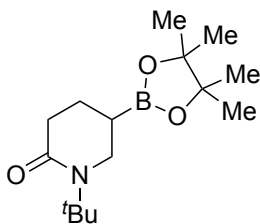


Following the general procedure, the reaction was conducted with 1-(*tert*-butyl)pyrrolidin-2-one⁴² (2.00 mmol, 282 mg), $[Ir(cod)OMe]_2$ (0.100 mmol, 66.3 mg),

B₂(pin)₂ (4.50 mmol, 1.14 g), TMPhen (0.200 mmol, 47.3 mg), MAD (0.200 mmol, 96.1 mg) and isooctane (10 mL) at 80 °C for 17 hours. Purification by column chromatography (eluent: hexane/AcOEt = 9/1 to 1/1) afforded the title compound in 76% yield (1.52 mmol, 406 mg) as a beige solid.

R_f: 0.45 (eluent: hexane/AcOEt = 1/1, KMnO₄); **Melting point**: 64-65 °C; **¹H NMR** (400 MHz, CDCl₃): δ 3.48 (t, *J* = 9.5 Hz, 1H), 3.30 (t, *J* = 9.5 Hz, 1H), 2.62 (dd, *J* = 16.4, 9.5 Hz, 1H), 2.55 (dd, *J* = 16.4, 9.5 Hz, 1H), 1.61 (quint, *J* = 9.5 Hz, 1H), 1.42 (s, 9H), 1.07 (s, 12H); **¹³C NMR** (101 MHz, CDCl₃): δ 175.6, 83.8, 53.9, 47.7, 35.4, 27.7, 24.8, 15.0; **HRMS (ESI)** exact mass calcd. for C₁₄H₂₆BNNaO₃: *m/z* 290.1898 ([M+Na]⁺), found: *m/z* 290.1896 ([M+Na]⁺).

(±)-1-(*tert*-Butyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-2-one (2n)



Following the general procedure, the reaction was conducted with 1-(*tert*-butyl)piperidin-2-one⁴² (1.00 mmol, 155 mmg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), B₂(pin)₂ (2.00 mmol, 508 mg), TMPhen (0.100 mmol, 23.6 mg), MAD (0.200 mmol, 96.1 mg) and isooctane (5.0 mL) at 80 °C for 11 hours. Purification by column chromatography (eluent: hexane/AcOEt = 100/ to 1/1) afforded the title compound in 63% yield (0.629 mmol, 177 mg) as a beige solid.

Note: Site selectivity was confirmed by ¹H-¹H COSY NMR analysis (Figure 4-6).

R_f: 0.50 (eluent: hexane/AcOEt = 2/1, KMnO₄); **Melting Point**: 77-78 °C; **¹H NMR** (400 MHz, CDCl₃): δ 3.41 (dd, *J* = 12.3, 4.9 Hz, 1H), 3.28 (dd, *J* = 12.3, 9.7 Hz, 1H), 2.42 (dd, *J* = 17.2, 5.8 Hz, 1H), 2.35-2.26 (m, 1H), 1.86-1.78 (m, 1H), 1.69-1.62 (m, 1H), 1.43 (s, 9H), 1.36-1.29 (m, 1H), 1.24 (s, 12H); **¹³C NMR** (101 MHz, CDCl₃): δ 171.4, 83.7, 57.4, 45.6, 35.3, 28.5, 24.9, 22.5 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **HRMS (ESI)** exact mass calcd. for C₁₅H₂₈BNNaO₃: *m/z* 304.2054 ([M+Na]⁺), found: *m/z* 304.2053 ([M+Na]⁺).

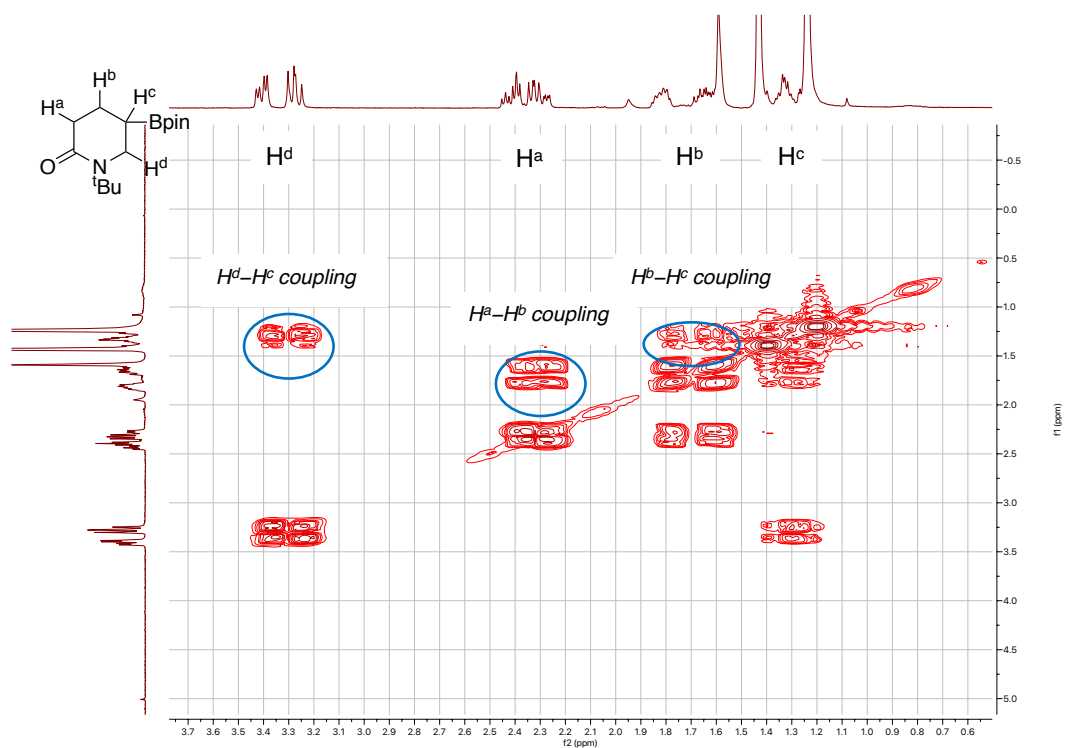


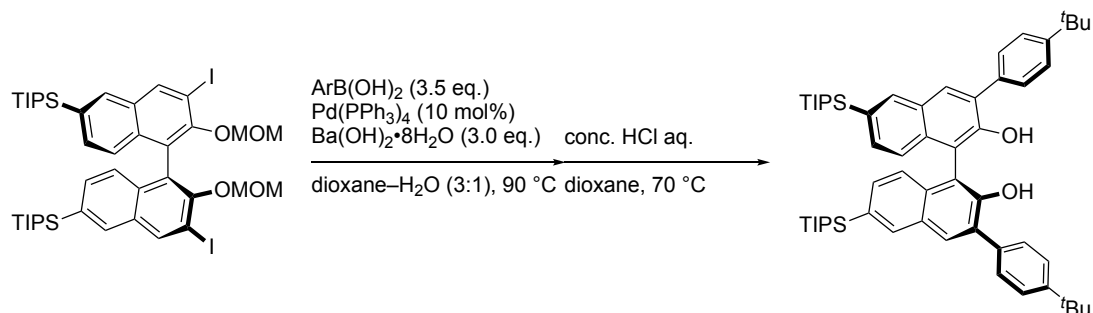
Figure 4-6 1H - 1H COSY analysis of **2m**

4.4.5 Enantioselective β -C–H Borylation of Cyclic Amines

4.4.5.1 Catalyst Preparation

The synthesis of **8b** was prepared according to the reported protocol.⁴³

(*S*)-3,3'-Bis(4-(*tert*-butyl)phenyl)-6,6'-bis(triisopropylsilyl)-[1,1'-binaphthalene]-2,2'-diol (**8a**)

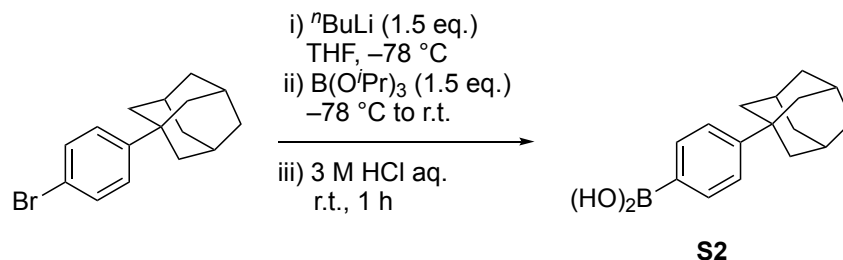


A 20 mL vial charged with (*S*)-**S1**⁴⁴ (1.00 mmol, 967 mg), 4-*tert*-butylphenylboronic acid (3.50 mmol, 623 mg), Pd(PPh₃)₄ (0.100 mmol, 116 mg), Ba(OH)₂·8H₂O 3.00 mmol, 496 mg) and degassed aqueous dioxane (10 mL, dioxane/H₂O = 3/1) was carefully evacuated and backfilled with argon for three times. The vial was sealed with a Teflon-lined cap and the vessel heated to 90 °C for 12 hours. The resulting orange mixture was cooled to room temperature and partitioned with Et₂O (20 mL), sat. NH₄Cl aq. (10 mL) and H₂O (5.0 mL), and the aqueous phase was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was dissolved in dioxane (10 mL), and concentrated HCl aq. (0.50 mL) was added to the solution at room temperature. The resulting mixture was stirred at 70 °C and held at this temperature. After 2 hours, the reaction mixture was quenched with sat. NaHCO₃ aq. (10 mL). The aqueous phase was extracted with Et₂O (5.0 mL × 3). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by MPLC (eluent: hexane/AcOEt = 100/0 to 90/10) followed by recrystallization from MeCN afforded the title compound in 71% yield (0.710 mmol, 613 mg over 2 steps) as a colorless solid.

R_f: 0.80 (eluent: AcOEt/hexanes = 9/1, UV); **Melting point**: 285 °C (decomp.); **¹H NMR** (400 MHz, CDCl₃): δ 8.04 (s, 2H), 8.03 (s, 2H), 7.71 (d, *J* = 8.1 Hz, 4H), 7.52 (d, *J* = 8.1 Hz, 4H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.41 (s, 2H), 1.47 (hept, *J* = 7.5 Hz, 6H), 1.39 (s, 18H), 1.11 (d, *J* = 7.5 Hz, 18H), 1.10 (d, *J* = 7.5 Hz, 18H); **¹³C NMR**

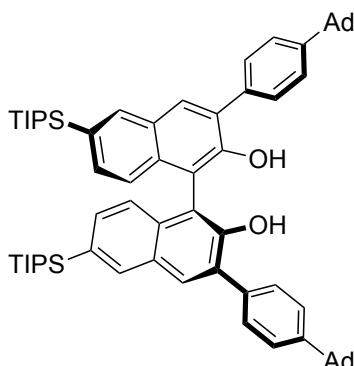
(101 MHz, CDCl₃): δ 150.7, 136.5, 134.8, 133.3, 132.9, 131.7, 130.6, 130.4, 129.4, 129.2, 125.6, 123.1, 112.2, 34.8, 31.5, 18.8, 11.1 (*One ¹³C signal is overlapping with others*); **HRMS (ESI)** exact mass calcd. for C₅₈H₇₈NaO₂Si₂: m/z 885.5433 ([M+Na]⁺), found: m/z 885.5424 ([M+Na]⁺); **Optical Rotation**: $[\alpha]_D^{20} = -86.6$ ($c = 0.320$, CH₂Cl₂).

(4-(Adamantan-1-yl)phenyl)boronic acid (S2)



To a 200 mL round-bottomed flask containing 1-(4-bromophenyl)adamantane⁴⁵ (5.50 mmol, 1.60 g) was added THF (30 mL) and the stirred solution was cooled to $-78\text{ }^\circ\text{C}$. $^n\text{BuLi}$ (1.6 M solution in hexane, 8.3 mmol, 5.2 mL) was added dropwise over 5 min and the resulting solution was maintained at $-78\text{ }^\circ\text{C}$ for 1 hour. To the resulting mixture was added B(O^{*i*}Pr)₃ (8.25 mmol, 1.89 mL) over 10 min. The cold bath was removed, and the reaction mixture was stirred at room temperature. After 3 hours, 3 M HCl aq. (5.0 mL) was added, and the resulting mixture was stirred for an additional 1 hour. The mixture was partitioned with AcOEt (25 mL) and H₂O (10 mL), and the aqueous phase was extracted with AcOEt (15 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue was triturated with cold hexanes. The resulting white precipitate was filtered to afford boronic acid **S2** as a colorless solid (860 mg), which was used in the next Suzuki coupling reaction without further purification.

(S)-3,3'-Bis-(4-(adamantan-1-yl)phenyl)-6,6'-bis(triisopropylsilyl)-[1,1'-binaphthalene]-2,2'-diol (8c)



Prepared using (*S*)-**1** (0.930 mmol, 896 mg) and boronic acid **S2** (3.36 mmol, 860 mg) following the procedure analogous to that for the preparation of **8a**. The title compound was obtained in 57% yield (0.521 mmol, 531 mg, over 2 steps) as a colorless solid.

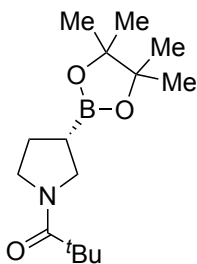
R_f: 0.85 (eluent: hexane/AcOEt = 9/1, UV); **Melting point**: 273 °C (decomp.); **¹H NMR** (400 MHz, CDCl₃): δ 8.04 (s, 2H), 8.03 (s, 2H), 7.72 (d, *J* = 8.2 Hz, 4H), 7.49 (d, *J* = 8.2 Hz, 4H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.43 (s, 2H), 3.70 (s, 2H), 2.13 (br, 6H), 1.99 (br, 12H), 1.84-1.77 (m, 12H), 1.46 (hept, *J* = 7.5 Hz, 6H), 1.11 (d, *J* = 7.5 Hz, 18H), 1.10 (d, *J* = 7.5 Hz, 18H); **¹³C NMR** (101 MHz, CDCl₃): δ 151.0, 150.7, 136.5, 134.8, 133.3, 132.9, 131.7, 130.5, 130.4, 129.4, 129.2, 125.2, 123.1, 112.2, 67.2, 43.3, 37.0, 36.3, 29.1, 18.8, 11.1; **HRMS (ESI)** exact mass calcd. for C₇₀H₉₀NaO₂Si₂: *m/z* 1041.6372 ([M+Na]⁺), found: *m/z* 1041.6354 ([M+Na]⁺); **Optical Rotation**: [α]_D²⁰ = −63.7 (*c* = 0.300, CH₂Cl₂).

4.4.5.2 General procedure and additional data for enantio-enriched products

In a N₂-filled glove box, a 4 mL vial equipped with a stir bar was charged with [Ir(cod)OMe]₂ (0.015 mmol, 9.9 mg.), B₂(pin)₂ (0.450 mmol, 114 mg), 3,4,7,8-tetramethyl-1,10-phenanthroline (TMPhen, 0.030 mmol, 7.1 mg) and isooctane (0.75 mL). The vial was sealed with a Teflon-lined cap and moved to a preheated metal heating block (70 °C). The reaction mixture was then stirred at 70 °C for 30 min, after which the color of the mixture had turned a deep-green color. Meanwhile, a separate 4 mL vial equipped with a stir bar was charged with (*S*)-BINOL derivative **8** (0.030 mmol) and isooctane (0.75 mL). A solution of trialkyl aluminum (0.033 mmol) in hexane was added at −35 °C and the mixture was allowed to warm to room temperature for 30 min before

cyclic amine substrate **1** (0.30 mmol) was added. The resulting mixture was stirred at room temperature for an additional 30 min before a cooled brown solution of the iridium complex (0.450 mmol, 114 mg) was added. The reaction vessel was sealed with a Teflon-lined cap and stirred at the indicated temperature for an indicated time. The reaction mixture was then cooled to room temperature and volatiles were removed under reduced pressure. The crude residue was purified by column chromatography on silica gel to afford the desired enantio-enriched borylation product.

(S)-2,2-Dimethyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl)propan-1-one (2a)

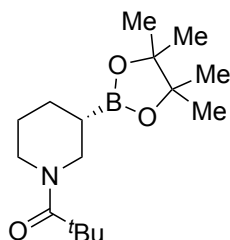


Following the general procedure, the reaction was conducted with **1a** (0.300 mmol, 44.6 mg), [Ir(cod)OMe]₂ (0.015 mmol, 9.9 mg), B₂(pin)₂ (0.900 mmol, 229 mg), TMPhen (0.030 mmol, 7.1 mg), (*S*)-**8c** (0.0300 mmol, 30.6 mg), Al(*t*Bu)₃ (0.55 M solution in hexane, 0.033 mmol, 60 μ L) and isooctane (1.5 mL) at 80 °C for 9 hours. Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 60/40) afforded the title compound (63% yield, 53.1 mg) [75% ee]. The spectroscopic data were in agreement with those reported above.

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/*i*PrOH = 90/10, flow rate = 1.0 mL/min, retention time; 25.0 min (minor) and 29.6 min (major)).

Optical Rotation $[\alpha]_{\text{D}}^{20} = +25.1$ ($c = 0.450$, CH₂Cl₂).

(S)-2,2-Dimethyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-yl)propan-1-one (2b)

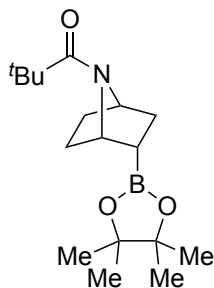


Following the general procedure, the reaction was conducted with **1b** (0.300 mmol, 50.8 mg), [Ir(cod)OMe]₂ (0.015 mmol, 9.9 mg), B₂(pin)₂ (0.900 mmol, 229 mg), TMPhen (0.030 mmol, 7.1 mg), (*S*)-**8a** (0.030 mmol, 25.9 mg), Al(*i*Bu)₃ (0.55 M solution in hexane, 0.033 mmol, 60 μ L) and isooctane (1.5 mL) at 100 °C for 10 hours. Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 60/40) afforded a beige solid (61.6 mg) consisting of 75:25 inseparable mixture of **2b** (51%) and **3** (13%), which were separated by recycling gel permeation chromatography (eluent: CHCl₃ only) to provide an analytically pure samples **2b** (36.3 mg, 41%, 52% ee) as a white solid and **3** (13.9 mg, 11%) as an off-white solid. The spectroscopic data were in agreement with those reported above.

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IE-3, hexane/*i*PrOH = 95/5, flow rate = 1.0 mL/min at 40 °C, retention time; 15.5 min (minor) and 16.8 min (major)).

Optical Rotation $[\alpha]_D^{20} = +8.8$ (*c* = 0.75, CH₂Cl₂).

2,2-Dimethyl-1-((1*S*,2*S*,4*R*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azabicyclo[2.2.1]heptan-7-yl)propan-1-one (2k)



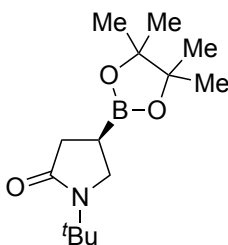
Following the general procedure, the reaction was conducted with **1k** (0.300 mmol, 54.4 mg), [Ir(cod)OMe]₂ (0.0225 mmol, 14.9 mg), B₂(pin)₂ (0.900 mmol, 229 mg), TMPhen (0.0450 mmol, 10.7 mg), (*S*)-**8a** (0.0300 mmol, 25.9 mg), Al(*i*Bu)₃ (0.55 M solution in

hexane, 0.033 mmol, 60 μ L) and isooctane (1.5 mL) at 110 $^{\circ}$ C for 12 hours. Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 70/30) afforded the title compound (54.4 mg, 58% yield) [89% ee]. The spectroscopic data were in agreement with those reported above.

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IE-3, hexane/*i*PrOH = 95/5, flow rate = 1.0 mL/min at 40 $^{\circ}$ C, retention time; 22.2 min (major) and 28.4 min (minor)).

Optical Rotation $[\alpha]_{\text{D}}^{20} = +13.0$ ($c = 0.230$, CH_2Cl_2).

(*R*)-1-(*tert*-Butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (2m)

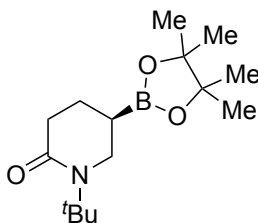


Following the general procedure, the reaction was conducted with **1m** (0.300 mmol, 42.4 mg), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.015 mmol, 9.9 mg), $\text{B}_2(\text{pin})_2$ (0.900 mmol, 229 mg), TMPhen (0.030 mmol, 7.1 mg), (*S*)-**8a** (0.0300 mmol, 25.9 mg), AlMe_3 (1.4 M solution in hexane, 0.033 mmol, 24 μ L) and isooctane (1.5 mL) at 80 $^{\circ}$ C for 5 hours. Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 50/50) afforded the title compound (40.9 mg, 51% yield) [98% ee]. The spectroscopic data were in agreement with those reported above.

The enantiomeric purity of the product was determined by chiral GC analysis (CP-Chirasil-Dex-CB, 25 m $\times$ 0.25 mm: 40 $^{\circ}$ C to 144 $^{\circ}$ C at 3 $^{\circ}$ C/min then 144 $^{\circ}$ C, retention time; 32.6 min (major) and 35.3 min (minor)).

Optical Rotation $[\alpha]_{\text{D}}^{20} = +6.1$ ($c = 0.56$, CH_2Cl_2).

(R)-1-(tert-Butyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-2-one
(2n)



Following the general procedure, the reaction was conducted with **1n** (0.300 mmol, 46.6 mg), [Ir(cod)OMe]₂ (0.015 mmol, 9.9 mg), B₂(pin)₂ (0.900 mmol, 229 mg), TMPhen (0.030 mmol), (*S*)-**8a** (25.9 mg, 0.030 mmol), AlMe₃ (1.4 M solution in hexane, 24 μL, 0.033 mmol, 7.1 mg) and isooctane (1.5 mL) at 80 °C for 30 hours. Purification by column chromatography (eluent: hexane/AcOEt = 90/10 to 60/40) afforded the title compound (46.4 mg, 55% yield) [30% ee]. The spectroscopic data were in agreement with those reported above.

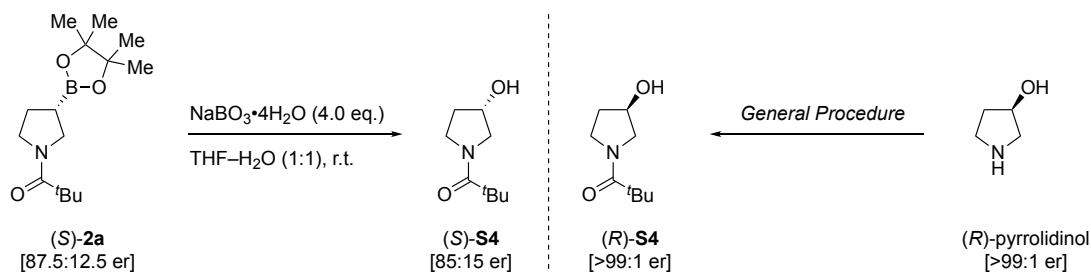
The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IE-3, hexane/*i*PrOH = 95/5, flow rate = 1.0 mL/min at 40 °C, retention time; 22.2 min (minor) and 23.2 min (major)).

Optical Rotation $[\alpha]_{\text{D}}^{20} = +7.6$ ($c = 0.54$, CH₂Cl₂).

4.4.5.3 Determination of the absolute stereochemistry

The absolute stereochemistry of **2a** and **2m** were assigned as (*S*) and (*R*) respectively. For all the other compounds, the absolute configurations were assigned by analogy.

Oxidation of enantio-enriched boronate ester (*S*)-**2a**



To a 20 mL vial containing a solution of (*S*)-**2a** (0.100 mmol, 28.1 mg, 87.5:12.5 er) in aqueous THF (1.0 mL, THF/H₂O = 1:1) add sodium perborate tetrahydrate (0.400 mmol, 61.5 mg) at room temperature. After 2 hours, the mixture was partitioned with CHCl₃ (5.0

mL) and H₂O (3.0 mL), and the aqueous phase was extracted with CHCl₃ (4.0 mL × 4). The combined organic layers were washed with brine (5.0 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: hexane/AcOEt = 60/40 to 0/100) to provide alcohol (*S*)-**S4** (12.7 mg, 74%) as a pale-yellow oil [70% ee].

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IG-3, hexane/*i*PrOH = 95/5, flow rate = 1.0 mL/min at 40 °C, retention time; 31.5 min (minor) and 36.9 min (major)).

R_f: 0.40 (eluent: AcOEt only, KMnO₄); **¹H NMR** (400 MHz, CDCl₃): δ 4.44 (br, 1H), 3.69 (br, 2H), 3.61 (br, 2H), 2.69 (br, 1H), 1.96 (br, 2H), 1.25 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 177.1, 72.0 & 68.0 (conformeric singlets), 56.9 & 55.8 (conformeric singlets), 45.8, 39.0, 35.3 & 31.5 (conformeric singlets), 27.6; **HRMS (ESI)** exact mass calcd. for C₉H₁₇NNaO₂: *m/z* 194.1152 ([M+Na]⁺), found: *m/z* 194.1149 ([M+Na]⁺); **Optical rotation** [α]_D²⁰ = +3.5 (*c* = 0.77, CH₂Cl₂).

Optical rotation of authentic (*R*)-S4**** [α]_D²⁰ = −4.5 (*c* = 0.77, CH₂Cl₂).

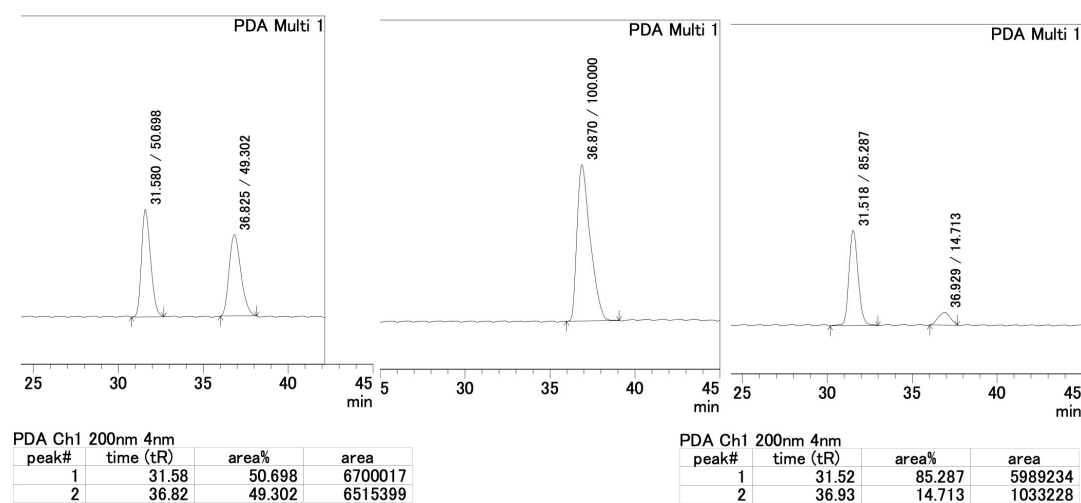
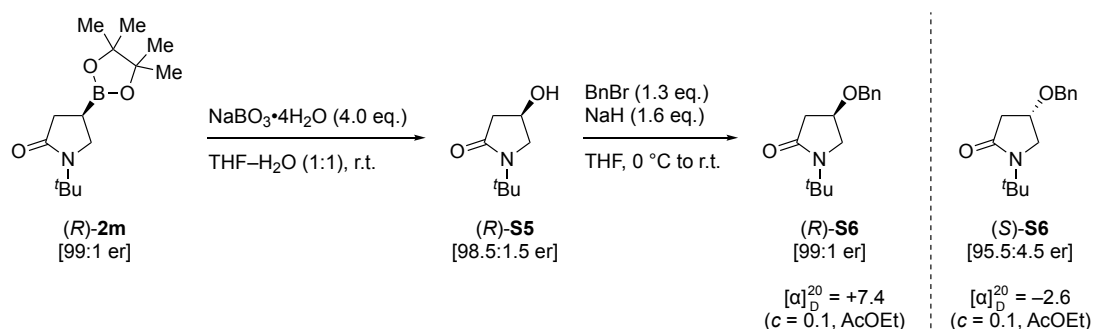


Figure 4-7 Chiral HPLC traces. (Left) *rac*-**S4**. (Center) (*R*)-**S4**. (Right) **S4** prepared from enantio-enriched **2a**.

(*R*)-1-(*tert*-Butyl)-4-hydroxypyrrolidin-2-one (*S5*)

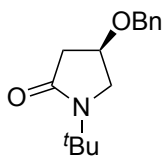


Prepared from (*R*)-**2m** (99:1 er) using a procedure analogous to that for the preparation of (*S*)-**S4** in 0.100 mmol scale. Purification by preparative thin-layer chromatography (eluent: hexane/AcOEt = 1/1) afforded the title compound in 81% yield (0.0808 mmol, 12.7 mg) as a colorless solid [97% ee].

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IA-3, hexane/*i*PrOH = 95/5, flow rate = 1.0 mL/min at 40 °C, retention time; 15.6 min (major) and 20.0 min (minor)).

R_f: 0.20 (eluent: AcOEt only, KMnO₄); **Melting point**: 56-58 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.40-4.36 (m, 1H), 3.67 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.41 (dd, *J* = 10.8, 1.8 Hz, 1H), 2.76 (br, 1H), 2.66 (dd, *J* = 17.2, 6.6 Hz, 1H), 2.33 (dd, *J* = 17.2, 2.3 Hz, 1H), 1.39 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 173.2, 64.1, 54.9, 54.2, 43.2, 27.8; **HRMS (ESI)** exact mass calcd. for C₈H₁₅NNaO₂: *m/z* 180.0995 ([M+Na]⁺), found: *m/z* 180.0993 ([M+Na]⁺); **Optical rotation** [α]_D²⁰ = +6.9 (*c* = 0.24, CH₂Cl₂).

(*R*)-4-(Benzyloxy)-1-(*tert*-butyl)pyrrolidin-2-one (*S6*)



To a 10 mL round-bottomed flask containing a solution of (*R*)-**S5** (0.0700 mmol, 11.0 mg, 99:1 er) in THF (0.75 mL) was added sodium hydride (0.11 mmol, 2.7 mg) at 0 °C and the resulting mixture was warmed to room temperature. After 30 min, the vessel was re-cooled to 0 °C, and benzyl bromide was added (0.091 mmol, 11 μL) and then warmed to room temperature. After 15 hours, the mixture was partitioned with AcOEt (7.0 mL) and H₂O (3.0 mL), and the aqueous phase was extracted with AcOEt (5.0 mL × 3). The

combined organic layers were washed with brine (5.0 mL), dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. Purification by preparative thin-layer chromatography (eluent: hexane/AcOEt = 2/1) afforded the title compound in 74% yield (0.0534 mmol, 13.2 mg) as a pale-yellow oil [98% ee].

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IBN-3, hexane/ i PrOH = 95/5, flow rate = 1.0 mL/min at 40 °C, retention time; 11.1 min (major) and 13.0 min (minor)).

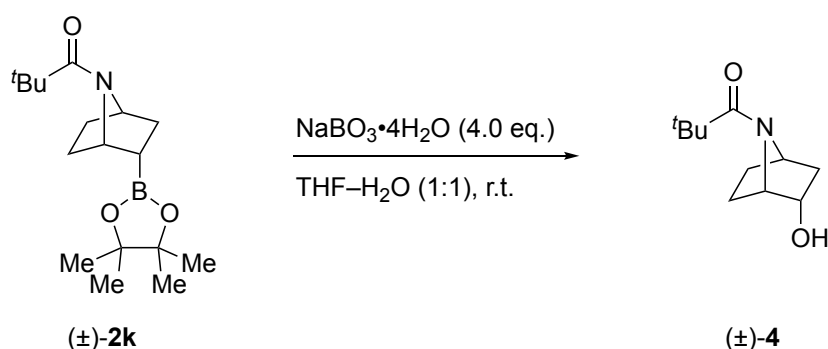
The comparison of the optical rotation with the reported value determined the absolute configuration of **S6** as *R*.⁴⁶

R_f: 0.25 (eluent: hexane/AcOEt = 2/1, UV); **¹H NMR** (400 MHz, CDCl_3): δ 7.38-7.28 (m, 5H), 4.56 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.12 (tt, J = 6.7, 3.6 Hz, 1H), 3.66 (dd, J = 10.5, 6.7 Hz, 1H), 3.47 (dd, J = 10.5, 3.6 Hz, 1H), 2.60 (dd, J = 17.1, 6.7 Hz, 1H), 2.50 (dd, J = 17.1, 3.6 Hz, 1H), 1.39 (s, 9H); **¹³C NMR** (101 MHz, CDCl_3): δ 172.7, 137.8, 128.7, 128.0, 127.8, 70.9, 70.6, 54.2, 52.2, 39.9, 27.9; **Optical rotation**: $[\alpha]_{\text{D}}^{20}$ = +7.4 (c = 0.10, EtOAc);

The spectroscopic data were in agreement with those reported previously.⁴⁶

4.4.6 Derivatization of Borylation Products

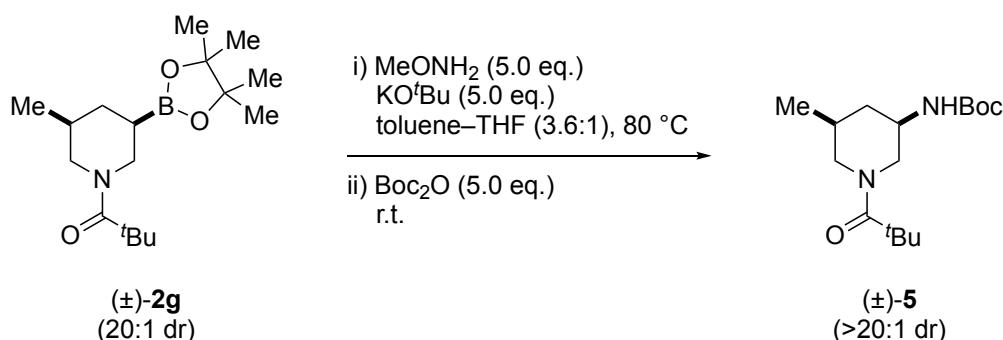
($\pm$)-1-((1*S**,2*S**,4*R**)-2-Hydroxy-7-azabicyclo[2.2.1]heptan-7-yl)-2,2-dimethylpropan-1-one (**4**)



Prepared from boronate ester **2k** using a procedure analogous to that for the preparation of (*S*)-**S4** in 0.200 mmol scale. Purification by preparative thin-layer chromatography (eluent: hexane/AcOEt = 1/1) afforded the title compound in 70% yield (0.140 mmol, 27.6 mg) as a colorless solid. Recrystallization from a saturated hexane solution at room temperature afforded single crystals suitable for X-ray crystallographic analysis.

R_f: 0.40 (eluent: AcOEt only, KMnO₄); **Melting point**: 85-87 °C; **¹H NMR** (400 MHz, CDCl₃): δ 4.49 (brs, 2H), 4.27 (brs, 1H), 3.63 (brs, 1H), 2.25-2.14 (m, 2H), 1.76 (brs, 1H), 1.58 (brs, 1H), 1.18 (s, 9H), 1.15-1.12 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃): δ 175.3, 70.4, 59.5, 57.2, 39.3, 39.1, 30.1, 28.0, 20.7; **HRMS (ESI)** exact mass calcd. for C₁₁H₁₉NNaO₂: *m/z* 220.1308 ([M+Na]⁺), found: *m/z* 220.1307 ([M+Na]⁺).

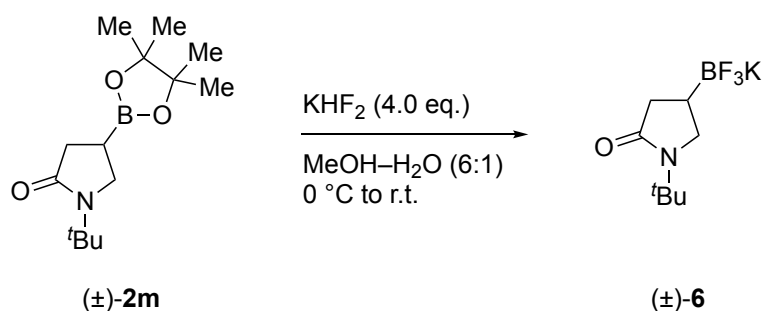
(±)-*tert*-Butyl (cis-5-methyl-1-pivaloylpiperidin-3-yl)carbamate (5)



According to a literature procedure,⁴⁷ a 4 mL vial was charged with **2g** (0.100 mmol, 30.9 mg), potassium *tert*-butoxide (0.500 mmol, 56.1 mg), *O*-methylhydroxylamine (3.56 M solution in THF, 0.50 mmol, 0.14 mL) and toluene (0.5 mL). The vessel was tightly sealed and heated to 80 °C and held at this temperature. After 16 hours, the reaction mixture was allowed to cool to room temperature and di-*tert*-butyl dicarbonate (0.50 mmol, 0.11 mL) was added. The resulting mixture was stirred for an additional 3 hours. The mixture was partitioned with AcOEt (5.0 mL) and H₂O (3.0 mL), and the aqueous phase was extracted with AcOEt (5.0 mL × 3). The combined organic layers were washed with brine (5.0 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by preparative thin-layer chromatography (eluent: hexane/AcOEt = 3/1) to provide the title compound in 67% yield (0.0670 mmol, 20.0 mg) as a colorless foam.

R_f: 0.25 (eluent: hexane/AcOEt = 2/1, KMnO₄); **¹H NMR** (400 MHz, CDCl₃): δ 4.55 (d, *J* = 12.4 Hz, 1H), 4.44 (brs, 1H), 4.41 (brs, 1H), 3.48 (brs, 1H), 2.40 (t, *J* = 11.7, 1H), 2.12-2.04 (m, 2H), 1.67-1.59 (m, 1H), 1.43 (s, 9H), 1.29 (s, 9H), 1.25-1.32 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ 176.6, 155.1, 79.7, 51.4, 50.9, 47.8, 40.3, 39.0, 30.5, 28.5(2), 18.8; **HRMS (ESI)** exact mass calcd. for C₁₆H₃₀N₂NaO₃: *m/z* 321.2149 ([M+Na]⁺), found: *m/z* 321.53 ([M+Na]⁺).

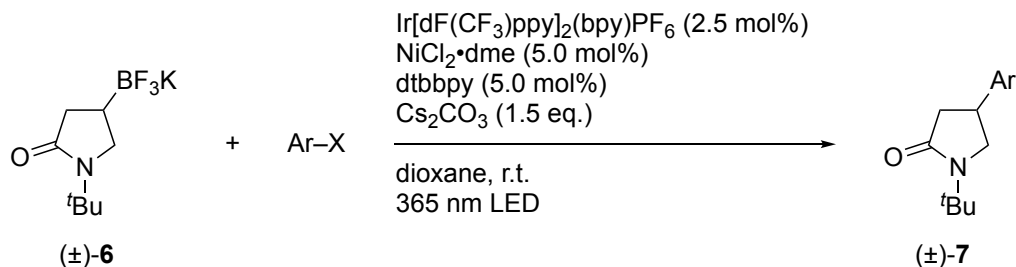
Preparation of trifluoroborate **6**



To a 100 mL round-bottomed flask containing **2m** (5.73 mmol, 1.53 g) was added MeOH (30 mL) and the stirred solution was cooled to 0 °C. KHF₂ (4.5 M solution in H₂O, 22.9 mmol, 5.1 mL) was added dropwise over 5 min and the resulting solution was warmed to room temperature. After 5 hours, volatiles were removed under reduced pressure and the crude residue was further dried under high vacuum. The resulting brown solid was dissolved in minimal amount of acetone and triturated with hexanes. The resulting precipitate was filtered to afford trifluoroborate **6** in 71% yield (4.09 mmol, 1.01 g) as a beige solid.

Melting point: 202-203 °C; **¹H NMR** (400 MHz, acetone-*d*₆): δ 3.30 (t, *J* = 9.2 Hz, 1H), 3.20 (t, *J* = 9.2 Hz, 1H), 2.08-1.91 (m, 2H), 1.30 (s, 9H), 1.07-0.92 (m, 1H); **¹³C NMR** (101 MHz, acetone-*d*₆): δ 178.7, 53.3, 49.9, 37.3, 27.9 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **¹⁹F NMR** (376 MHz, acetone-*d*₆): δ -144.9; **HRMS (ESI)** exact mass calcd. for C₈H₁₄BF₃NO: *m/z* 208.1115 ([M]⁻), found: *m/z* 208.1125 ([M]⁻).

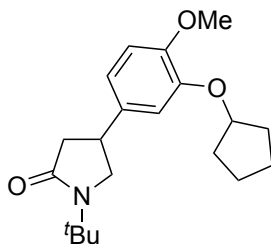
General procedure for metallophotoredox cross-coupling



According to a literature procedure,²² a 4 mL vial equipped with a stir bar was charged with NiCl₂·dme (0.0050 mmol, 1.1 mg), 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) (0.0050 mmol, 1.3 mg) and THF (0.5 mL). The vial was capped and the resulting

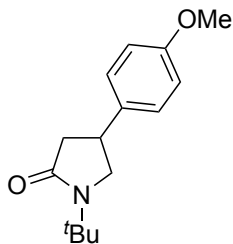
suspension was heated with a heat gun for 10 seconds. The solvent was then removed under vacuum to give a pale-green solid. To this vial was added aryl halide (0.10 mmol), trifluoroborate **6** (0.150 mmol, 37.1 mg), Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.0025 mmol, 2.5 mg) and Cs₂CO₃ (0.150 mmol, 48.9 mg) and the vial was brought into a N₂-filled glove box. Anhydrous 1,4-dioxane (2.0 mL) was then added and the vial was tightly sealed, removed from the glovebox, and stirred approximately 1.5 cm away from two 365 nm LED lamps (OptCode, LED365-100STND) with adequate fans to keep the reaction temperature around 25 °C. After 24 hours, the mixture was partitioned with Et₂O (5.0 mL) and 1M HCl aq. (3.0 mL), and the aqueous phase was extracted with Et₂O (4.0 mL × 4). The combined organic layers were washed with brine (5.0 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by preparative thin-layer chromatography to provide the desired coupling product **7**.

(±)-1-(*tert*-Butyl)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one (7a)



Following the general procedure, the reaction was conducted with 2-(cyclopentyloxy)-4-iodo-1-methoxybenzene (0.200 mmol, 63.6 mg), trifluoroborate **6** (0.300 mmol, 63.6 mg), NiCl₂·dme (0.010 mmol, 2.2 mg), dtbbpy (0.010 mmol, 2.7 mg), Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.0050 mmol, 5.1 mg), Cs₂CO₃ (0.300 mmol, 97.7 mg) and 1,4-dioxane (4.0 mL). Purification by purified by preparative thin-layer chromatography (eluent: hexane/AcOEt = 2/1) to provide the title product in 54% yield (0.108 mmol, 35.8 mg) as a colorless oil. **R_f**: 0.35 (eluent: hexane/AcOEt = 4/1, KMnO₄); **¹H NMR** (400 MHz, CDCl₃): δ 6.81-6.79 (m, 1H), 6.74-6.73 (m, 2H), 4.77-4.73 (m, 1H), 3.84-3.78 (m, 1H), 3.81 (s, 3H), 3.40-3.31 (m, 2H), 2.73 (dd, *J* = 16.5, 8.4 Hz, 1H), 2.49 (dd, *J* = 16.5, 8.2 Hz, 1H), 1.94-1.78 (m, 6H), 1.62-1.55 (m, 2H), 1.41 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 174.4, 149.1, 148.0, 135.4, 118.8, 113.7, 112.3, 80.6, 56.2, 54.1, 53.5, 40.9, 36.7, 32.9, 27.9, 24.1; **HRMS (ESI)** exact mass calcd. for C₂₀H₂₉NNaO₃: *m/z* 354.2040 ([M+Na]⁺), found: *m/z* 354.2042 ([M+Na]⁺).

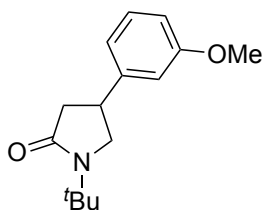
(±)-1-(*tert*-Butyl)-4-(4-methoxyphenyl)pyrrolidin-2-one (7b)



Following the general procedure, the reaction was conducted with 1-bromo-4-methoxybenzene (0.100 mmol, 23.4 mg), trifluoroborate **6** (0.150 mmol, 37.1 mg), NiCl₂·dme (0.0050 mmol, 1.1 mg), dtbbpy (0.0050 mmol, 1.3 mg), Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.0025 mmol, 2.5 mg), Cs₂CO₃ (0.150 mmol, 48.9 mg) and 1,4-dioxane (2.0 mL). Purification by purified by preparative thin-layer chromatography (eluent: hexane/AcOEt = 2/1) to provide the title product in 46% yield (0.0461 mmol, 11.4 mg) as a pale-yellow solid.

R_f: 0.20 (eluent: hexane/AcOEt = 3/1, KMnO₄); **Melting point**: 40–42 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.84–3.82 (m, 1H), 3.80 (s, 3H), 3.44–3.34 (m, 2H), 2.73 (dd, *J* = 16.6, 8.6 Hz, 1H), 2.50 (dd, *J* = 16.5, 8.7 Hz, 1H), 1.42 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 174.5, 158.7, 134.8, 127.8, 114.3, 55.5, 54.2, 53.5, 41.0, 36.5, 27.9; **HRMS (ESI)** exact mass calcd. for C₁₅H₂₁NNaO₂: *m/z* 270.1465 ([M+Na]⁺), found: *m/z* 270.1464 ([M+Na]⁺).

(±)-1-(*tert*-Butyl)-4-(3-methoxyphenyl)pyrrolidin-2-one (7c)

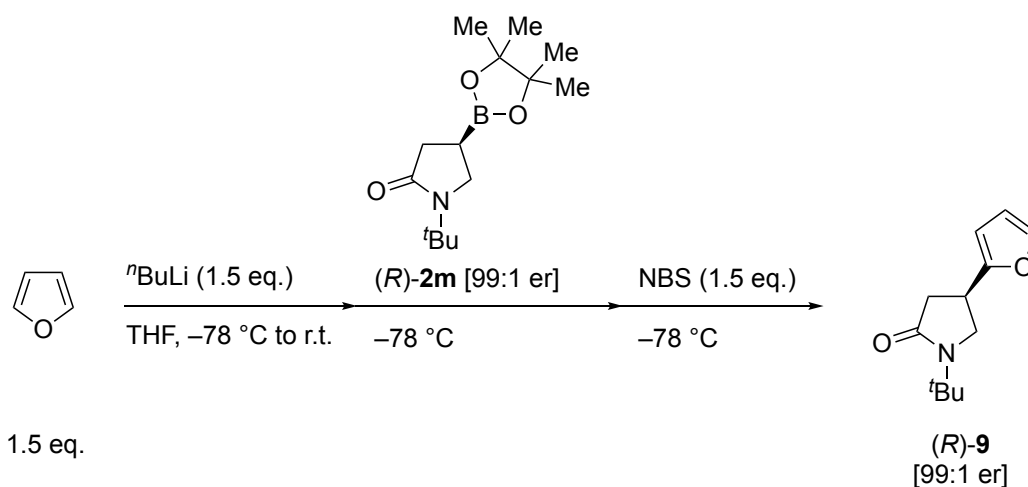


Following the general procedure, the reaction was conducted with 1-bromo-3-methoxybenzene (0.100 mmol, 23.4 mg), trifluoroborate **6** (0.150 mmol, 37.1 mg), NiCl₂·dme (0.0050 mmol, 1.1 mg), dtbbpy (0.0050 mmol, 1.3 mg), Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.0025 mmol, 2.5 mg), Cs₂CO₃ (0.150 mmol, 48.9 mg) and 1,4-dioxane (2.0 mL). Purification by purified by preparative thin-layer chromatography (eluent: hexane/AcOEt = 2/1) to provide the title product in 49% yield (0.0489 mmol, 12.1 mg) as a pale-yellow oil.

R_f: 0.20 (eluent: hexane/AcOEt = 3/1, KMnO₄); **¹H NMR** (400 MHz, CDCl₃): δ 7.23 (d, *J* = 7.8 Hz, 1H), 6.82–6.77 (m, 3H), 3.86–3.83 (m, 1H), 3.80 (s, 3H), 3.45–3.37 (m, 2H), 2.77–2.71 (m, 1H), 2.55–2.49 (m, 1H), 1.42 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 174.3, 160.0, 144.5, 130.0, 119.1, 112.8, 112.1, 55.3, 54.2, 53.1, 40.7, 37.1, 27.9; **HRMS (ESI)** exact mass calcd. for C₁₅H₂₁NNaO₂: *m/z* 270.1465 ([M+Na]⁺), found: *m/z* 270.1465 ([M+Na]⁺).

Enantio-specific coupling with furan

(*R*)-1-(*tert*-Butyl)-4-(furan-2-yl)pyrrolidin-2-one (**9**)



According to a literature procedure,²⁹ a 20 mL round-bottomed flask containing a solution of furan (0.15 mmol, 11 μL) in THF (1.0 mL) was cooled to −78 °C. *n*-BuLi (1.6 M solution in hexane, 0.15 mmol, 0.090 mL) was added dropwise over 1 min and the resulting solution was warmed to room temperature. After 1 hour, the reaction mixture was cooled to −78 °C and a solution of (*R*)-**2m** (0.100 mmol, 26.7 mg, 99:1 er) in THF (1.0 mL) was added dropwise over 1 min and the resulting solution was maintained at −78 °C for 1 hour. To the resulting mixture was added a solution of NBS (0.150 mmol, 26.7 mg) in THF (0.5 mL). After stirring at −78 °C for 1 hour, the reaction was quenched with sat. Na₂S₂O₃ aq. (3.0 mL) and the resulting mixture was allowed to warm to room temperature. The mixture was partitioned with Et₂O (5.0 mL) and H₂O (1.0 mL), and the aqueous phase was extracted with Et₂O (3.0 mL × 3). The combined organic layers were washed with brine (3.0 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by preparative thin-layer chromatography (eluent: hexane/AcOEt = 2/1) to provide the title product in 59% yield (0.0588 mmol,

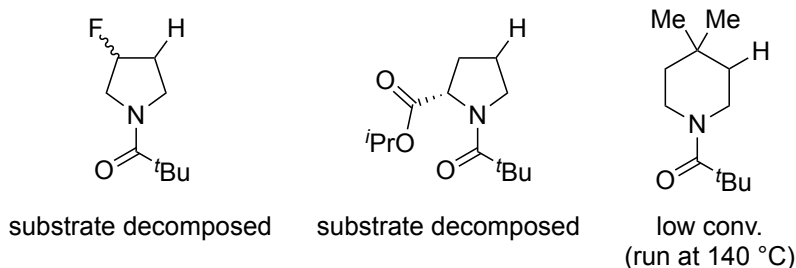
12.2 mg) as a colorless solid.

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK® IA-3, hexane/*i*PrOH = 95/5, flow rate: 1.0 mL/min at 40 °C, retention time; 8.1 min (major) and 8.8 min (minor)).

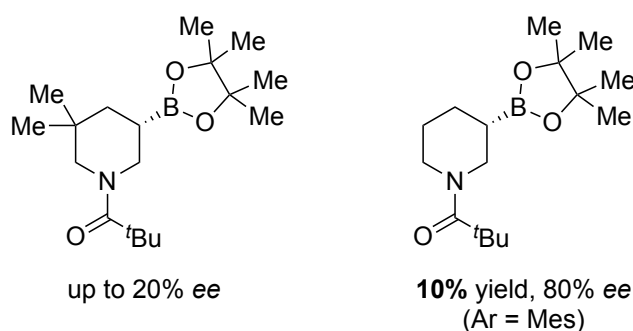
R_f: 0.35 (eluent: hexane/AcOEt = 2/1, KMnO₄); **Melting point**: 35-37 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.33 (s, 1H), 6.30-6.29 (m, 1H), 6.09 (d, *J* = 3.0 Hz, 1H), 3.79-3.72 (m, 1H), 3.55-3.45 (m, 2H), 2.70-2.64 (m, 1H), 2.60-2.54 (m, 1H), 1.40 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ 173.7, 155.3, 141.9, 110.3, 105.2, 54.3, 50.5, 38.3, 31.0, 27.8; **HRMS (ESI)** exact mass calcd. for C₁₂H₁₇NNaO₂: *m/z* 230.1152 ([M+Na]⁺), found: *m/z* 230.1149 ([M+Na]⁺); **Optical rotation** [α]_D²⁰ = +21.0 (*c* = 0.400, CH₂Cl₂).

4.4.7 Unsuccessful Substrates

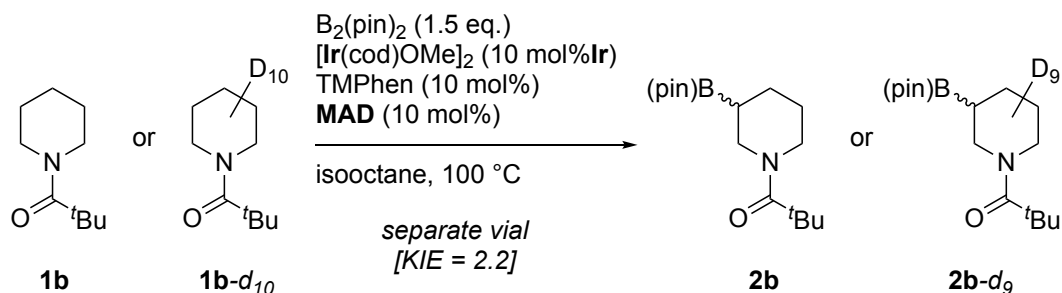
<racemic reaction>



<asymmetric reaction>



4.4.8 Deuterium Labeling Experiments



In a nitrogen-filled glovebox, a 4 mL vial equipped with a stir bar was charged with $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0200 mmol, 13.3 mg), $B_2(\text{pin})_2$ (0.600 mmol, 152 mg), TMPhen (0.040 mmol, 9.5 mg) and isooctane (1.0 mL). The vial was sealed with a Teflon-lined cap and moved to a preheated metal heating block (70 °C). The reaction mixture was then stirred at 70 °C for 30 min, after which the color of the mixture had turned a deep-green color. The half-volume of the cooled solution of the iridium complex was transferred to a separated 4 mL vial containing a solution of **1b** (0.200 mmol, 33.9 mg), MAD (0.100 mmol, 48.1 mg) and *n*-dodecane (20 μL as an internal standard) in isooctane (0.5 mL). The other half-volume of the solution was transferred to a separated 4 mL vial containing a solution of **1b-d₁₀** (0.200 mmol, 35.9 mg), MAD (0.100 mmol, 48.1 mg) and *n*-dodecane (20 μL as an internal standard) in isooctane (0.5 mL). The reaction vessels were sealed with Teflon-lined caps and stirred at 100 °C. Aliquots (*ca.* 10 μL) were taken via a pipette every 10 minutes over 2 hours. The samples taken out from the glovebox were diluted with AcOEt (*ca.* 1.6 mL) and the yields of borylation products were determined by quantitative GC-FID analysis (Figure 4-8). The experiment was repeated three times and the kinetic isotope effect (KIE) was determined to be 2.2 ± 0.03 ($n = 3$).

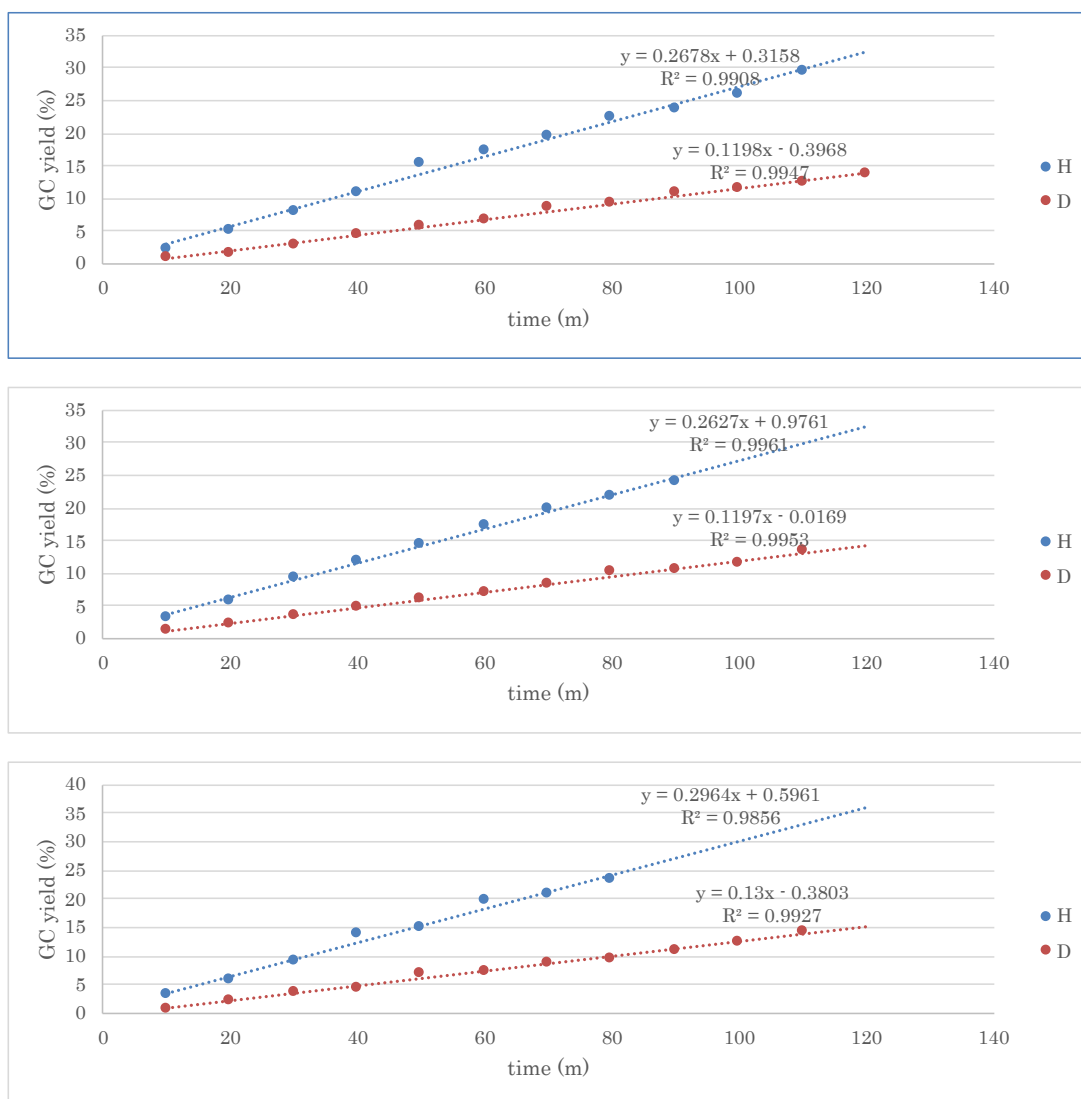
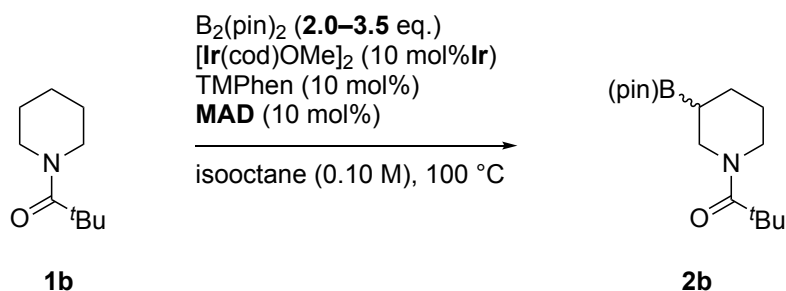


Figure 4-8 Rate profiles of **1b** vs **1b- d_{10}**

4.4.9 Kinetic Experiments



In a nitrogen-filled glovebox, a 15 mL vial equipped with a stir bar was charged with $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0400 mmol, 26.5 mg), $\text{B}_2(\text{pin})_2$ (1.60 mmol, 406 mg), TMPhen (0.0800 mmol, 18.9 mg) and isooctane (3.6 mL). The vial was sealed with a Teflon-lined cap and moved to a preheated metal heating block (70 °C). The reaction mixture was then stirred at 70 °C for 30 min, after which the color of the mixture had turned deep green. The one-fourth volume of the cooled solution of the iridium complex was transferred to separated 4 mL vials containing $\text{B}_2(\text{pin})_2$ (0 mg for 2.0 eq., 25.4 mg for 2.5 eq., 50.8 mg for 3.0 eq., and 76.2 mg for 3.5 eq., respectively) and sealed with a Teflon-lined cap and moved to a preheated metal heating block (70 °C). After 30 min, the solution was cooled to room temperature. In another 4 mL vial, a solution of **1b** (0.800 mmol, 135 mg), MAD (0.0800 mmol, 38.5 mg) and *n*-dodecane (80 μL as an internal standard) in isooctane (2.0 mL) was prepared. To a 2.0 mL volumetric flask, the one-fourth volume of the solution and the above-mentioned solution of the iridium complex was added. Then, the volume was adjusted to just 2.0 mL by the addition of isooctane, and the solution was transferred into a 4 mL vial equipped with a stir bar. The reaction vessels were sealed with Teflon-lined caps, removed from the glovebox, and stirred at 100 °C. After 15 min, the reactions were immediately cooled to 0 °C with ice water and taken into a nitrogen-filled glovebox. Aliquots (*ca.* 20 μL each) were taken *via* a pipette. The reaction mixture and the samples were taken out from the glovebox. The reaction was re-heated to 100 °C. This cycle was repeated after 30, 45, 60, 90, 150, 240, 360 min. The samples were diluted with AcOEt (*ca.* 1.5 mL) and the yields of borylated product were determined by quantitative GC-FID analysis (Figure 4-9). The experiment was repeated five times, and a -0.45^{th} order dependence of the reaction rate on the concentration of $\text{B}_2(\text{pin})_2$ could be estimated.



Figure 4-9 Rate profile and order dependence on $[B_2(\text{pin})_2]$ (continued)

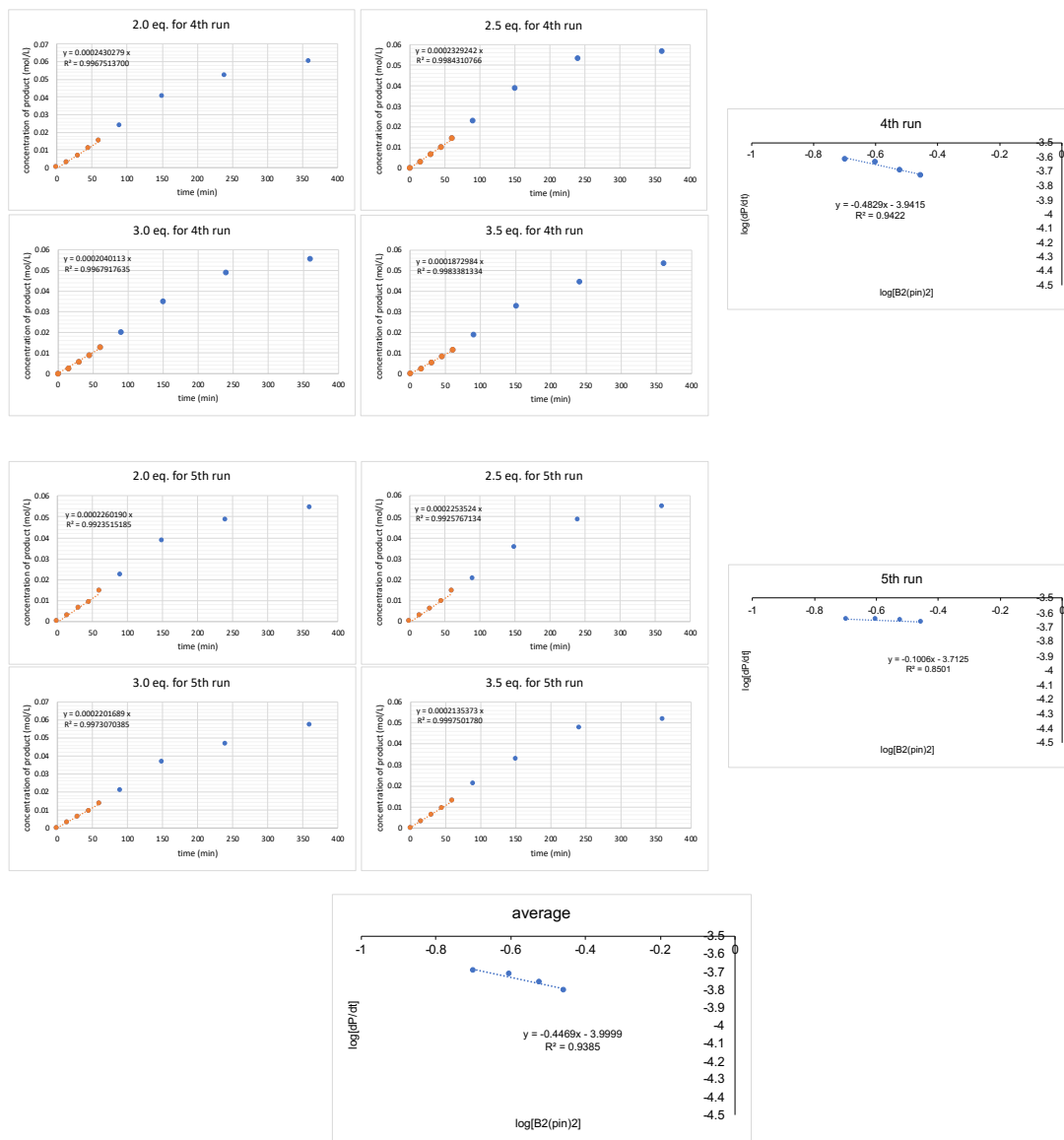


Figure 4-9 Rate profile and order dependence on $[B_2(\text{pin})_2]$. (continued)

4.4.10 DFT Calculations

4.4.10.1 Computational Details

Benchmark calculation in our recent work³⁵ showed that the DFT optimization in gas phase using the B3PW91-D3 functional,^{48,49} where D3 denotes the third-generation dispersion correction by Grimme and co-workers,⁵⁰ reproduced well the geometry of the crystal structure of Ir(B(pin))₃(^tBu-bpy)(cod).⁵¹ Therefore, all geometry optimizations in this work were performed by the B3PW91-D3 functional in gas phase, using small basis set system named BS-I; in this BS-I, the Stuttgart-Dresden-Bonn basis set⁵² was employed for valence electrons of Ir with the effective core potentials representing its core electrons and 6-31G(d) basis sets were used for other atoms. To evaluate better potential energy, the author also performed benchmark calculations³⁵ and found that the root mean squared error (RMSE) of ω B97XD functional⁵³ was the smallest, where MP4(SDQ)-calculated values were taken as reference. In this work, single-point calculations were performed using the ω B97XD functional where larger basis set system (BS-II) was employed; in the BS-II, two f polarization functions⁵⁴ were added to Ir and 6-311+G(d, p) basis sets were used for other atoms.⁵⁵⁻⁵⁷ Solvation effect (2,2,4-trimethylpentane) was evaluated with polarizable continuum model (PCM)⁵⁸⁻⁶⁰ using the geometries optimized above. In this work, discussion is presented using the Gibbs energy. Thermal correction and entropy contribution to the Gibbs energy were evaluated at 298.15 K and 1 atm, where the translational entropy in solution was corrected by the method of Whiteside and co-workers.⁶¹ All these calculations were carried out using Gaussian09 program.⁶²

The author wish to briefly discuss here the modeling because the author employed AlMe₃ and 1,10-phenanthroline for MAD and tetramethyl-1,10-phenanthroline to reduce the computational cost. It is likely that AlMe₃ exhibits smaller binding energy with the C=O bond of substrate because MAD has electron-withdrawing substituent. However, the author clearly observed significant effect by AlMe₃. The other issue to be considered is the relative energies of TS_{12/13} and TS_{14/15} which are transition state for C–H oxidative addition and that for B–C reductive elimination, respectively. Because the energy difference between TS_{12/13} and TS_{14/15} is small, the author must be afraid that the use of real MAD provides the reverse trend that TS_{12/13} is at lower energy than TS_{14/15}. However, AlMe₃ is less bulky than MAD and the Al-base is more distant from the Ir moiety in TS_{12/13} than in TS_{14/15}, the larger MAD induces larger steric repulsion in TS_{14/15}

than in **TS**_{12/13}, suggesting that the use of MAD does not change the relative stabilities of **TS**_{12/13} and **TS**_{14/15}.

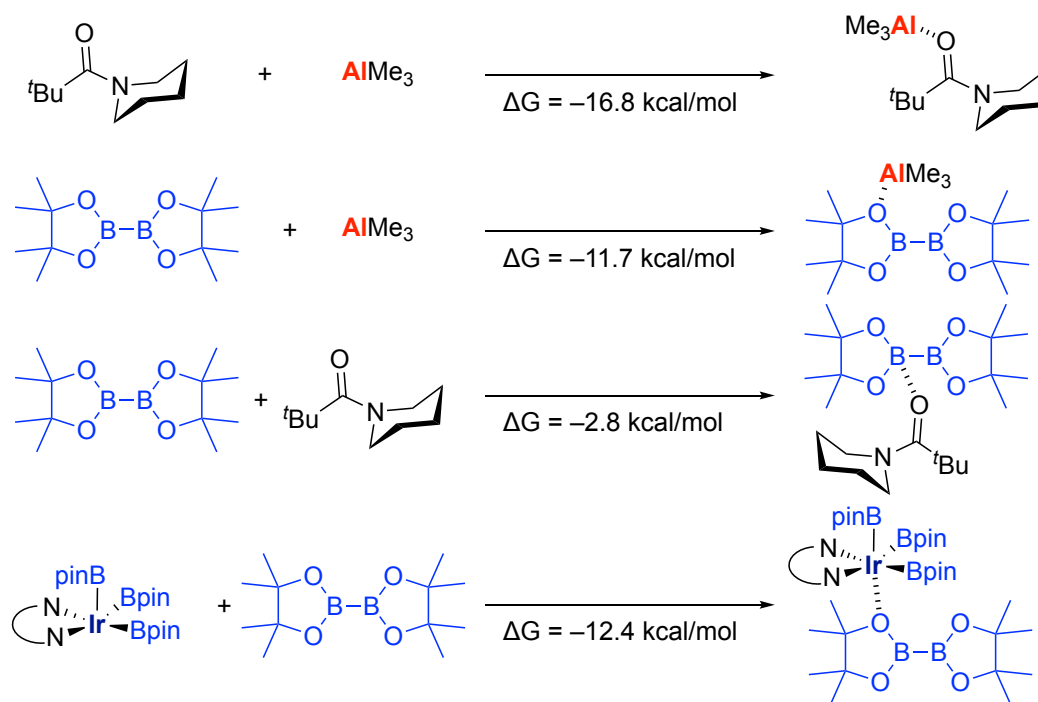


Figure 4-10 Possible Lewis acid-base interactions in the Ir/Al-co-catalyzed C–H borylation.

AlMe_3 can interact with $\text{B}(\text{pin})$ ligated with Ir, but it is likely that the interaction is weaker than that with free $\text{B}_2(\text{pin})_2$ because of the congested geometry. The substrate also interacts with the B atom of $\text{B}_2(\text{pin})_2$, but it is also weaker than the interaction of AlMe_3 with the substrate. On the basis of these computational results, it is concluded that AlMe_3 interacts with the O atom of the substrate.

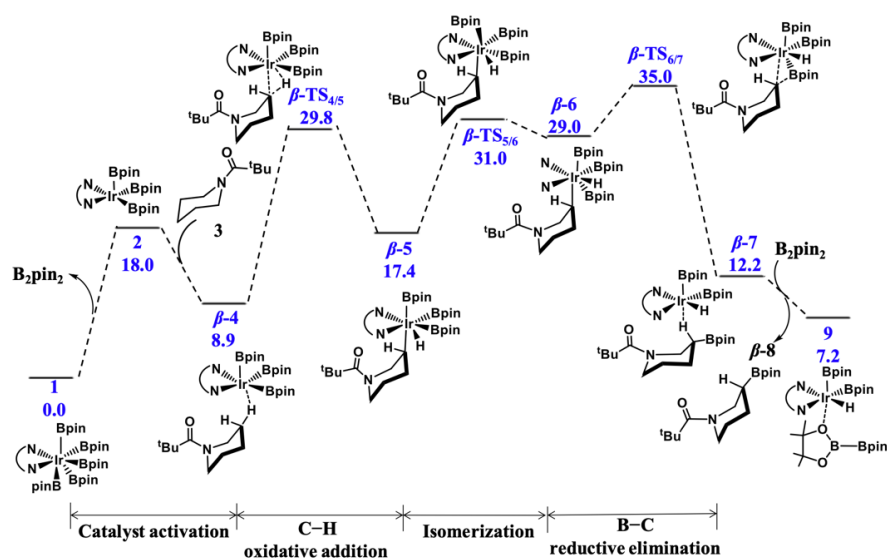
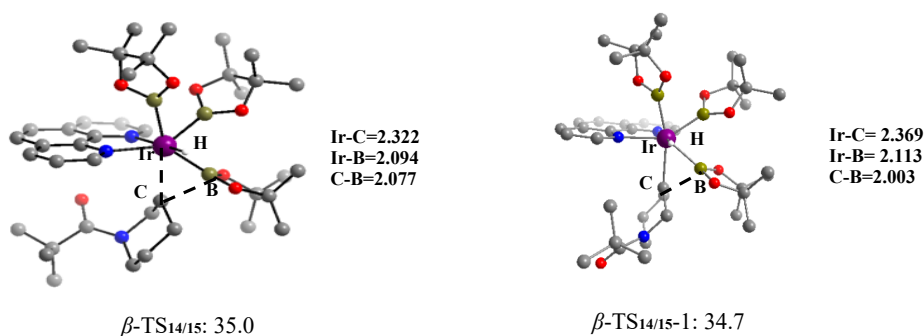


Figure 4-11 Gibbs energy profile (in kcal mol⁻¹) of iridium(III)-catalyzed β -C(sp³)-H borylation of *N*-pivaloylpiperidine (**1b**) in the absence of AlMe₃.

(A) The 3-C interacting β -TS_{14/15} and the 5-C interacting β -TS_{14/15}-1.



(B) The 3-C interacting β -TS_{14/15}[Al] and the 5-C interacting β -TS_{14/15}[Al]-1.

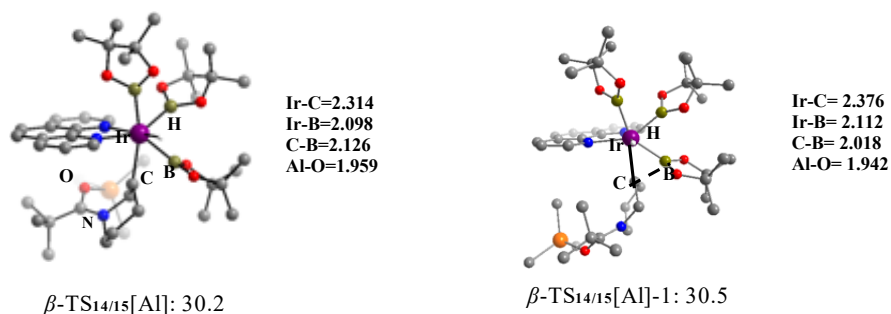


Figure 4-12 Transition state conformations in the reductive elimination step (in kcal mol⁻¹). (A) in the absence of AlMe₃. (B) in the presence of AlMe₃.

4.4.10.2 Kinetic Isotope Effect and Rate-determining step

The kinetic isotope effect was experimentally observed, as mentioned above (Figure 4-8). This kinetic isotope effect suggests that the rate-determining step involves the C–H σ -bond cleavage, in the author's general understanding. However, the kinetic isotope effect can be observed even when C–H σ -bond activation is not involved by the rate-determining step, if the Gibbs energy change occurs as shown in Figure 4-4; in this energy profile, the intermediate **13** after the C–H σ -bond cleavage is in equilibrium with the starting system **10** + substrate and the elementary step, $13 \rightarrow$ the final product, is rate-determining. In the case of energy changes shown in Figure 4-4, the Gibbs energy of activation is determined by the energy difference between TS_{14/15} and the starting system consisting of **10** and substrate. The starting system has C–H σ -bond and TS_{14/15} contains the Ir–H bond. Because the C–H σ -bond exhibits stretching frequency at about 3400 nm⁻¹ and the Ir–H bond exhibits stretching frequency at much lower energy. Accordingly, the kinetic isotope effect can be observed even when the C–H σ -bond activation is not rate-determining. This isotope effect is similar to that observed for the C–H σ -bond activation because the C–H σ -bond has been already broken but the Ir–H bond is almost formed at TS_{12/13} for C–H σ -bond frequency. The essentially the same explanation has been presented recently.³⁵ Hartwig and coworkers explained that the kinetic isotope effect was observed on the basis of kinetics using steady-state approximation when the reaction occurs with the Gibbs energy profile shown by Figure 4-4.⁶³

4.4.10.3 Explanation of Deformation/Interaction Analysis

The activation barrier E_a (in potential energy) is defined as energy difference from the resting state. This E_a differs little from the Gibbs energy for activation ($\Delta G^{\circ\ddagger}$), indicating that the analysis of E_a provides meaningful discussion about the $\Delta G^{\circ\ddagger}$. In this analysis, the author defined activation barrier E_a^1 relative to the active species [(phen)Ir(B(pin))₃], as shown in eq. (1), for convenience;

$$E_a^1 = E_t\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_2(\text{H})(\text{R}\cdots\text{B}(\text{pin}))\}_{\text{TS}} - [E_t\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3\}_{\text{eq}} + E_t(\text{R-H})_{\text{eq}}] \quad (1)$$

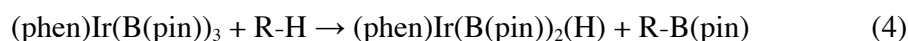
This is no problem for making comparison among α -, β -, and γ -borylation because the E_a is parallel to the E_a^1 . The interaction energy (E_{int}) is defined by eq. (2);

$$E_{\text{int}} = E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_2(\text{H})(\text{R}\cdot\text{B}(\text{pin}))\}_{\text{TS}} - [E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_2(\text{H})\}_{\text{TS}} + E_{\text{t}}\{(\text{R}\cdot\text{B}(\text{pin}))\}_{\text{TS}}] \quad (2)$$

Using eq. (2), eq. (1) is converted, as follows:

$$E_{\text{a}}^1 = [E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_2(\text{H})\}_{\text{TS}} + E_{\text{t}}\{(\text{R}\cdot\text{B}(\text{pin}))\}_{\text{TS}} + E_{\text{int}}] - [E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3\}_{\text{eq}} + E_{\text{t}}(\text{R-H})_{\text{eq}}] \quad (3)$$

The ΔE value is defined using the eq. (4).



$$\Delta E = [E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_2(\text{H})\}_{\text{eq}} + E_{\text{t}}(\text{R-B}(\text{pin}))_{\text{eq}}] - [E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3\}_{\text{eq}} + E_{\text{t}}(\text{R-H})_{\text{eq}}] \quad (5)$$

Also, the deformation energy is defined by eqs. (6) and (7);

$$E_{\text{def-a}} = E_{\text{t}}\{\text{Ir}(\text{NN})(\text{B}(\text{pin}))_2(\text{H})\}_{\text{TS}} - E_{\text{t}}\{\text{Ir}(\text{NN})(\text{B}(\text{pin}))_2(\text{H})\}_{\text{eq}} \quad (6)$$

$$E_{\text{def-b}} = E_{\text{t}}\{\text{R-B}(\text{pin})\}_{\text{TS}} - E_{\text{t}}\{\text{R-B}(\text{pin})\}_{\text{eq}} \quad (7)$$

where the subscripts “def-a” and “def-b” represent deformation energies of $(\text{phen})\text{Ir}(\text{B}(\text{pin}))_2(\text{H})$ and R-B moieties, respectively. Then, eq. (3) is converted, as follows:

$$E_{\text{a}}^1 = [E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_2(\text{H})\}_{\text{eq}} - E_{\text{t}}\{(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3\}_{\text{eq}}] + E_{\text{def-a}} + E_{\text{def-b}} + E_{\text{int}} + E_{\text{t}}\{(\text{R}\cdot\text{B}(\text{pin}))\}_{\text{eq}} - E_{\text{t}}(\text{R-H})_{\text{eq}} = \Delta E + E_{\text{def-a}} + E_{\text{def-b}} + E_{\text{int}} \quad (8)$$

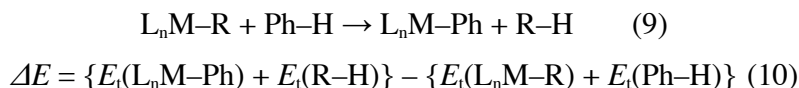
4.4.10.4 The reason why the author discuss the Ir–C and Ir–C[Al] interactions by separating Ir and C (or C[Al]) in a homolytic manner and the author employed SOMO energy of R group for discussing the Ir–R interaction

There are two methods to evaluate the bond energy; in one, the Ir–C is separated into Ir cation moiety and C anion moiety in a heterolytic manner. In the other, the Ir–C is separated into two neutral species (radicals) in a homolytic manner. In this work, the

author separated the Ir–C in a homolytic manner. Sakaki and co-workers already discussed the reasons and the discussion about the bond strength can be presented in a reasonable way by the homolytic separation, in the recent work.³⁵ The author will present brief discussion below:

The author employed the SOMO energy of R radical in the author's discussion. However, the author do not think that radical species are involved in this reaction. It is not the reason why the author employed the SOMO of R radical for the discussion. The author employed the SOMO energy of R radical as a measure of valence orbital of the R group.

In many cases, eq. (9) has been used to discuss the difference in strength between M–R and M–Ph bonds.



This ΔE is related to the difference in bond energy between the M–Ph and M–R bonds when the author employ eq. (11) for defining the M–Ph and M–R bond energies.

$$\text{BDE}(\text{L}_n\text{M–R}) = E_t(\text{L}_n\text{M–R}) - \{E_t(\text{L}_n\text{M}\cdot) + E_t(\text{R}\cdot)\} \quad (11)$$

This definition is reasonable when M–R bond is understood to be covalent bond but is not when M–R is ionic bond. I will describe the reason why the author employed this definition, below.

Eq. (10) can be converted to eq. (12) using eq. (11), as follows:

$$\begin{aligned} \Delta E &= \{E_t(\text{L}_n\text{M–Ph}) + E_t(\text{R–H})\} - \{E_t(\text{L}_n\text{M–R}) + E_t(\text{Ph–H})\} \\ &= [\{E_t(\text{L}_n\text{M}\cdot) + E_t(\text{Ph}\cdot) + \text{BDE}(\text{L}_n\text{M–Ph})\} + E_t(\text{R–H})] - [\{E_t(\text{L}_n\text{M}\cdot) + E_t(\text{R}\cdot) + \text{BDE}(\text{L}_n\text{M–R})\} + E_t(\text{Ph–H})] \\ &= \{E_t(\text{Ph}\cdot) + \text{BDE}(\text{L}_n\text{M–Ph}) + E_t(\text{R–H})\} - \{E_t(\text{R}\cdot) + \text{BDE}(\text{L}_n\text{M–R}) + E_t(\text{Ph–H})\} \quad (12) \end{aligned}$$

Here, the BDE(R–H) is defined, as follows:

$$\text{BDE}(\text{R–H}) = E_t(\text{R–H}) - \{E_t(\text{R}\cdot) + E_t(\text{H}\cdot)\} \quad (13)$$

This definition is reasonable because the R–H bond is covalent in almost all cases. Using eq. (13), ΔE is further converted to eq. (14), as shown in eq. (14), starting from eq. (12);

$$\begin{aligned}\Delta E &= \text{BDE}(\text{L}_n\text{M–Ph}) - \text{BDE}(\text{L}_n\text{M–R}) + E_t(\text{Ph}\cdot) - E_t(\text{R}\cdot) + E_t(\text{R–H}) - E_t(\text{Ph–H}) \\ &= \text{BDE}(\text{L}_n\text{M–Ph}) - \text{BDE}(\text{L}_n\text{M–R}) + E_t(\text{Ph}\cdot) - E_t(\text{R}\cdot) + \{\text{BDE}(\text{R–H}) + E_t(\text{R}\cdot) + E_t(\text{H}\cdot)\} - \\ &\quad \{\text{BDE}(\text{Ph–H}) + E_t(\text{Ph}\cdot) + E_t(\text{H}\cdot)\} \\ &= \text{BDE}(\text{L}_n\text{M–Ph}) - \text{BDE}(\text{L}_n\text{M–R}) + \text{BDE}(\text{R–H}) - \text{BDE}(\text{Ph–H}) \quad (14)\end{aligned}$$

Because $\text{BDE}(\text{R–H})$ and $\text{BDE}(\text{Ph–H})$ can be calculated easily, the eq. (14) is useful to evaluate the bond energy difference between $\text{L}_n\text{M–R}$ and $\text{L}_n\text{M–Ph}$. This useful relationship can be presented when the author employed the definitions of eqs. (11) and (13). If the author employed eq. (15) to define the $\text{L}_n\text{M–R}$ bond energy, the author have to use the different definition eq. (16) for R–H bond energy.

$$\text{BDE}(\text{L}_n\text{M–R}) = E_t(\text{L}_n\text{M–Ph}) - \{E_t(\text{L}_n\text{M}^+) + E_t(\text{R}^-)\} \quad (15)$$

$$\text{BDE}(\text{R–H}) = E_t(\text{R–H}) - \{E_t(\text{R}^-) + E_t(\text{M}^+)\} \quad (16)$$

In this case, eq. (14) is obtained from eq. (1), using eqs. (15) and (16). In other words, if the author take eq. (15) because this is coordinate bond, then eq. (16) must be used to discuss $\text{BDE}(\text{M–Ph})$ and $\text{BDE}(\text{M–R})$. If the author think that eq. (13) is reasonable, then the author have to use eq. (11) for evaluating M–R bond energy.

Here, the author took the definition of eq. (13) (not eq. (16)), because the R–H bond should be considered to be covalent. In this case, the author took the definition of eq. (11) for the M–R bond. This is not very unreasonable because the M–R bond has characters of both coordinate bond and covalent bond. Ziegler and coworkers evaluated the M-alkyl bond energy using alkyl radical like in our work. The author wish to state that the combination of eqs. (11) and (13) provides the correct understanding of eq. (10) and also the combination of eqs. (15) and (16) provides the correct understanding of eq. (10) and both combinations provide essentially the same discussion on the bond energy.

4.4.10.5 Discussion of the Ir–C and Ir–C[Al] interactions

The Ir–C bond energy was calculated by the homolytic splitting shown in Figure 4-14. This separation differs from that of energy decomposition analysis. If the author separated TS into two moieties like in the energy decomposition analysis, the Ir–C bond energy must be calculated between (phen)Ir(B(pin))₂(H) and R (R–H = substrate). The (phen)Ir(B(pin))₂(H) is a distorted Ir(III) complex which has a closed-shell singlet electronic state. If the author can calculate the triplet state of (phen)Ir(B(pin))₂(H) which has one SOMO extending toward R and the other SOMO extending toward B(pin), the author can use the orbital energy as valence orbital energy for the Ir–C bond. However, such localized valence orbitals cannot be obtained generally. Here, the author calculated the Ir–C bond energy using assumed equations shown in Figure 4-14. Though this separation differs from that of the deformation/interaction energy analysis, this bond energy is not unreasonable because the Ir–B(pin) bond energy is similar between the presence and the absence of aluminum Lewis acid. Also, this bond energy involves the R–B(pin) interaction which also influences the stability of TS. The bond energy difference between the presence and the absence of aluminum Lewis acid is 8.9 kcal/mol, which is almost the same as the difference (8.7 kcal/mol) in E_{int} between β -TS_{14/15}[Al] and β -TS_{14/15}. This agreement strongly suggests that this bond energy is useful for discussing the effects of aluminum Lewis acid.

Explanation of relation between covalent bond energy and valence orbital energy gap

Here, the sp³ orbital energy (in eV) of neutral radical was discussed as valence orbital energy. As expected, the valence orbital energy of (phen)Ir(B(pin))₃(H) differs little between β -TS_{14/15} and β -TS_{14/15}[Al]. As shown in Figure 4-13, the Ir–C[Al] interaction is stronger than the Ir–C interaction. The covalent bond energy is approximately represented by eq. (17) on the basis of the simple Hückel MO method, where ε_A and ε_B are the orbital energies of the SOMOs and β is the resonance integral;

$$\Delta E_{\text{cov}} = \sqrt{(\varepsilon_A - \varepsilon_B)^2 + 4\beta^2} \quad (17)$$

This eq. (17) indicates that the larger energy difference between two valence orbitals A and B leads to the larger covalent bond energy. Because the valence orbital energy of C[Al] is calculated at lower energy than that of C without Al (Figure 4-14) and both are at lower energy than that of (phen)Ir(B(pin))₃(H), the energy difference between the Ir

valence orbital and that of the C[Al] is larger than that between the Ir and the C valence orbitals. Therefore, the Ir–C[Al] interaction is stronger than the Ir–C.³⁵

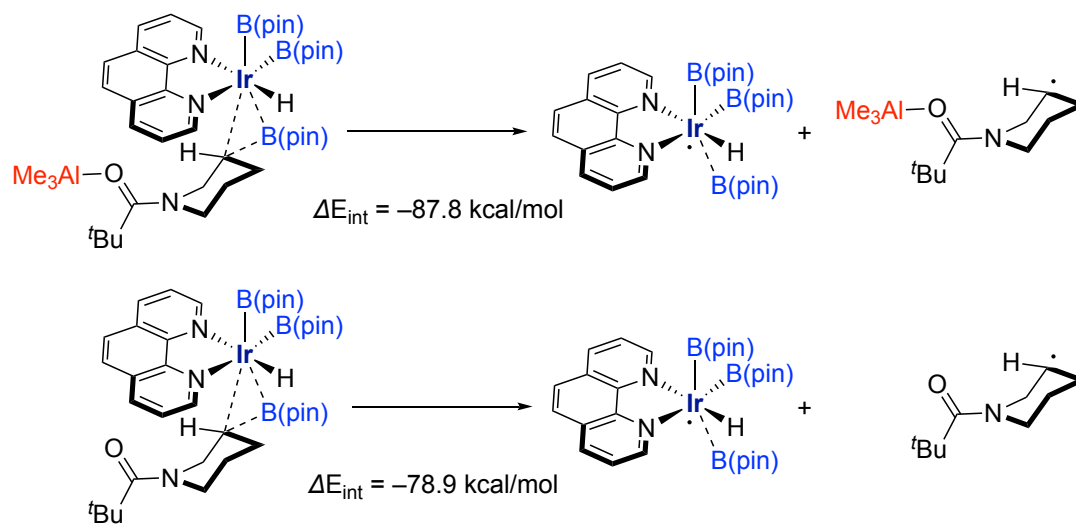
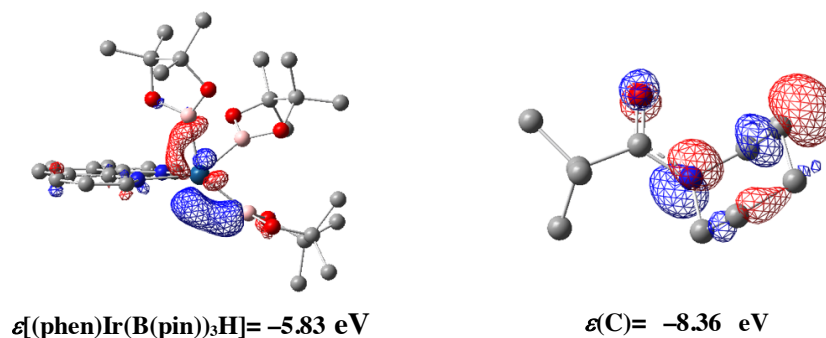


Figure 4-13 The bond energy of Ir–C and Ir–C[Al] interactions

(A) β -TS_{14/15}



(B) β -TS_{14/15}[Al]

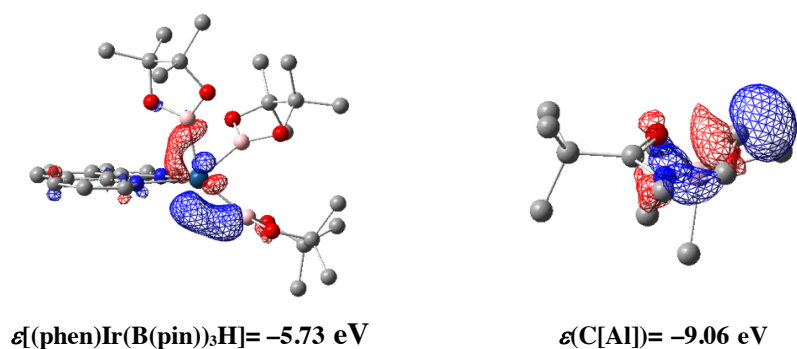
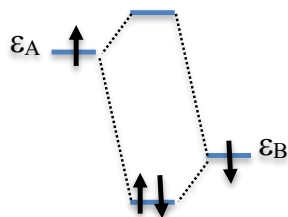


Figure 4-14 Valence orbital energies. (A) in the absence of AlMe_3 . (B) in the presence of AlMe_3 .

4.4.10.6 Brief explanation of eq. (17)

The eq. (17) seems inconsistent with the author's intuitive understanding of the interaction energy because the energy difference between bonding and anti-bonding MOs is the largest when two orbitals have the same orbital energy. However, the energy stabilization of two electrons which occupy one valence orbital A and the other valence orbital B is represented by eq. (17) on the basis of simple Hückel MO method.

$$\epsilon^a = (1/2)[(\epsilon_A + \epsilon_B) + \{(\epsilon_A - \epsilon_B) + 4\beta^2\}^{1/2}] \quad (18a)$$



$$\epsilon^b = (1/2)[(\epsilon_A + \epsilon_B) - \{(\epsilon_A - \epsilon_B) + 4\beta^2\}^{1/2}] \quad (18b)$$

The total stabilization energy ΔE by two electrons is represented, as shown below:

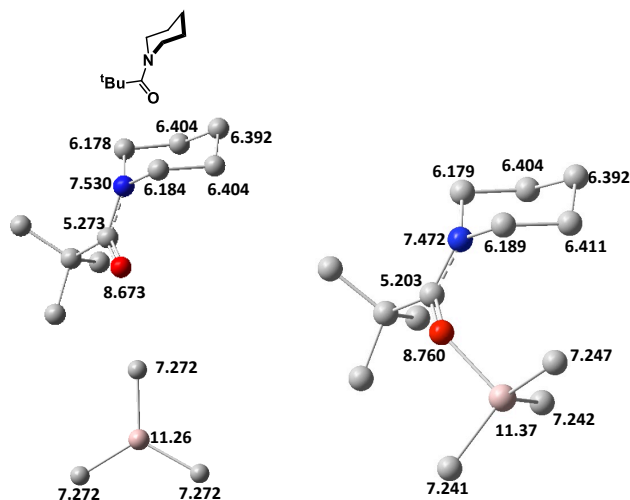
$$\Delta E = (\epsilon_A + \epsilon_B) - 2 \times (1/2)[(\epsilon_A + \epsilon_B) - \{(\epsilon_A - \epsilon_B) + 4\beta^2\}^{1/2}] = \{(\epsilon_A - \epsilon_B) + 4\beta^2\}^{1/2}$$

When ϵ_A becomes the same as ϵ_B , the $\epsilon_B - \epsilon^b$ becomes large but the $\epsilon_A - \epsilon^b$ becomes small. The eq. (17) is similar to the definition of electronegativity by Pauling; in his definition, the strong covalent bond is formed when the electronegativity is different between two atoms.

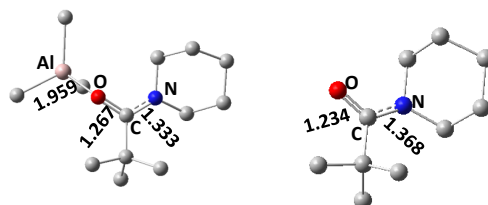
4.4.10.7 Brief discussion about the difference in β -C(sp³) valence orbital energy

The NBO C^β -atomic population little differs between the presence and the absence of AlMe₃ but the N -atomic population decreases by the interaction with AlMe₃ compared to that without AlMe₃ (Figure 4-15 (A)). Accordingly, the N p_π orbital energy becomes lower, which weakens the anti-bonding overlap of the N p_π with the β -C(sp³) orbital (Figure 4-15 (C)). In other words, the inductive effect of AlMe₃ does not directly influence the C^β atomic charge but decreases the N negative charge to lower the N p orbital energy and therefore lower the β -C(sp³) orbital. This is the reason why the β -C(sp³) orbital exists at lower energy in the presence of AlMe₃ than in the absence of AlMe₃.

(A) NBO atomic population of substrate with and without AlMe₃



(B) Geometries of substrates with and without AlMe₃



(C) β -C(sp³) valence orbitals with and without AlMe₃

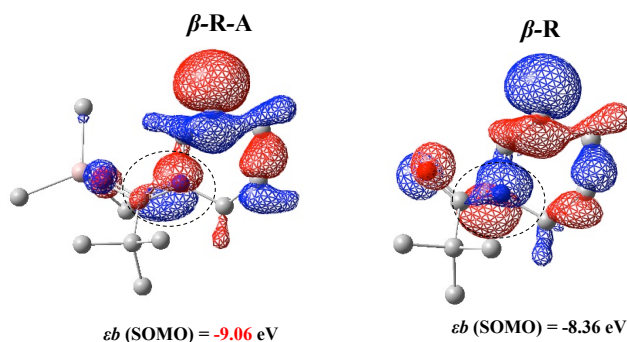


Figure 4-15 Comparisons of NBO atomic charges, geometries, and β -C(sp³) valence orbitals between substrates with and without AlMe₃.

4.4.10.8 Regioselectivity for α -, β - and γ -borylation

Because the B–C reductive elimination is a rate-determining step in all these cases, the author compared the transition states among α -, β - and γ -borylations. Apparently, β -TS_{14/15}[Al] is at lower energy than α -TS_{14/15}[Al] and γ -TS_{14/15}[Al], which is consistent with experimental results that C–H borylation occurred with complete β -selectivity. As shown in Figure 4-16, important geometrical parameters of these three

transition states do not differ very much. The author employed the deformation/interaction energy analysis here, separating the reaction system into the (Phen)Ir(H)(B(pin))₂ (**frag-a**) and R[Al]...B(pin) (**frag-b**) moieties. As listed in Figure 4-4 (B), α -TS_{14/15}[Al] is less stable than β -TS_{14/15}[Al] mainly because $E_{\text{def-b}}$ is larger in the former TS than in the latter one. This feature seems to arise from steric repulsion between ^tBu-carbonyl and boryl groups (Figure 4-16). Also, the E_{int} of α -TS_{14/15}[Al] is less negative than in β -TS_{14/15}[Al], indicating that the Ir–C[Al] interaction is weaker in α -TS_{14/15}[Al] than in β -TS_{14/15}[Al]. This weaker interaction in α -TS_{14/15}[Al] arises from the higher valence orbital energy of C ^{α} [Al] group than C ^{β} [Al] because the higher valence orbital energy leads to the presence of smaller energy difference from the valence orbital of the Ir center. It is concluded that both electronic and steric effects are responsible for the easier β -borylation than the α -one.

In the γ -borylation, the situation differs a little; the steric repulsion between AlMe₃ and ligand is small because AlMe₃ exists at a distant position from the ligand group in this case (Figure 4-16). Even though AlMe₃ is distant from the boryl group, γ -TS_{14/15}[Al] is less stable than β -TS_{14/15}[Al]. The deformation/interaction energy analysis clearly indicates that E_{int} is less negative in γ -TS_{14/15}[Al] than in β -TS_{14/15}[Al]. This result arises from the higher valence orbital energy of C ^{γ} [Al] group than C ^{β} [Al]. In other words, electronic effect is responsible for the β -regioselectivity.

The next question is the reason why the valence orbitals of C ^{α} [Al] and C ^{γ} [Al] groups are at higher energy than that of C ^{β} [Al]. The valence orbital of C ^{α} [Al] induces anti-bonding overlap with the N lone pair and accordingly its energy becomes higher. This was discussed recently by the previous work on the β -regioselective borylation of THF.³⁵ This anti-bonding orbital overlap does not induce the difference between C ^{β} [Al] and C ^{γ} [Al]. One of the plausible reasons is the inductive effect because the C ^{β} is influenced by the effect of electron-withdrawing N atom more than the C ^{γ} . However, the NBO atomic population is 6.184, 6.408, and 6.392 for α -, β - and γ -C atoms, respectively, indicating that the inductive effect of the N is not responsible for the difference in the C sp³ orbital energy between the C ^{β} [Al] and C ^{γ} [Al]. As shown in Figure 4-17, the sp³ orbital of the C ^{β} atom suffers from one anti-bonding overlap with one neighboring C–C bond but that of the C ^{γ} atom suffers from two anti-bonding overlaps with two neighboring C–C bonds. This is reasonable because the N atom has valence orbital at lower energy than the C atom due to its large electronegativity. Accordingly, the C ^{γ} (sp³) orbital exists at higher

energy than the $C^\beta(sp^3)$ orbital.

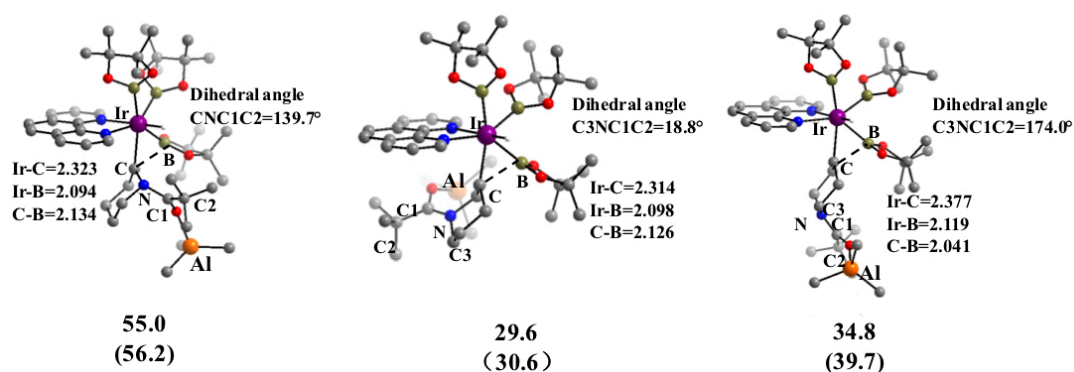
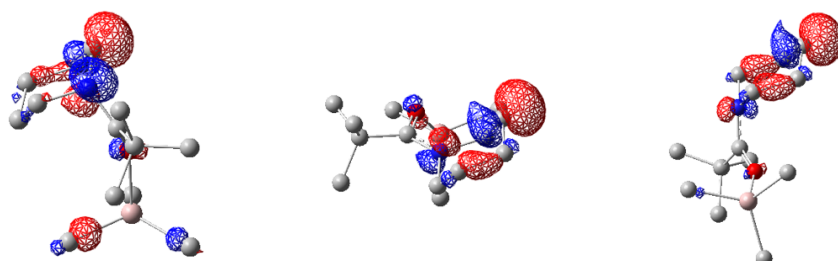
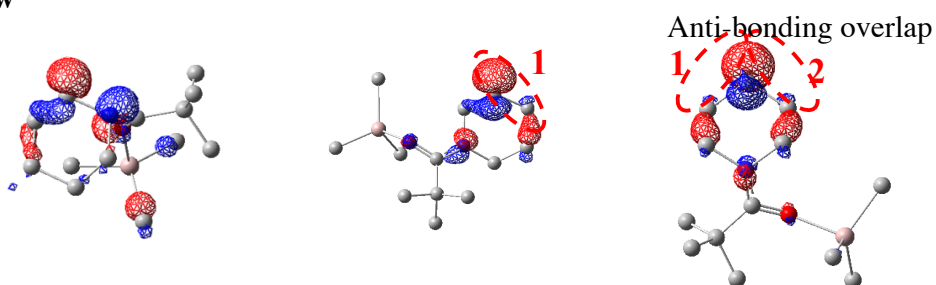


Figure 4-16 Important geometrical parameters and Gibbs energy of α -TS_{14/15}[Al], β -TS_{14/15}[Al] and γ -TS_{14/15}[Al] relative to the resting state (potential energy is shown in the parentheses).

Side-view



Top-view

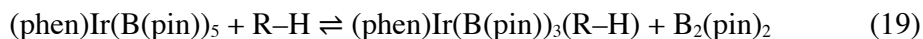


$$\epsilon(\text{frag-b})-\alpha = -8.46 \text{ eV} \quad \epsilon(\text{frag-b})-\beta = -9.06 \text{ eV} \quad \epsilon(\text{frag-b})-\gamma = -8.75 \text{ eV}$$

Figure 4-17. Valence orbital energies of frag-b ($C[AlMe_3]$) at α -, β - and γ -positions.

4.4.10.9 Brief discussion about the pentaboryl resting state

As mentioned in Figure 4-4, the author proposed the pentaboryl complex (phen)Ir(B(pin))₅ as a resting state, resulting from theoretical calculations.



As shown in Figure 4-4 (A), the right-hand side has 2.5 kcal/mol higher energy than the left-hand side, so the equilibrium constant K (defined as K_{cal}) of eq. (19) is calculated as follow,

$$K_{\text{cal}} = \exp(-\Delta G^\circ/RT) = \exp\left(\frac{-2.5 \times 1000 \times 4.21}{8.31 \times 373}\right) = 0.034$$

To provide experimental evidence for this, the author conduct kinetic experiments (see Figure 4-9).

$$v = k[(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3(\text{R-H})] \quad (20)$$

$$[\text{Ir total}] = [(\text{phen})\text{Ir}(\text{B}(\text{pin}))_5] + [(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3(\text{R-H})] \quad (21)$$

$$K = \{[(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3(\text{R-H})][\text{B}_2(\text{pin})_2]\} / \{[(\text{phen})\text{Ir}(\text{B}(\text{pin}))_5][\text{R-H}]\} \quad (22)$$

From eq. (22),

$$[(\text{phen})\text{Ir}(\text{B}(\text{pin}))_5] = \{[(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3(\text{R-H})][\text{B}_2(\text{pin})_2]\} / \{K[\text{R-H}]\} \quad (23)$$

Using eq. (23), eq. (21) is converted as follows:

$$[\text{Ir total}] = \{[(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3(\text{R-H})][\text{B}_2(\text{pin})_2]\} / \{K[\text{R-H}]\} + [(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3(\text{R-H})] \quad (24)$$

Thus,

$$[(\text{phen})\text{Ir}(\text{B}(\text{pin}))_3(\text{R-H})] = [\text{Ir total}][\text{R-H}] / \{[\text{R-H}] + [\text{B}_2(\text{pin})_2]/K\} \quad (25)$$

Using this equation, eq. (20) is converted as follows:

$$v = k[\text{Ir total}][\text{R-H}]/\{[\text{R-H}] + [\text{B}_2(\text{pin})_2]/K\} \quad (26)$$

In the author's kinetic experiment, the molality of the substrate [R-H] is 0.15 mol/kg, and the range of [B₂(pin)₂] is between 0.29 and 0.51 mol/kg. From these results and eq. (26), the experimental value of K is calculated as 0.05. This result is in good agreement with K_{cal}.

4.4.10.10 Brief discussion about a transition state of an enantio-determining step

To gain insight into the stereochemical outcome, the author carried out a computational study. DFT calculations of racemic C-H borylation process using aluminum co-catalyst indicated that the rate-determining step was reductive elimination (See Figure 4-4). Based on these results, the author assumed that reductive elimination step would be the rate and enantio-determining in this enantioselective process (Figure 4-18 (B)).

The author wish to briefly discuss the modeling because the author employed chiral aluminum having SiMe₃ (TMS) group instead of SiⁱPr₃ (TIPS) group to reduce computational costs (Figure 4-18 (A)).

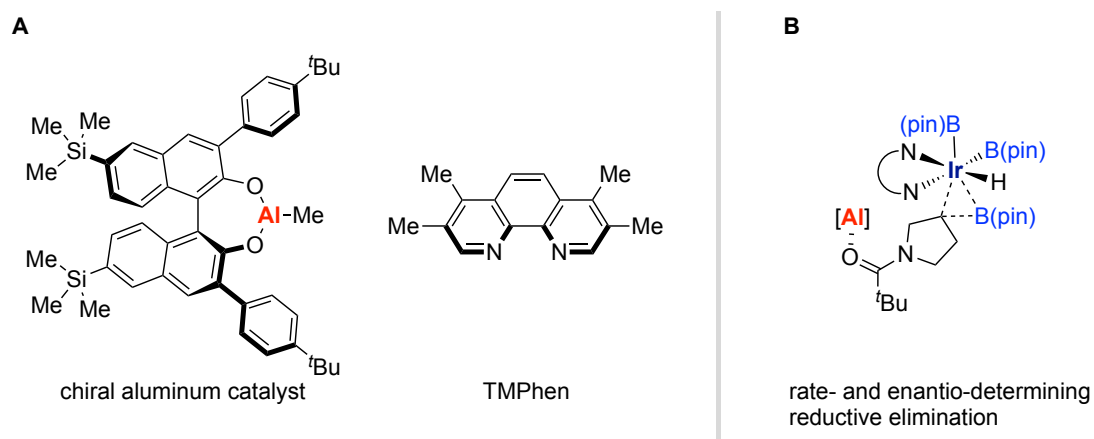


Figure 4-18. (A) Catalyst structures used in DFT calculations. (B) TS structure for rate- and enantio-determining C–B bond-forming reductive elimination.

The author calculated the TS structures in the C–B bond-forming reductive elimination step. The DFT calculations have clearly indicated that the transition state

leading to the *S* enantiomer (Figure 4-19, right) is more favorable than the *R* enantiomer (Figure 4-19, left), being consistent with the author's experimental results (Figure 4-3). The length of C–B bond in TS_{minor} is longer than that in TS_{major} due to the steric congestion between *t*Bu group of the Al-BINOLate catalyst and the B(pin) group bound to the Ir center, which should contribute to the destabilization of TS_{minor} (Figure 4-19).

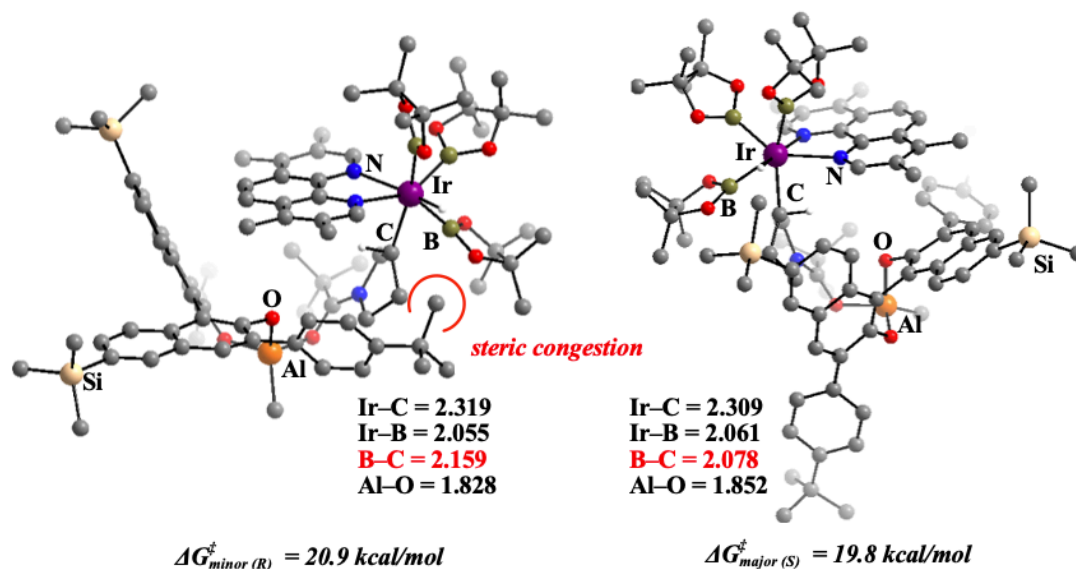
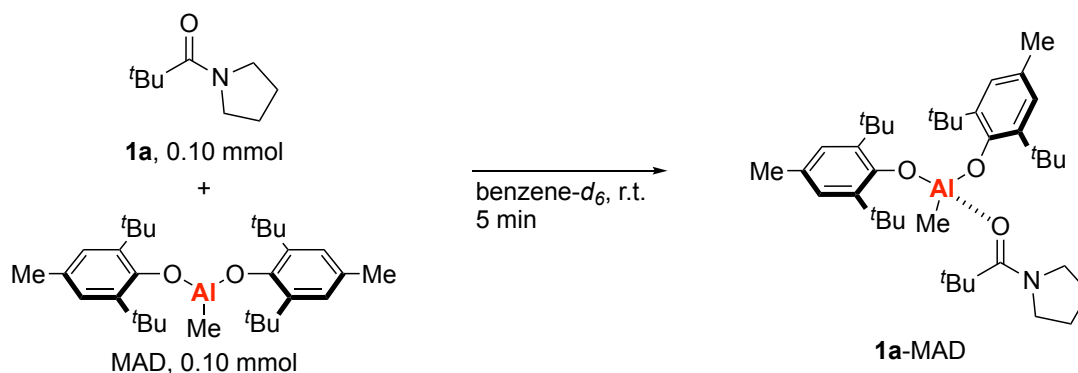


Figure 4-19 Transition state conformations in the reductive elimination step. (Left) TS_{minor} (Right) TS_{major} (S)

1.1.1 NMR Studies on an Aluminum Turnover

As the author showed in the main text, the use of a catalytic amount of MAD was sufficient for the full conversion of the substrate. This observation clearly shows the turnover of the MAD catalyst. To verify this, the author conducted some NMR experiments using **1a**, **2a**, and MAD. First, the author mixed **1a** and **2a** with MAD respectively in benzene-*d*₆ at ambient temperature (*ca.* 20 °C, Scheme 4-1 and Scheme 4-2). Next, the author mixed **2a** with MAD to form a **2a**–MAD adduct, to which **1a** was added, and the author observed an equilibrium between **2a**–MAD and **1a**–MAD (Scheme 4-3). These results clearly support the turnover of MAD. Detailed reaction conditions for each experiment were shown below.

4.4.10.11 Formation of 1a–MAD Adduct



Scheme 4-1 Interaction between **1a** and MAD

In a nitrogen-filled glovebox, a 4 mL vial equipped with a stirrer bar was charged with **1a** (0.100 mmol, 15.5 mg), MAD (0.100 mmol, 48.1 mg), and benzene- d_6 (1.0 mL). The resulting solution was stirred for 5 min at ambient temperature and analyzed by ^1H NMR. ^1H NMR (400 MHz, benzene- d_6): δ 7.18 (s, 4H), 3.10 (t, $J = 6.9$ Hz, 2H), 2.56 (t, $J = 6.5$ Hz, 2H), 2.36 (s, 6H), 1.60 (s, 36H), 0.92 (s, 9H), 0.90–0.78 (m, 4H), 0.18 (s, 3H).

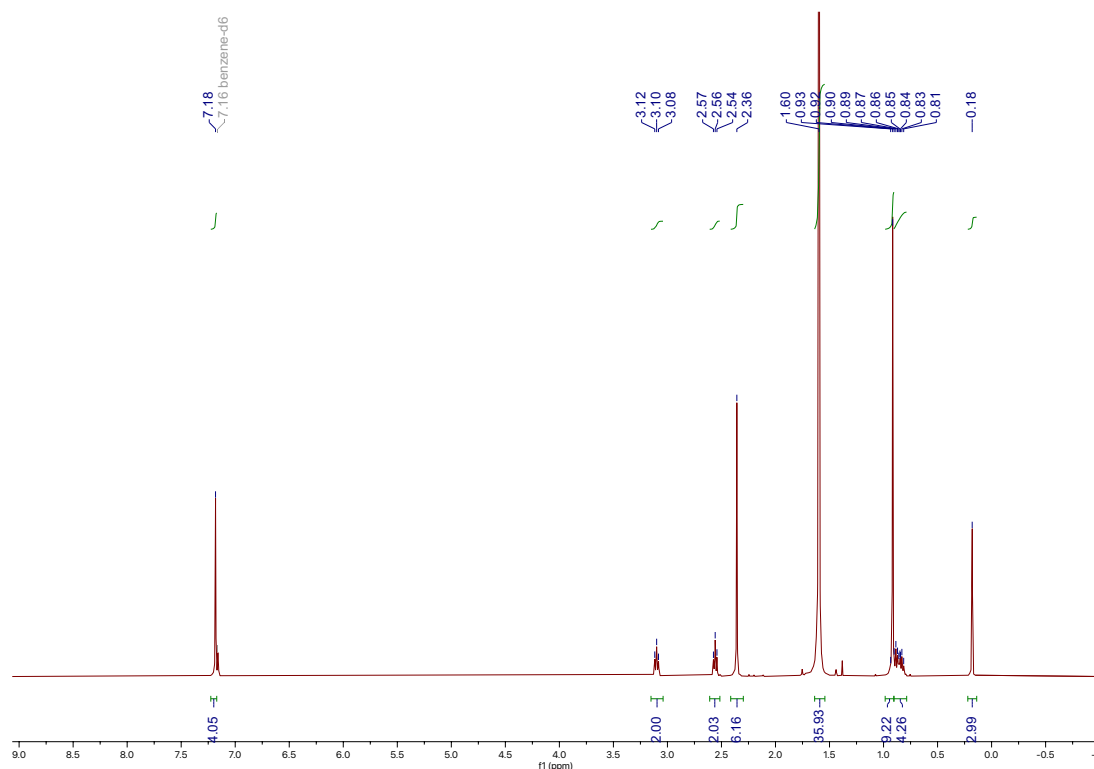


Figure 4-20 ^1H NMR of **1a**–MAD

Reaction scheme showing the synthesis of **2a-MAD** from **2a** and MAD.

Reactants:

- 2a** (0.10 mmol): A pinacol boronate ester derivative.
- MAD (0.10 mmol): A diaryl ether derivative.

Reaction conditions:

- benzene-*d*₆, r.t.
- 5 min

Product: **2a-MAD** (labeled **2a-MAD** in blue).

¹H NMR Spectrum (CDCl₃)

Chemical Shifts (ppm): 7.14, 7.11, 7.09, 7.09, 3.58, 3.55, 3.44, 3.42, 3.38, 3.36, 3.35, 3.32, 3.19, 3.18, 3.17, 3.15, 3.14, 3.12, 3.11, 3.10, 2.96, 2.86, 2.85, 2.83, 2.82, 2.92, 2.91, 2.90, 2.48, 2.46, 2.45, 2.44, 2.43, 2.41, 2.36, 2.33, 2.30, 2.28, 2.25, 1.61, 1.56, 1.49, 1.48, 1.32, 1.31, 1.24, 1.23, 1.21, 1.21, 1.19, 1.07, 0.95, 0.92, 0.89, 0.87, 0.87, 0.87, 0.87.

Integration Values: 3.80, 3.80, 0.14, 0.12, 0.20, 0.75, 1.20, 0.75.

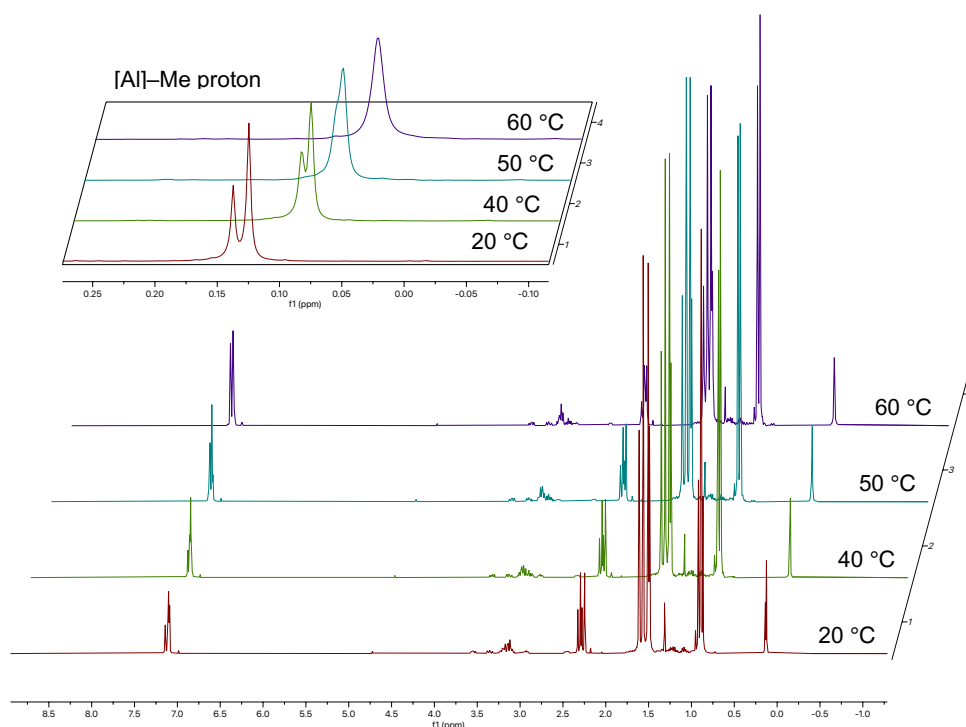
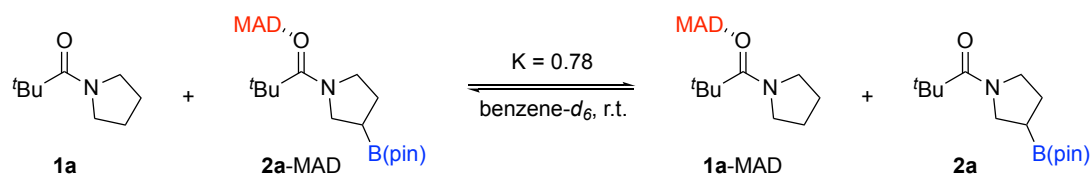


Figure 4-22 VT measurement of **2a**–MAD



Scheme 4-3 Equilibrium among **1a**, **1a**–MAD, **2a**, and **2a**–MAD

In a nitrogen-filled glovebox, a 4 mL vial was charged with **2a** (0.030 mmol, 8.4 mg), MAD (0.0300 mmol, 14.4 mg), and benzene-*d*₆ (1.0 mL). After stirring for 5 min at ambient temperature, ¹H NMR analysis indicated the clean formation of **2a**–MAD. To this solution was added **1a** (0.100 mmol, 15.5 mg), and the resulting mixture was stirred for 5 min at ambient temperature to reach an equilibrium state, and the ratio of integration did not change after 45 min. Based on the signals of the methyl group in MAD at the equilibrium state, **1a**–MAD : **2a**–MAD = 2.77 : 1. Thus, the amount of each species was estimated to be: **1a** (0.0780 mmol), **2a**–MAD (0.00796 mmol), **1a**–MAD (0.0220 mmol), **2a** (0.0220 mmol). Equilibrium constant $K = \{[\text{1a-MAD}] \times [\text{2a}]\} / \{[\text{1a}] \times [\text{2a-MAD}]\} = (0.0220 \times 0.0220) / (0.0780 \times 0.00796) = 0.78$

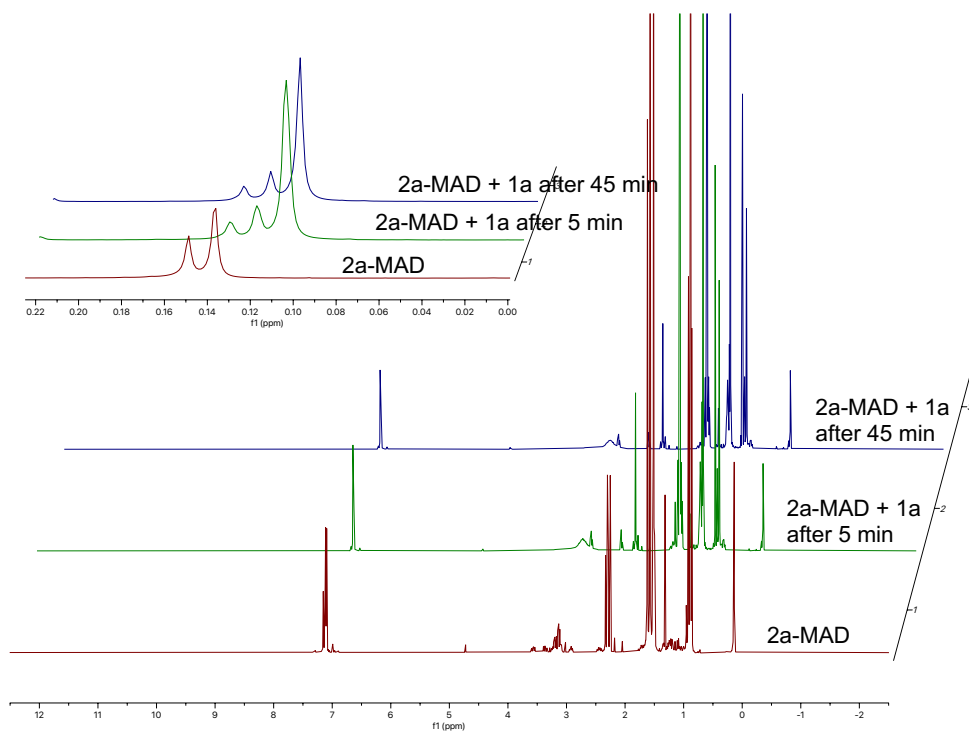


Figure 4-23 Time-course NMR study for the MAD turnover

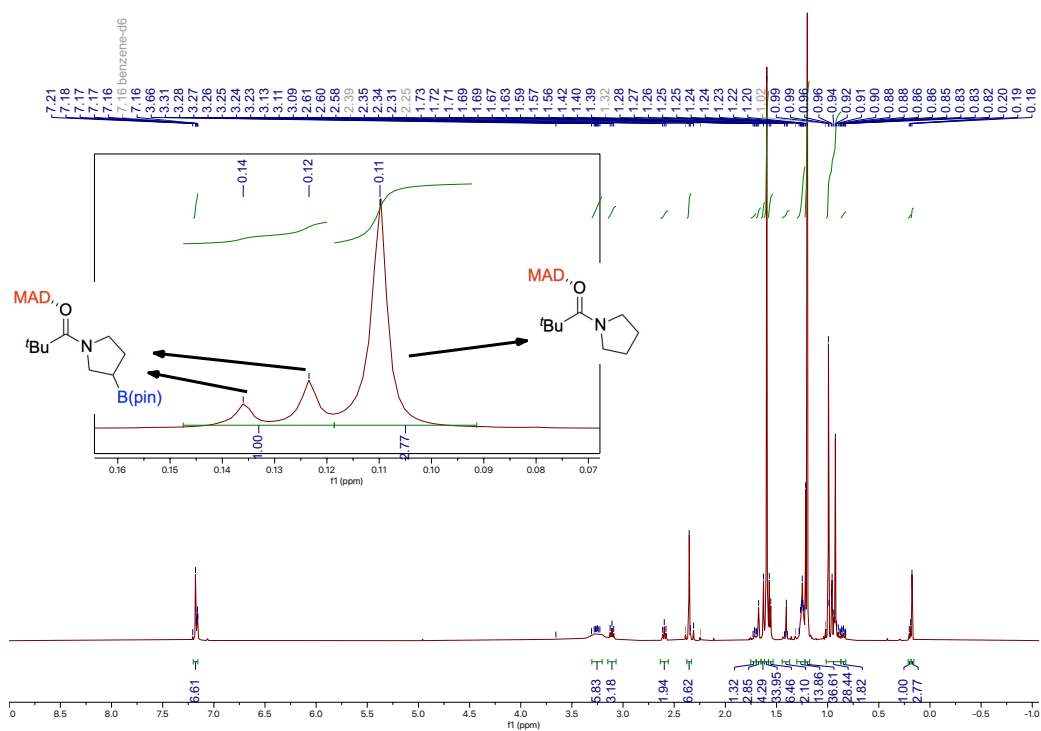
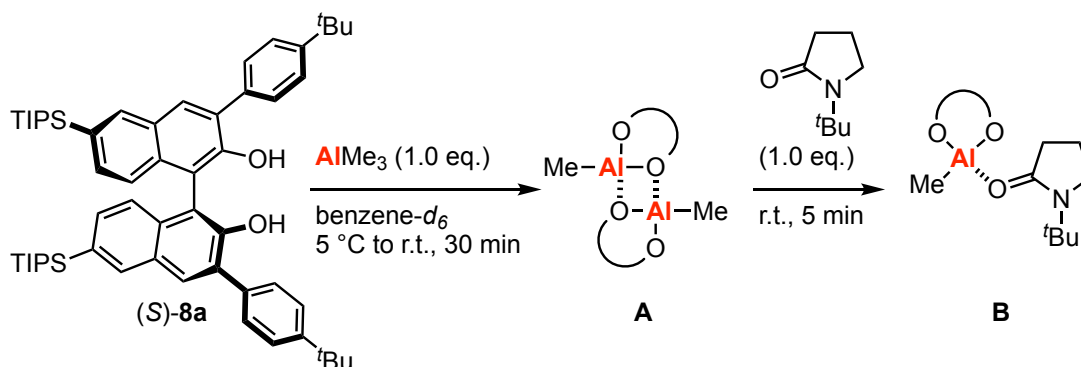


Figure 4-24 ^1H NMR spectra after 45 min aging at ambient temperature

1.1.2 NMR Studies on the Chiral Aluminum Species



To a 4 mL vial containing a solution of **(S)-8a** (0.0300 mmol, 25.9 mg) in $\text{benzene-}d_6$ (0.75 mL) was added AlMe_3 (1.4 M solution in hexane, 0.030 mmol, 22 μL) at 5 °C in a N_2 -filled glove box, and the mixture was warmed to room temperature. After 30 min, the solution was transferred to a J-Young NMR tube and analyzed by ^1H NMR (Figure 4-25, (B)). The spectrum clearly showed the disappearance of phenolic hydroxy groups (5.24 ppm in Figure 4-25, (A)) and the generation of a less symmetric aluminum species **A** consisting of 1:1 ratio of **8a** and the Al-Me group. This result is not consistent with the related study on binaphthol-derived aluminum complexes by Yamamoto and co-workers who reported the generation of a Lewis-acid-assisted Brønsted acid upon mixing equimolar amounts of a binaphthol derivative and AlMe_3 .⁶⁴ On the basis of the previous studies by Harder and co-workers,^{65,66} the author tentatively assigned the structure of **A** as a dimer shown above in which one of the oxygen atoms of the binaphthol bridges the aluminum center with remaining methyl groups being terminal. Upon mixing with a solution of **1m** (0.030 mmol, 4.2 mg) in $\text{benzene-}d_6$ (0.05 mL), the generation of a more symmetric aluminum species **B** consisting of 1:1:1 ratio of **8a**, the Al-Me group and **1m** was observed (Figure 4-25, (C)). Additionally, two enantiotopic pairs of methylene protons of **1m** were split into four diastereotopic protons (blue circle), supporting the formation of a Lewis pair. In light of the related studies,^{67,68} the author assigned the structure of **B** as a Lewis pair consisting of a monomer of **A** and **1m** as shown above.

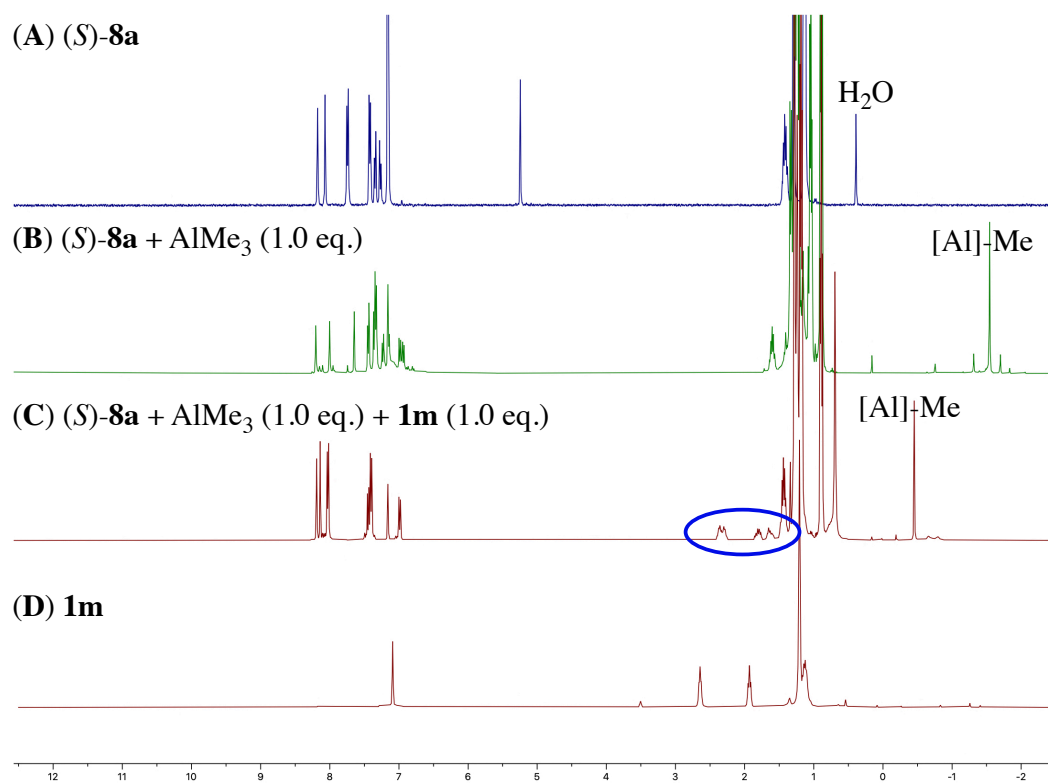


Figure 4-25 ¹H NMR spectra in benzene-*d*₆. (A) (*S*)-**8a**. (B) (*S*)-**8a**+AlMe₃. (C) (*S*)-**8a**+AlMe₃+**1m** (D) **1m**

1.1.3 X-ray Crystallographic Analysis

X-ray data were collected on a Rigaku/Saturn70 CCD diffractometer using graphite-monochromated MoK α radiation ($\lambda = 0.71075 \text{ \AA}$) at 143 K, and processed using CrystalClear (Rigaku).^{69,70} The structures were solved by a direct method using SHELXT-2014/5 program and refinement was carried out by least-squares methods based on F^2 with all measured reflections using SHELXL-2014/7 program.^{71,72} The non-hydrogen atoms were refined anisotropically.

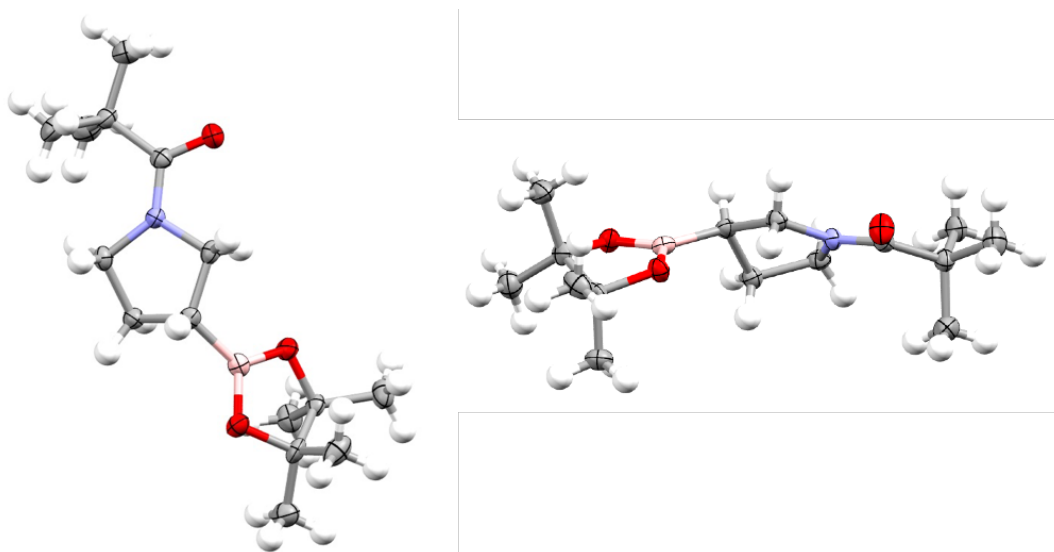


Figure 4-26 Single-crystal X-ray diffraction structure of **2a** (atomic displacement parameters set at 30% probability).

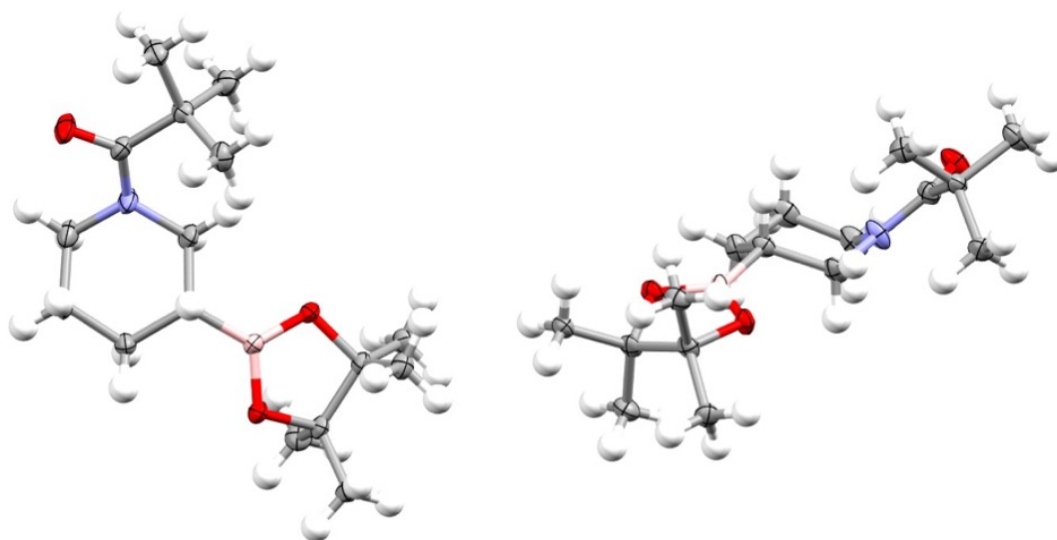


Figure 4-27 Single-crystal X-ray diffraction structure of **2b** (atomic displacement parameters set at 30% probability)

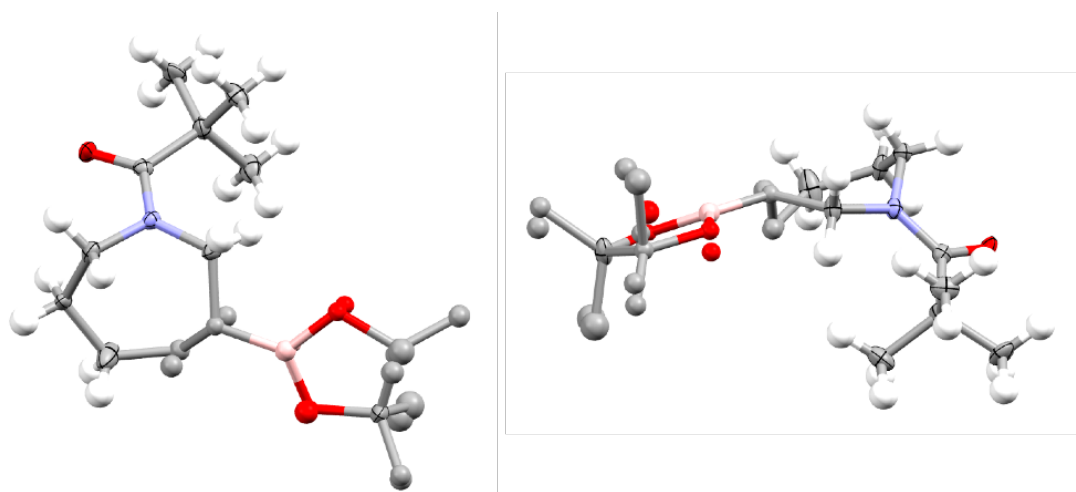


Figure 4-28 Single-crystal X-ray diffraction structure of **2c** (atomic displacement parameters set at 30% probability)

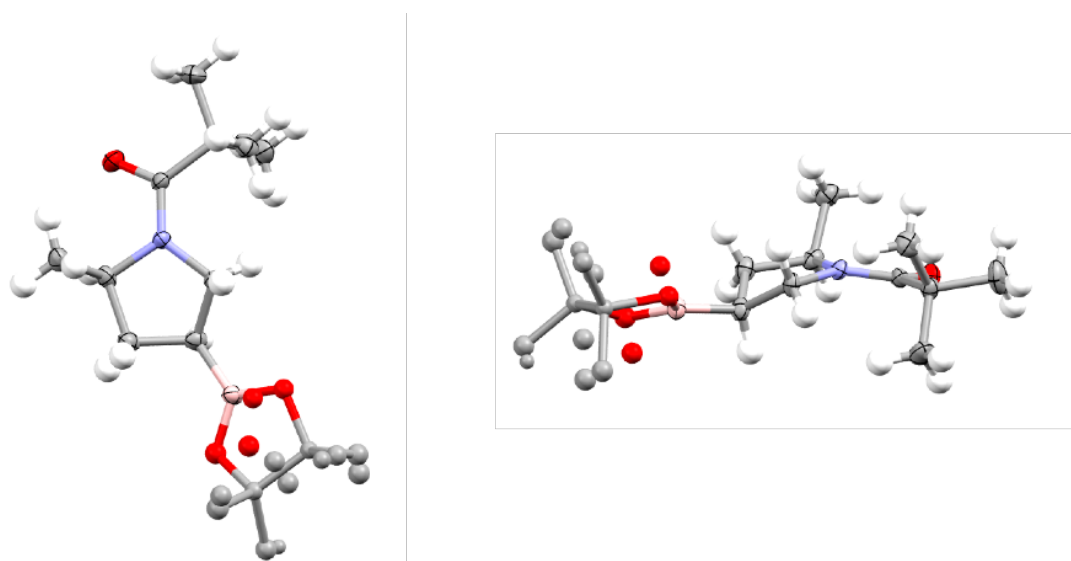


Figure 4-29 Single-crystal X-ray diffraction structure of **2d** (atomic displacement parameters set at 30% probability)

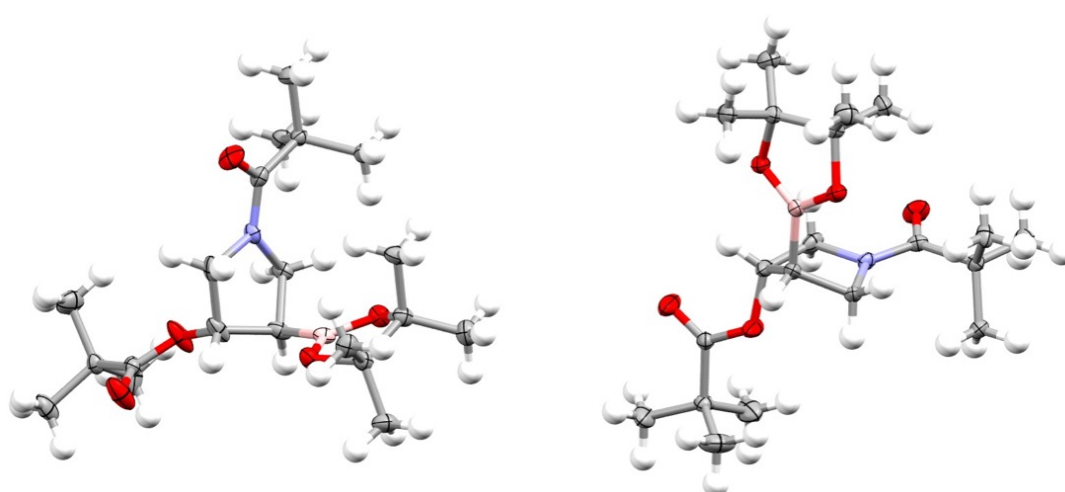


Figure 4-30 Single-crystal X-ray diffraction structure of **2e** (atomic displacement parameters set at 30% probability)

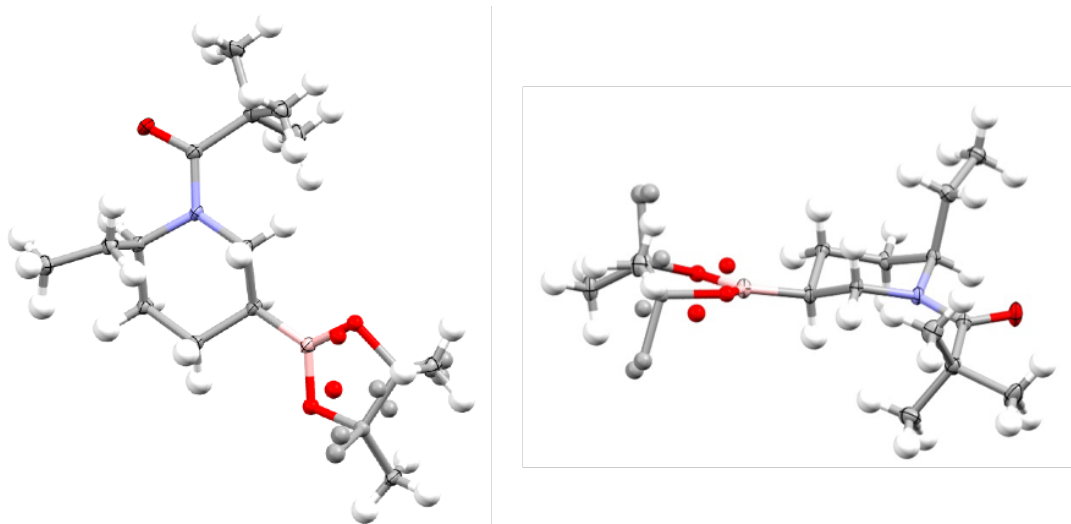


Figure 4-31 Single-crystal X-ray diffraction structure of **2f** (atomic displacement parameters set at 30% probability)

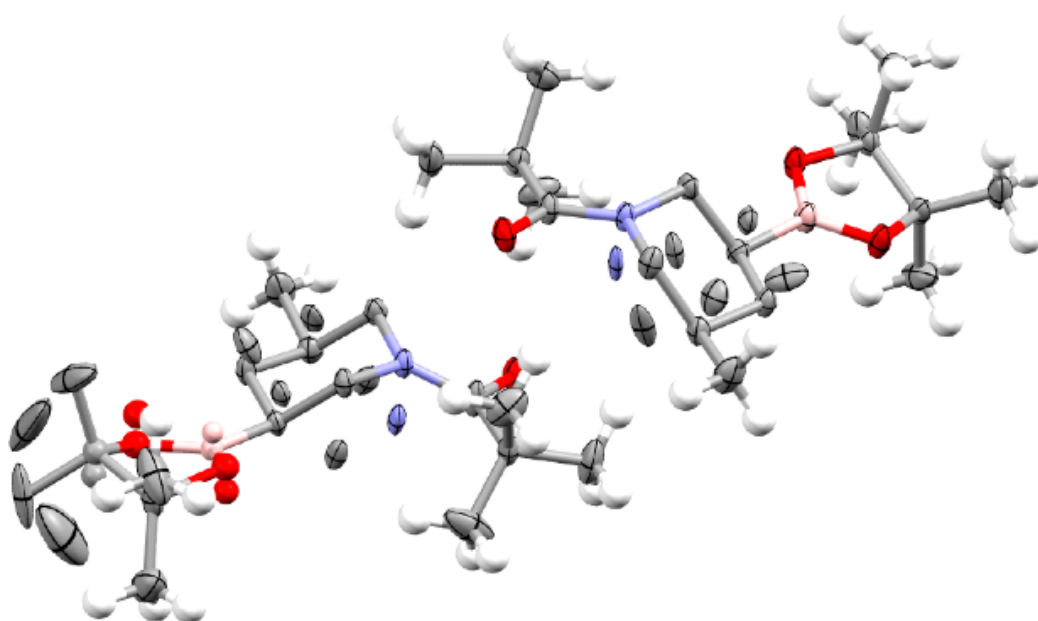


Figure 4-32 Single-crystal X-ray diffraction structure of **2g** (atomic displacement parameters set at 30% probability)

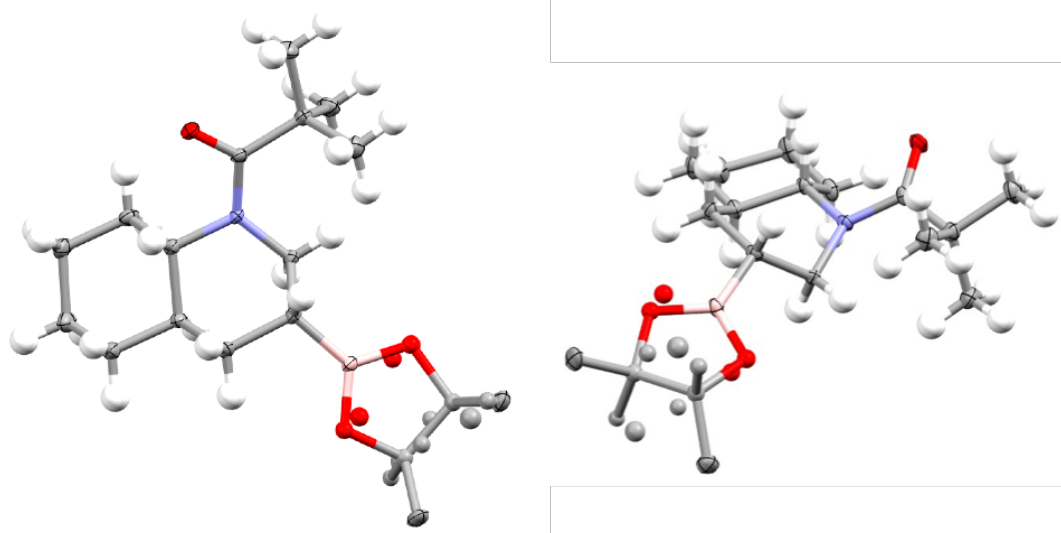


Figure 4-33 Single-crystal X-ray diffraction structure of **2l** (atomic displacement parameters set at 30% probability)

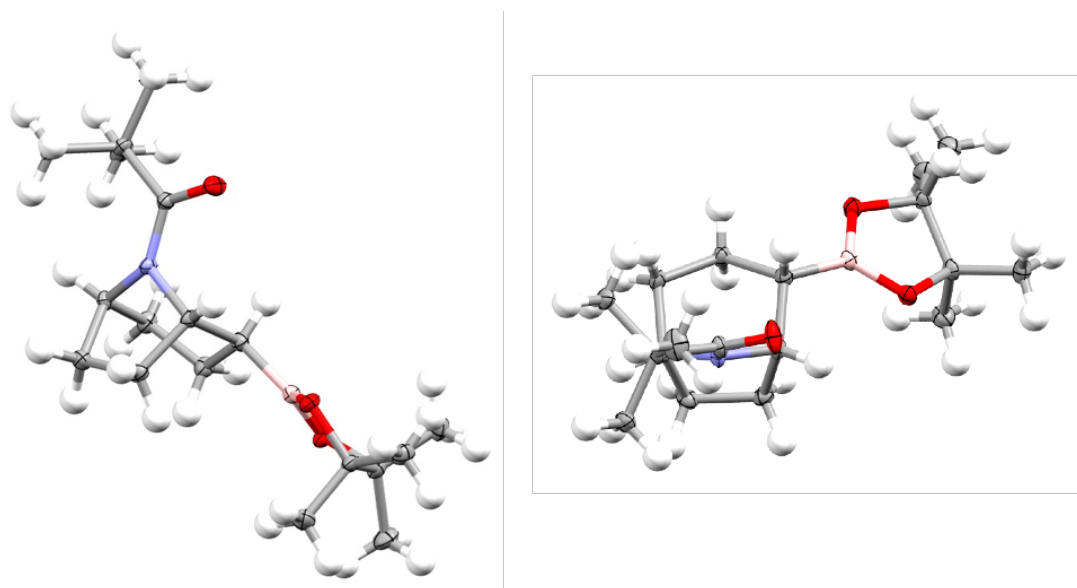


Figure 4-34 Single-crystal X-ray diffraction structure of **2k** (atomic displacement parameters set at 30% probability).

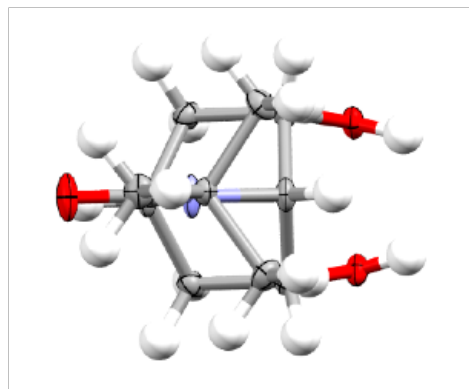
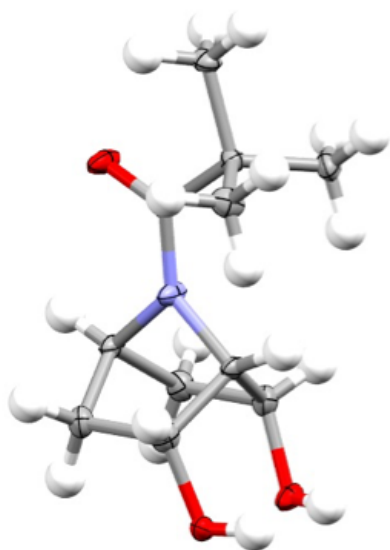


Figure 4-35 Single-crystal X-ray diffraction structure of **4** (atomic displacement parameters set at 30% probability). The oxygen atoms attached to the C2- and C6-positions of the azanorbornane possess 0.5 occupancy.

Table 4-3 Crystallographic Data

Compound	2a	2b	2c	2d	2e	2f
Empirical formula	C ₁₈ H ₃₈ BNO ₃	C ₁₆ H ₃₀ BNO ₃	C ₁₇ H ₃₂ BNO ₃	C ₁₆ H ₃₀ BNO ₃	C ₂₀ H ₃₈ BNO ₅	C ₁₈ H ₃₈ BNO ₃
Formula weight	281.19	295.22	309.24	295.22	381.31	323.27
Crystal description	Prism	Prism	Prism	Block	Chip	Platelet
Crystal color	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Crystal size (mm)	0.28 × 0.21 × 0.19	0.24 × 0.18 × 0.16	0.25 × 0.17 × 0.11	0.10 × 0.08 × 0.05	0.22 × 0.11 × 0.07	0.15 × 0.11 × 0.09
Crystallizing solution	Hexane (−15 °C)	Hexane (−15 °C)	Hexane (−15 °C)	Hexane (23 °C)	Heptane (23 °C)	Heptane (23 °C)
Crystal system	Triclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> -1 (#2)	<i>P</i> 2 ₁ 2 ₁ 2 ₁ (#19)	<i>P</i> 2 ₁ / <i>n</i> (#14)	<i>P</i> 2 ₁ / <i>c</i> (#14)	<i>P</i> 2 ₁ / <i>n</i> (#14)	<i>P</i> 2 ₁ / <i>n</i> (#14)
<i>a</i> (Å)	6.083(9)	6.102(4)	9.829(9)	6.239(3)	6.1049(15)	6.3627(15)
<i>b</i> (Å)	10.131(15)	9.800(6)	9.737(9)	15.013(8)	29.917(7)	9.872(2)
<i>c</i> (Å)	13.91(2)	29.470(16)	19.607(18)	18.8410(10)	12.176(3)	30.778(7)
α (°)	95.92(2)	90	90	90	90	90
β (°)	101.00(3)	90	99.305(15)	90.789(8)	92.569(3)	90.007(4)
γ (°)	91.707(18)	90	90	90	90	90
Volume (Å ³)	836(2)	1762.4(17)	1852(3)	1764.6(13)	2221.6(9)	1933.2(7)
Z value	2	4	4	4	4	4
<i>D</i> _{calc} (g/cm ³)	1.117	1.113	1.109	1.111	1.140	1.111
Measurement temp. (°C)	−130	−130	−130	−127	−127	−127
μ (Mo K α) (mm ^{−1})	0.075	0.074	0.073	0.074	0.079	0.073
Diffractionmeter	Rigaku Saturn70	Rigaku Saturn70	Rigaku Saturn70	Rigaku Saturn70	Rigaku Saturn70	Rigaku Saturn70
Radiation	MoK α	MoK α	MoK α	MoK α	MoK α	MoK α
Monochromator	Graphite	Graphite	Graphite	Graphite	Graphite	Graphite
Reflections collected	6421	13727	13822	13846	17638	15088
Independent reflections	3521 (<i>R</i> _{int} = 0.0594)	4001 (<i>R</i> _{int} = 0.1182)	4165 (<i>R</i> _{int} = 0.0730)	3980 (<i>R</i> _{int} = 0.0585)	4983 (<i>R</i> _{int} = 0.0299)	4421 (<i>R</i> _{int} = 0.0313)
Reflections observed (> 2 σ)	1586	2260	2552	2470	4230	3658
Abs. correction type	Empirical	Empirical	Empirical	Empirical	Empirical	Empirical
Abs. transmission	0.646 (min.), 1.000 (max.)	0.662 (min.), 1.000 (max.)	0.858 (min.), 1.000 (max.)	0.845 (min.), 1.000 (max.)	0.893 (min.), 1.000 (max.)	0.837 (min.), 1.000 (max.)
<i>R</i> ₁ (<i>I</i> > 2 σ (<i>I</i>))	0.0590	0.0663	0.1612	0.1072	0.0732	0.0696
<i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>))	0.1317	0.1332	0.3999	0.3037	0.1845	0.2028
<i>R</i> ₁ (all data)	0.0930	0.1109	0.2113	0.1529	0.0828	0.0785
<i>wR</i> ₂ (all data)	0.1438	0.1560	0.4413	0.3401	0.1931	0.2144
Data/Restraints / Parameters	3521 / 0 / 209	4001 / 0 / 220	4165 / 0 / 204	3980 / 0 / 201	4983 / 0 / 280	4421 / 0 / 231
GOF	0.879	0.920	1.454	1.069	1.065	1.061
Largest diff. peak and hole	0.256 and −0.195 e.Å ^{−3}	0.219 and −0.192 e.Å ^{−3}	0.997 and −0.415 e.Å ^{−3}	0.535 and −0.354 e.Å ^{−3}	0.908 and −0.643 e.Å ^{−3}	0.715 and −0.415 e.Å ^{−3}

Table 4-3 Crystallographic Data (continued)

Compound	2g	2i	2k	4
Empirical formula	C ₁₇ H ₃₂ BN ₃	C ₂₀ H ₂₄ BN ₃	C ₁₈ H ₃₂ BN ₃	C ₁₁ H ₁₉ NO ₂
Formula weight	309.24	338.22	321.25	197.27
Crystal description	Block	Platelet	Prism	Prism
Crystal color	Colorless	Colorless	Colorless	Colorless
Crystal size (mm)	0.19 × 0.10 × 0.08	0.15 × 0.100 × 0.100	0.26 × 0.13 × 0.11	0.14 × 0.10 × 0.08
Crystallizing solution	Hexane (23 °C)	Hexane (−15°C)	Hexane (−15°C)	Hexane (23 °C)
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> -1 (#2)	<i>P</i> 2 ₁ / <i>c</i> (#14)	<i>P</i> 2 ₁ / <i>n</i> (#14)	<i>P</i> 2 ₁ / <i>m</i> (#11)
<i>a</i> (Å)	10.2249(17)	14.823(3)	6.2931(15)	6.680(4)
<i>b</i> (Å)	10.9649(19)	11.673(3)	9.439(2)	10.178(6)
<i>c</i> (Å)	18.972(4)	11.783(3)	31.153(8)	8.253(4)
α (°)	76.475(9)	90	90	90
β (°)	76.353(9)	98.546(4)	92.525(4)	102.0450(10)
γ (°)	66.908(8)	90	90	90
Volume (Å ³)	1877.5(6)	2016.2(8)	1848.7(8)	548.8(5)
Z value	4	4	4	2
<i>D</i> _{calc} (g/cm ³)	1.094	1.114	1.154	1.194
Measurement temp. (°C)	−127	−130	−130	−127
μ (Mo K α) (mm ^{−1})	0.072	0.073	0.076	0.080
Diffractionmeter	Rigaku Saturn70	Rigaku Saturn70	Rigaku Saturn70	Rigaku Saturn70
Radiation	MoK α	MoK α	MoK α	MoK α
Monochromator	Graphite	Graphite	Graphite	Graphite
Reflections collected	15218	16066	14660	4372
Independent reflections	8233 (<i>R</i> _{int} = 0.0489)	4568 (<i>R</i> _{int} = 0.0459)	4212 (<i>R</i> _{int} = 0.0492)	1287 (<i>R</i> _{int} = 0.0220)
Reflections observed ($> 2\sigma$)	5434	3146	3375	1078
Abs. correction type	Empirical	Empirical	Empirical	Empirical
Abs. transmission	0.822 (min.), 1.0000 (max.)	0.7970 (min.), 1.000 (max.)	0.839 (min.), 1.000 (max.)	0.904 (min.), 1.000 (max.)
<i>R</i> ₁ (<i>I</i> $> 2\sigma(I)$)	0.1081	0.0783	0.0551	0.0424
<i>wR</i> ₂ (<i>I</i> $> 2\sigma(I)$)	0.3318	0.2401	0.1337	0.1211
<i>R</i> ₁ (all data)	0.1311	0.0974	0.0713	0.0474
<i>wR</i> ₂ (all data)	0.3603	0.2661	0.1445	0.1248
Data / Restraints / Parameters	8233 / 0 / 562	4568 / 0 / 245	4212 / 0 / 240	1287 / 0 / 100
GOF	1.296	1.094	1.079	1.083
Largest diff. peak and hole	0.844 and −0.561 e.Å ^{−3}	0.686 and −0.413 e.Å ^{−3}	0.415 and −0.204 e.Å ^{−3}	0.305 and −0.156 e.Å ^{−3}

4.5 References and notes

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Chapter 5

Site-Selective C(sp³)-H Borylation of 3-Azabicyclo[3.1.0]hexanes by Cooperative Iridium/Aluminum Catalysis

Functionalized 3-azabicyclo[3.1.0]hexanes are highly interesting for their physiochemical and pharmacological properties. The author report an unprecedented direct bridge-head C(sp³)-H borylation by cooperative iridium/aluminum catalysis. This reaction proceeds under mild conditions in good yields with moderate to complete site selectivities. Moreover, the use of a BINOL-based chiral aluminum catalyst renders the synthesis of enantioenriched alkylboronate products. The author also disclose its synthetic utility through rapid diversifications without any loss of the stereochemical information.

5.1 Introduction

Nitrogen-containing heterocycles are abundant in bioactive compounds, including natural alkaloids and pharmaceuticals.¹ Conventionally, medicinal chemists have mainly focused on C(sp²)-rich flat molecules because of their easy accessibility by well-developed transformations on arenes.² Over the past decades, however, their interests have moved to incorporating out-of-plane fragments into drug candidates to improve their physiochemical and pharmacological properties. Among these, a 3-azabicyclo[3.1.0]hexane scaffold is frequently found in biologically active molecules, owing to their chemical stability and structural diversity, which allows the exploration of novel chemical space to obtain new drug molecules (Figure 5-1).^{3,4}

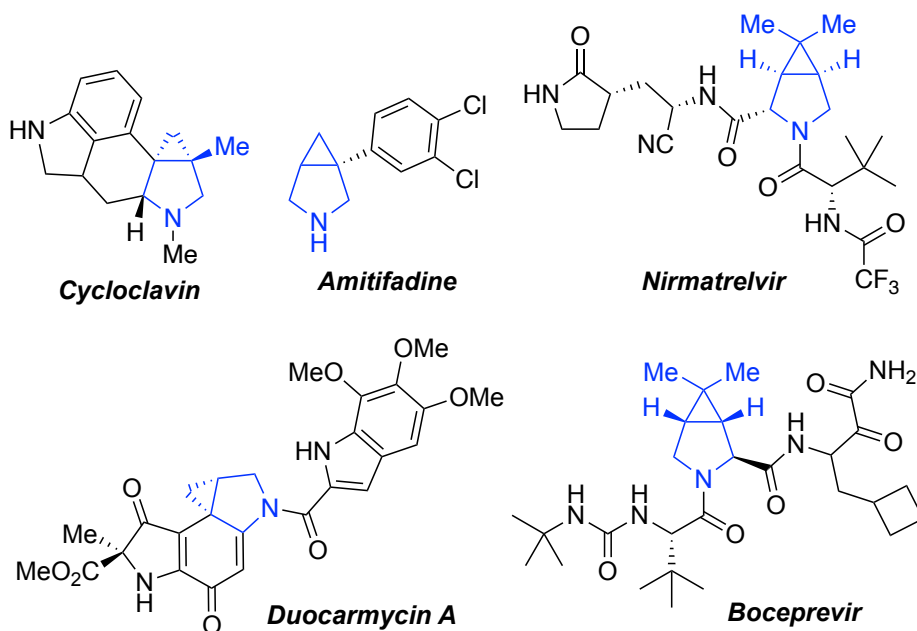


Figure 5-1 Representative bioactive compounds containing 3-azabicyclo[3.1.0]hexane core

Traditionally, the preparation of functionalized 3-azabicyclo[3.1.0]hexanes has relied on α -lithiation,⁵ α -oxidation,⁶ or nucleophilic addition reactions to the corresponding imide precursors,^{6c} with which only α -functionalization has been viable. β - and/or γ -Functionalized 3-azabicyclo[3.1.0]hexanes can be accessed only by multi-step synthetic strategies (Figure 5-2).⁷⁻⁹ From the viewpoint of rapid drug discovery, common intermediates that can participate in rapid diversification are highly desirable.¹⁰

In this context, site-selective direct C–H functionalization should be one of the ideal transformations.¹¹ Transition-metal-catalyzed C(sp³)–H bond functionalization has been well studied in the last few decades. Despite the rapid development of numerous strategies for these transformations, the direct C(sp³)–H functionalization of 3-azabicyclo[3.1.0]hexane has still been limited mainly to the α - or γ -position.^{12,13} To the best of the author's knowledge, there has been no report on the direct β -C(sp³)–H functionalization of 3-azabicyclo[3.1.0]hexanes.¹⁴

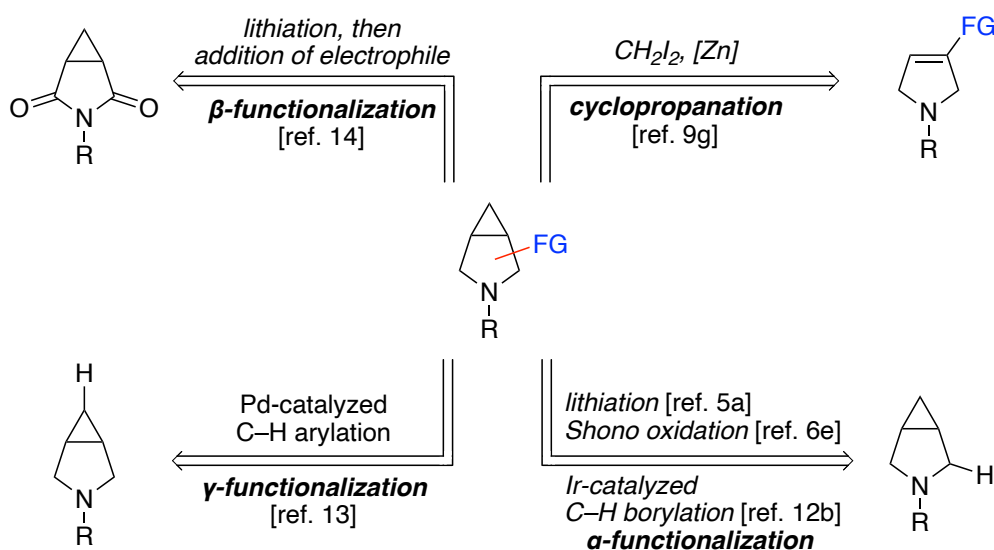


Figure 5-2 Representative synthetic scheme of functionalized 3-azabicyclo[3.1.0]hexane

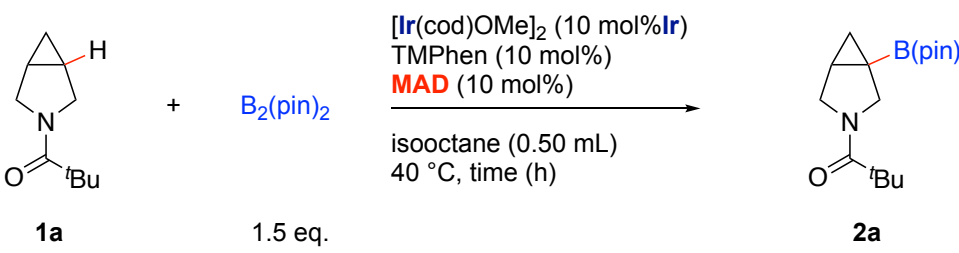
The author's group has developed transition metal/Lewis acidic metal cooperative strategies for site-selective direct C–H functionalization reactions,¹⁵ among which the author has recently reported an iridium/aluminum cooperative catalysis for β -selective C(sp³)–H borylation of cyclic amines and lactams.¹⁶ Using this protocol, highly enantio-enriched nitrogen-containing alkylboronates were obtained in modest to excellent stereoselectivities and complete site-selectivities. The author has imagined bicyclic amines could serve as substrates for this new protocol, which could be useful in drug discovery and synthetic chemistry.

The author reports herein a catalytic cooperative strategy for a site-selective bridge-head tertiary C(sp³)–H borylation^{17,18} of nitrogen-containing bicyclic compounds. This reaction proceeds under mild reaction conditions and moderate to complete site-selectivity with a broad substrate scope.

5.2 Results and Discussion

First, the author commenced with the identification of proper reaction conditions for the borylation of *N*-pivaloyl-3-azabicyclo[3.1.0]hexane (**1a**) (Table 5-1). Following the author's previous work,¹⁶ borylation product **2a** was obtained in quantitative yield using MAD as a Lewis acid under mild reaction conditions (entry 1).¹⁹ Under these conditions, the *tert*-alkylboronate was exclusively observed without any detection of other isomers.^{17,18} In the previous work,¹⁶ DFT calculations clearly indicated that both steric and electronic effects were responsible for the β -selectivity. At this stage, the author also investigated an *N*-protecting group, and the author found a Boc group instead sluggish the borylation reaction (entry 2).²⁰ The use of other iridium precatalyst and ligands including TMsPhen also decreased the product yield (entries 3–5, see also Table 5-3).²¹ Then, The author shifted his attention to the investigation of the effect of Lewis acidic co-catalysts, and noted that AlMe₃ or BEt₃ did not promote the reaction, while the borylation slightly proceeded in their absence (entries 6–8, see also Table 5-4). Using an equimolar amount of B₂(pin)₂ decreased the product yield (entry 10), and the borylation was sluggish under the ambient temperature (entry 11).

Table 5-1 Optimization of reaction conditions^a

		
1a	1.5 eq.	2a
Entry	Deviations from standard conditions	Yield (%) ^b
1	None	>99
2	Boc instead of Piv	<5
3	[Ir(cod)Cl] ₂ instead of [Ir(cod)OMe] ₂	33
4	Phen instead of TMPhen	4
5	Dtbpy instead of TMPhen	66
6	AlMe ₃ instead of MAD	13
7	BEt ₃ instead of MAD	17
8	w/o MAD	16
9	w/o [Ir(cod)OMe] ₂ and TMPhen	<5
10	1.0 eq. of B ₂ (pin) ₂	86
11	Run at room temperature	9

^aTypical reaction conditions: **1a** (0.10 mmol), B₂(pin)₂ (0.15 mmol), [Ir(cod)OMe]₂ (0.0050 mmol), TMPhen (0.010 mmol), MAD (0.010 mmol) in isooctane (0.50 mL). ^bGC yield (*n*-dodecane as internal standard).

With the optimized reaction conditions in hand, the author investigated the scope of substrates (Figure 5-3). **2a** was successfully isolated in 89% yield, which was slightly lower than the GC yield probably due to its over-adsorption on silica gel during purification.²² A substrate bearing a methyl group at the other bridge-head position (**1b**) was also borylated to afford **2b** in excellent yield without any loss of site-selectivity. On the other hand, **1c** was converted into a mixture of **2c** and *iso*-**2c** in 60% total yield with a ratio of 86:14, while complete β -selectivity was maintained. A more sterically demanding group at the α -position of nitrogen was found to affect the site-selectivity, and **2d** was isolated as a single isomer in 39% yield.²³ Unfortunately, even after several investigations of reaction conditions, substrate **1e** was not fully converted, probably due to its serious steric hindrance, to give **2e** in a moderate yield.²⁴ Both *exo*- and *endo*-**1f** bearing a sterically demanding functionality at the 6-position reacted smoothly to give the corresponding borylated products in good yields.

Next, borylation reactions of other related bicyclic amine motifs were examined.

An azabicyclo[3.2.0]heptane core could be a viable substrate for this reaction to afford **2g** in 77% yield.^{14b,25} Again, the borylation proceeded only at the bridge-head position, and any other isomers were not observed.^{14b} Azabicyclo[3.3.0]octane **1h** could not be borylated, and the substrate was recovered.^{6c,12b,26} *N*-Piv-2-azabicyclo[3.1.0]hexane (**1i**) was borylated under mild reaction conditions albeit with low site-selectivity, while maintaining β -selectivity, to afford an inseparable mixture of **2i** and *iso*-**2i** in 96% combined yield.^{6b,27} These products were separated and identified after derivatizing the boron functionality (Scheme 5-13). Additionally, azabicyclo[4.1.0]heptane substrate **1j** participated in the reaction in a manner similar to **1a**, and borylated product **2j** was isolated in 68 % yield.^{6b,27c,28}

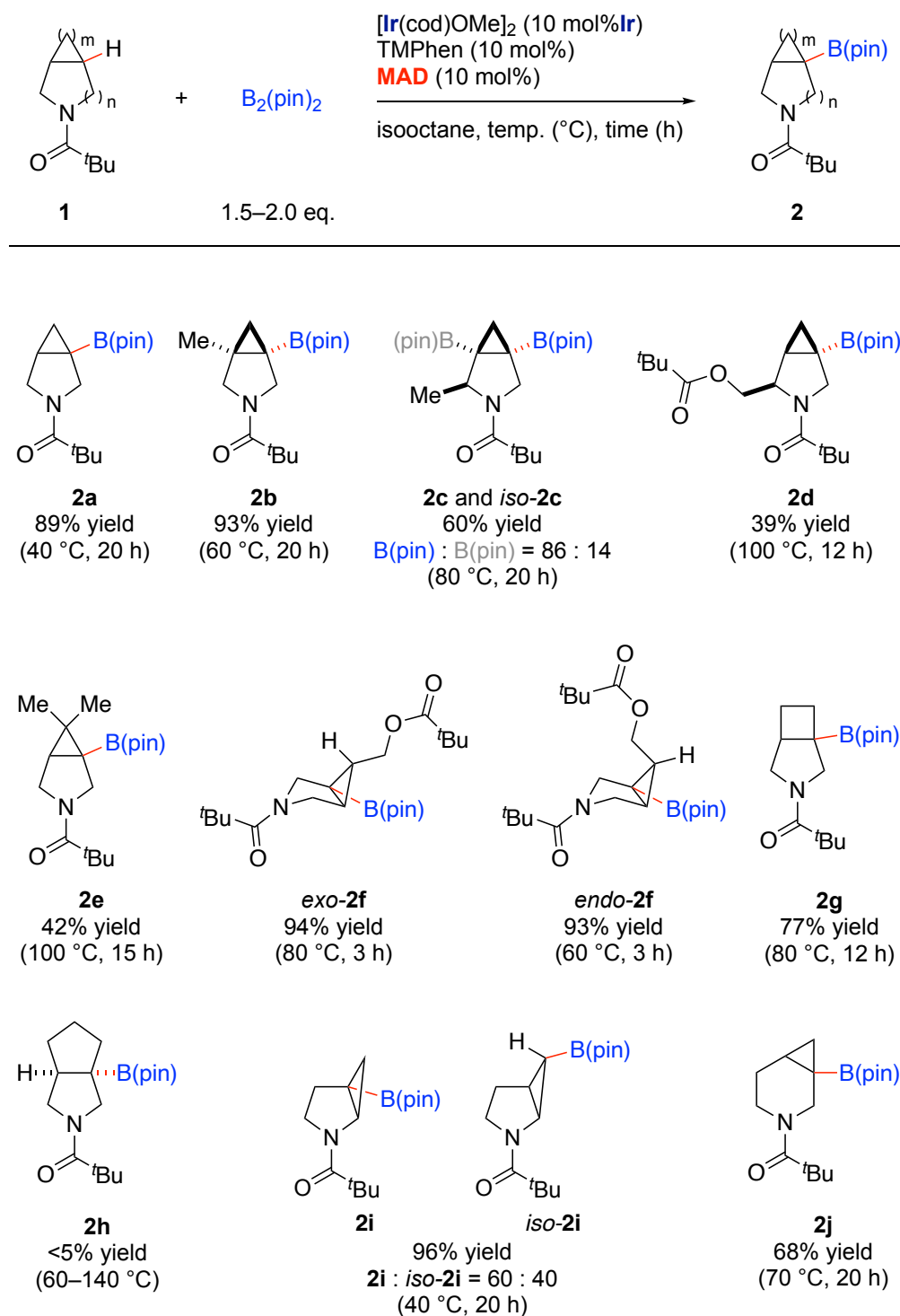
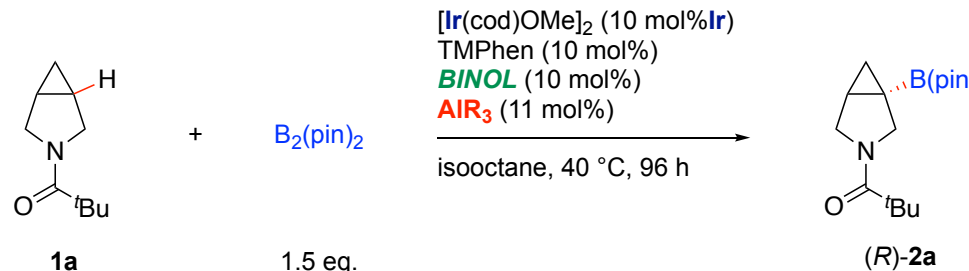
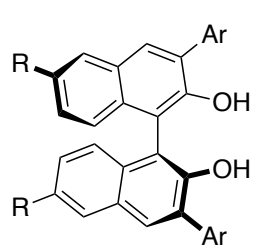


Figure 5-3 Scope of substrates. Reactions were conducted on 1.0 mmol scale. Isolated yields after purification were shown.

Then, the author became interested in an asymmetric variant of this site-selective borylation protocol, following the author's recent success with chiral aluminum-based Lewis acids.²⁹ First, the author investigated a proper chiral diol, which was required to secure good solubility as well as an enantio-discrimination in a non-polar isooctane solvent (Table 5-2). TIPS groups were introduced at the 6,6'-positions of BINOL,³⁰ and the author also examined substituent effects at the 3-position.¹⁶ The author particularly focused on steric effects derived from the aryl groups at this position. In his previous work, the author confirmed the clean 1:1 complexation of a BINOL derivative with trimethylaluminum,¹⁶ and the author followed this procedure to prepare chiral aluminum complexes in situ and directly used without their isolation in this study. The use of **3a** or **3b**, bearing *para*- or *meta*-substituted aryl rings afforded **2a** in moderate yield with low enantioselectivity (entries 1 and 2). The author found *ortho*- and *para*-substituents were effective for yield and enantioselectivity, probably because of an increased rotational barrier between the aryl substituent and the BINOL core to rigidify the chiral catalyst (entry 3).³¹ The author also tested **3d**, which has a bulkier adamantyl group instead of methyl at the *para*-position. However, its steric bulkiness likely lowered the enantioselectivity, and **2a** was isolated only with 29% ee (entry 4). **3e**, which had less hindered ethyl groups instead of methyl was effective to give **2a** with the same level of enantioselectivity in a slightly lower yield, compared with **3c** (entry 5). After several investigations, the combination of **3e** and triethylaluminum was found to be optimal (entry 6, see also Table 5-5). Lastly, the author also tested the importance of the TIPS groups to use **3f**, but **2a** was obtained in a lower yield with miserable enantioselectivity, which certainly supported that the TIPS groups play an important role also in the enantio-determining step.³²

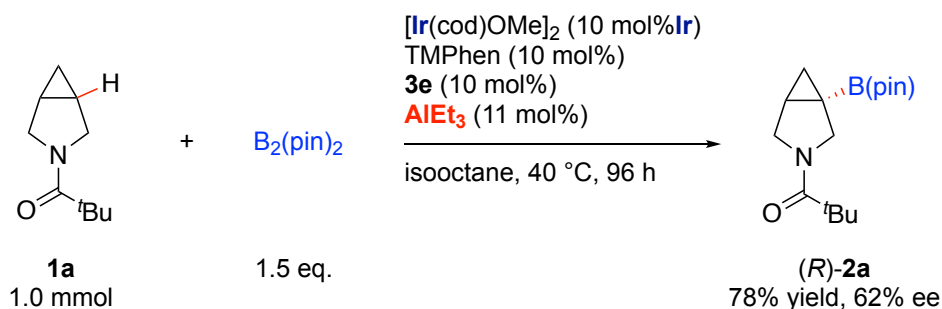
Table 5-2 Screening of chiral Lewis acid^a

				
 3a: R = TIPS, Ar = 4-^tBuC₆H₄ 3b: R = TIPS, Ar = 3,5-^tBu₂C₆H₃ 3c: R = TIPS, Ar = Mes 3d: R = TIPS, Ar = 4-(1-adamantyl)-2,6-Me₂C₆H₂ 3e: R = TIPS, Ar = 2,4,6-Et₃C₆H₂ 3f: R = H, Ar = 2,4,6-Et₃C₆H₂				
Entry	BINOL	AlR ₃	Yield (%) ^b	Ee (%) ^c
1	3a	AlMe ₃	65	38
2	3b	AlMe ₃	53	15
3	3c	AlMe ₃	78	54
4	3d	AlMe ₃	65	29
5	3e	AlMe ₃	66	54
6	3e	AlEt ₃	79	60
7	3f	AlMe ₃	43	17

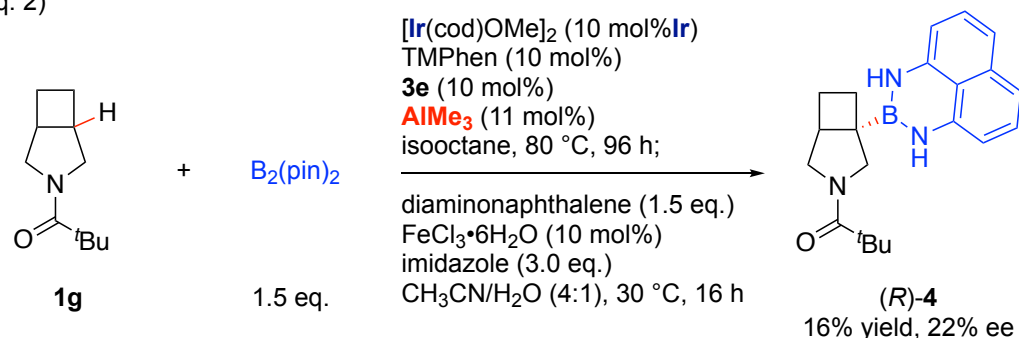
^aTypical reaction conditions: **1a** (0.30 mmol), B₂(pin)₂ (0.45 mmol), [Ir(cod)OMe]₂ (0.0050 mmol), TMPhen (0.030 mmol), **3** (0.030 mmol), and AlR₃ (0.033 mmol) in isooctane (0.50 mL). ^bGC yield (*n*-dodecane as internal standard). ^cEe was determined by chiral HPLC analysis after derivatization (see also Scheme 5-14)

With the optimal reaction conditions in hand, the author turned his attention to the scope of the enantioselective borylation (Scheme 5-1). As a result, the author succeeded in isolating (*R*)-**2a** on a 1.0 mmol scale in 78% yield with 62% ee (eq. 1). However, the author found the optimal reaction conditions were not generally applicable to other heterocycles including **1g**, which gave (*R*)-**4** in low yield and enantioselectivity, partially because of the higher reaction temperature required (eq. 2).³³

(eq. 1)



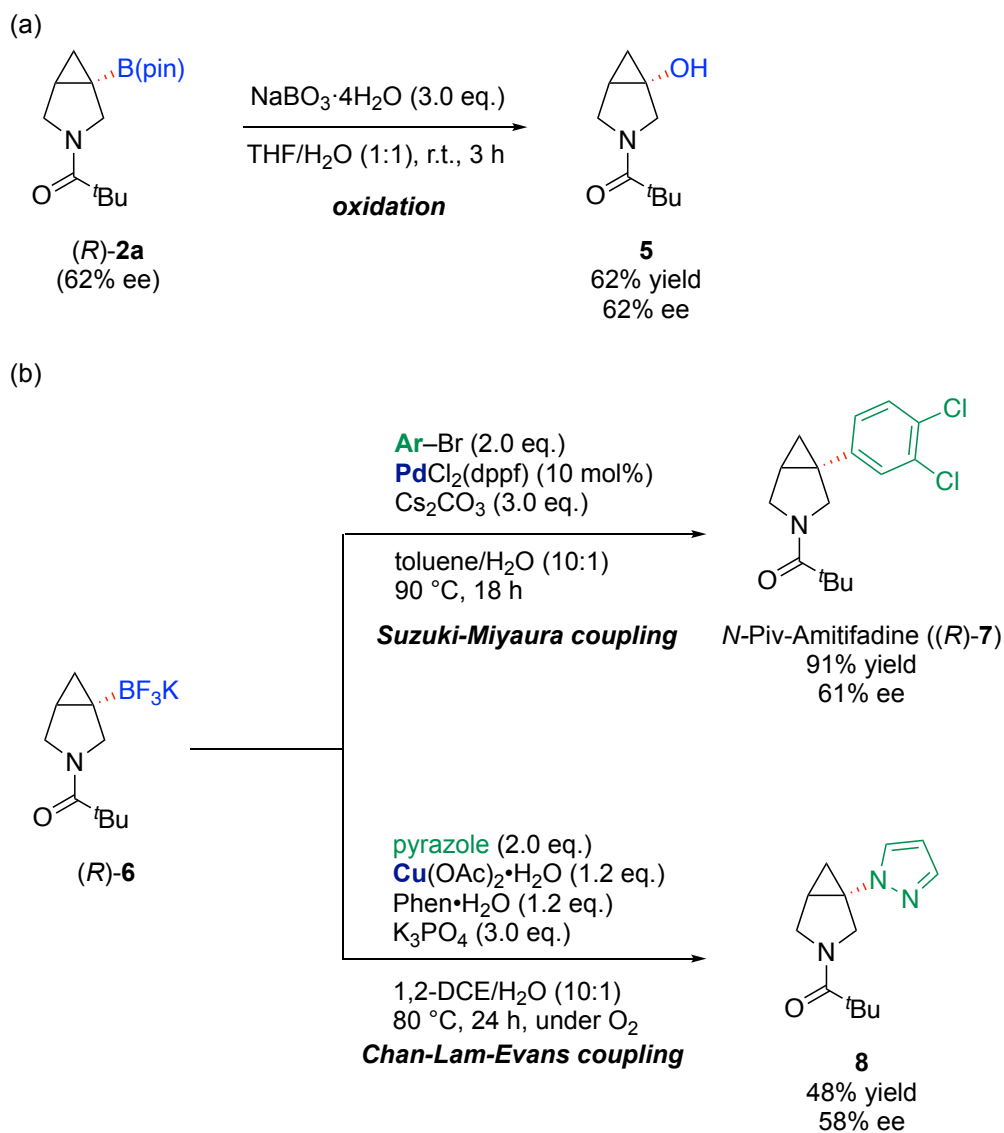
(eq. 2)



Scheme 5-1 Asymmetric borylation. Reactions were conducted on 1.0 mmol scale.

Isolated yields after purification were shown. Ee was determined by chiral HPLC analysis.

With the enantioenriched alkylboronic ester in hand, the author examined its transformation to demonstrate the synthetic utility of this borylation reaction (Scheme 5-2). Oxidation of (R) -**2a** afforded **5** without any loss of the enantiomeric excess. (R) -**2a** was also converted into potassium trifluoroborate (R) -**6**. (R) -**6** was then subjected to the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction to give *N*-protected Amitifidine,^{4b,34} a potent drug for antidepressant, and the copper-mediated Chan-Lam-Evans coupling also proceeded to give **8** without significant loss of stereochemistry.³⁵ At this stage, the author could determine the absolute configuration of **7** by comparing its chiral HPLC traces and specific rotation with an authentic sample prepared. All the other absolute configurations of enantioenriched products were assigned as analogs of **7** (see also Figure 5-9).



Scheme 5-2 Transformation of enantioenriched alkyl boronate. (a) oxidation of (R)-2a (b) palladium-catalyzed Suzuki-Miyaura cross-coupling reaction and copper-mediated Chan-Lam-Evans cross-coupling reaction

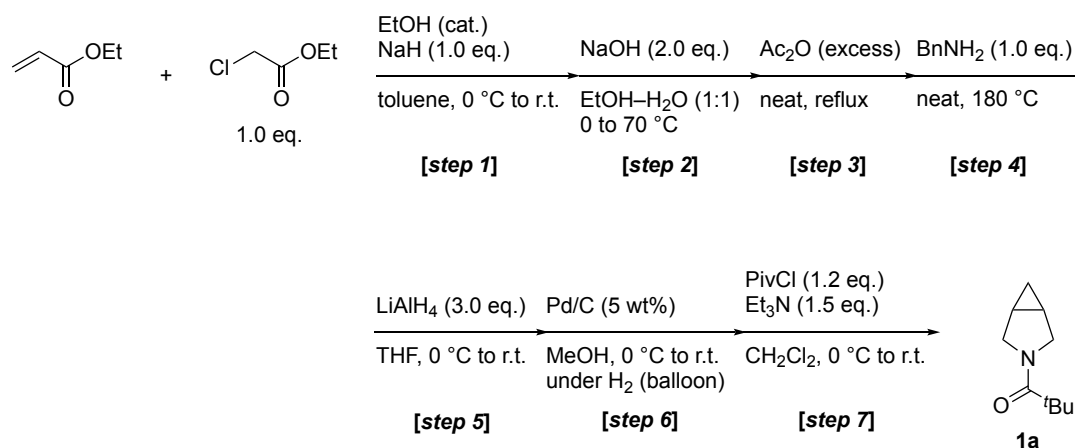
5.3 Conclusion

In conclusion, the author has successfully developed tertiary C(sp³)-H borylation of bicyclic amines. The key to success is an iridium/ aluminum cooperative strategy. This reaction proceeds in good yields with moderate to excellent site-selectivities. Furthermore, enantioenriched alkylboronates can be prepared by using a chiral Lewis acid catalyst, albeit with moderate enantioselectivities, demonstrating the first catalytic asymmetric synthesis of bridge-head functionalized bicyclic amines. The obtained enantioenriched alkylboronate can be derivatized into various valuable compounds. The author believes that this unprecedented protocol will open new strategies in the field of synthetic organic chemistry.

5.5 Experimental Section

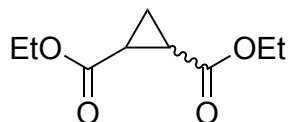
5.5.1 Substrate Preparation

3-Pivaloyl-3-azabicyclo[3.1.0]hexane (1a)



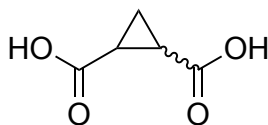
Scheme 5-3 Synthetic route to 1a

Diethyl cyclopropane-1,2-dicarboxylate



To a flame-dried three-necked round-bottom flask (equipped with a dropping funnel) containing a suspension of NaH (60% in mineral oil, 1.00 mol, 40.0 g) in anhydrous toluene (250 mL) was added a few drops of absolute EtOH under argon atmosphere and cooled to 0 °C. To the resulting suspension, a mixture of ethyl 2-chloroacetate (1.00 mol, 107 mL) and ethyl acrylate (1.00 mol, 107 mL) was added over 11 hours at this temperature *via* dropping funnel with vigorous stirring (**Caution:** gas bubbles vigorously). After the addition, the reaction was warmed to room temperature and further stirred for 12 hours, followed by the slow addition of H₂O to quench the reaction. After that, two layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give the crude title compound (*cis/trans* mixture), which was directly used to the next step without further purification (not weighed).

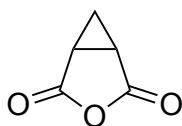
Cyclopropane-1,2-dicarboxylic acid



To a round-bottom flask containing the aforementioned crude mixture in EtOH (400 mL) was added NaOH (2.00 mol, 80.0 g) in H₂O (400 mL) dropwise over 10 min at 0 °C under air. The resulting mixture was warmed up to 70 °C and further stirred for 4 hours at this temperature. All volatiles were removed under reduced pressure. The resulting mixture was acidified with 6 M HCl aq. (*ca.* 360 mL) whilst cooling with an ice bath (**Caution:** *the internal temperature was kept below 50 °C*). The resulting mixture was extracted with hot AcOEt (300 mL × 6), and the combined organic layers were evaporated under reduced pressure, which was used in the next step without purification (not weighed).

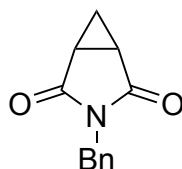
Note: *The same reaction (steps 1 and 2) was performed on the same scale (1.00 mol) in two batches. These were combined and used in the next step (not weighed).*

3-Oxabicyclo[3.1.0]hexane-2,4-dione



To the aforementioned combined crude residue, acetic anhydride (400 mL) was added and stirred for 12 hours under reflux. Upon cooling to *ca.* 80 °C, an excess amount of acetic anhydride was removed under reduced pressure. The crude residue was roughly purified by vacuum distillation (bath temp. 140–180 °C) to afford the title compound (0.343 mol, 38.5 g, considered to be 100% purity) as a colorless solid, which was used without further purification.

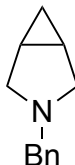
3-Benzyl-3-azabicyclo[3.1.0]hexane-2,4-dione



To the above-mentioned acid anhydride in a round-bottom flask equipped with a reflux condenser, benzylamine (0.350 mol, 38.3 mL) was slowly added at room temperature

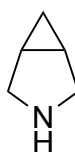
(**Caution:** very exothermic). After 2 hours at 180 °C, the reaction mixture was cooled to room temperature and roughly purified by recrystallization from hot *i*PrOH (crystallization aging at –35 °C) to give the title compound (0.283 mol, 57.0 g, considered to be 100% pure) as a pale yellow solid and used without further purification.

3-Benzyl-3-azabicyclo[3.1.0]hexane



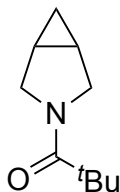
To a flame-dried three-necked round-bottom flask containing LiAlH₄ (0.850 mol, 32.2 g) in anhydrous THF (800 mL) was added dropwise the solution of 3-benzyl-3-azabicyclo[3.1.0]hexane-2,4-dione (283 mmol, 57.0 g, considered to be 100% pure) in anhydrous THF (300 mL) for 40 min under argon atmosphere at 0 °C (**Caution:** the reaction temperature was kept below 10 °C). After 17 hours at 0 °C to room temperature, the reaction mass was quenched by the sequential slow addition of H₂O (40 mL, over 60 min), 15% NaOH aq. (40 mL), H₂O (120 mL) with vigorous stirring. After filtering through a Celite pad (the pad cake was then washed with a minimal amount of AcOEt), the mixture was extracted with AcOEt. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give a pale-yellow oil, which was directly used without purification.

3-Azabicyclo[3.1.0]hexane



Removal of benzyl protection was performed with 10% Pd/C (2.75 g) in MeOH (50 mL) under ambient pressure of hydrogen gas for 3 days at room temperature (**Note:** the reaction was monitored by ¹H NMR). The resulting reaction mass was filtered through a Celite pad and evaporated under reduced pressure. The crude residue was purified by vacuum distillation to give the analytically pure title compound in 9.6% yield (0.193 mol, 16.0 g over 6 steps) as pale-yellow oil.

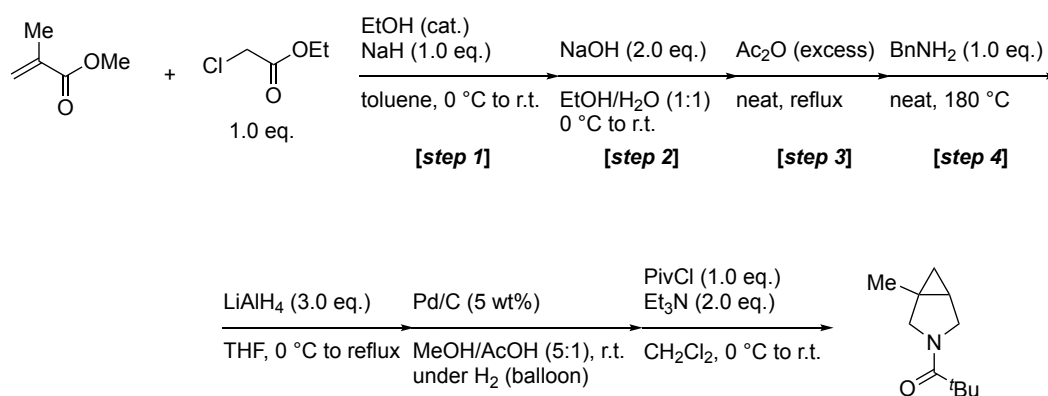
N-Pivaloyl-3-azabicyclo[3.1.0]hexane (**1a**)



To a flame-dried three-necked round-bottom flask containing 3-azabicyclo[3.1.0]hexane (20.0 mmol, 1.66 g) in anhydrous CH₂Cl₂ (50 mL) were sequentially added Et₃N (30.0 mmol, 4.18 mL) and PivCl (24.0 mmol, 2.92 mL) at 0 °C under argon atmosphere. After stirring for 18 hours at 0 °C to room temperature, the resulting reaction mixture was quenched with 1 M HCl aq. (30 mL). Two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The resulting crude oil was purified by MPLC (eluent: hexane/AcOEt = 80/20 to 30/70), followed by vacuum distillation over CaH₂ (0.10 kPa, b.p. 50 °C) to afford the title compound in 66% yield (13.3 mmol, 2.23 g) as a colorless oil.

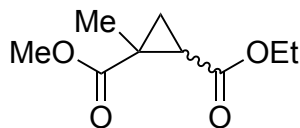
Rf: 0.27 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde or PMA); **¹H NMR** (400 MHz, CDCl₃) δ 3.90 (d, *J* = 10.9 Hz, 2H), 3.46 (*virt s*, 2H), 1.50 (*virt s*, 2H), 1.22 (s, 9H), 0.67-0.63 (m, 1H), 0.16-0.07 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.4, 49.6, 39.0, 27.5, 14.5 (br), 8.3; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₈ON: *m/z* 168.1383 ([M+H]⁺), found: *m/z* 168.1380 ([M+H]⁺).

rac-3-Pivaloyl-(1*S*,5*R*)-1-methyl-3-azabicyclo[3.1.0]hexane (*rac*-**1b**)



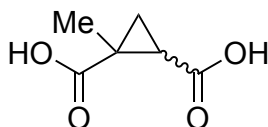
Scheme 5-4 Synthetic route to *rac*-**1b**

2-Ethyl 1-methyl 1-methylcyclopropane-1,2-dicarboxylate



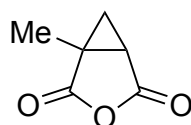
To a flame-dried three-necked round-bottom flask (equipped with a dropping funnel) containing NaH (60% in mineral oil, 0.500 mol, 20.0 g) in toluene (125 mL) was added absolute EtOH (0.40 mL) at 0 °C under argon atmosphere. To this suspension, the mixture of methyl methacrylate (0.500 mol, 53.3 mL) and ethyl chloroacetate (0.500 mol, 53.3 mL) was added dropwise over 2 hours *via* dropping funnel (**Caution:** *gas bubbles vigorously*). After the addition, the reaction was further stirred for 2 hours at this temperature and quenched with the slow addition of H₂O. Two layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was roughly purified by vacuum distillation (0.10 kPa, b.p. 70 °C, bath temp. 100 °C) to give the title compound (14.0 g, *cis/trans* mixture, 15% yield considered to be 100% pure) as a colorless oil, which was used in the next step without further purification.

1-Methylcyclopropane-1,2-dicarboxylic acid



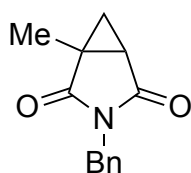
To a round-bottom flask containing NaOH (0.150 mol, 6.00 g.) in H₂O (30 mL) was added dropwise the aforementioned dicarboxylate in EtOH (30 mL) at 0 °C. After stirring overnight at 0 °C to room temperature, all volatiles were removed by a rotary evaporator, followed by acidification with 6 M HCl (pH~1) at room temperature. The resulting reaction mass was extracted with hot AcOEt (100 mL × 3), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give a pale yellow solid, which was directly used without further purification (not weighed).

1-Methyl-3-oxabicyclo[3.1.0]hexane-2,4-dione



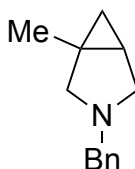
To the aforementioned crude residue, acetic anhydride (40 mL) was added and stirred overnight under reflux (bath temp. 180 °C). Upon cooling to *ca.* 80 °C, an excess amount of acetic anhydride was removed under reduced pressure. The crude residue was roughly purified by vacuum distillation to give the title compound (35.7 mmol, 4.50 g, considered to be 100% pure) as a pale-yellow oil and used without further purification.

3-Benzyl-1-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione



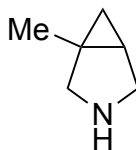
To the aforementioned product, benzylamine (35.7 mmol, 3.90 mL) was added at room temperature (**Caution:** *very exothermic*). After 2 hours at 180 °C, the resulting yellow solution was cooled to room temperature and quenched with wet *i*PrOH. After the removal of *i*PrOH under reduced pressure, the crude residue was used in the next step without further purification (not weighed).

3-Benzyl-1-methyl-3-azabicyclo[3.1.0]hexane



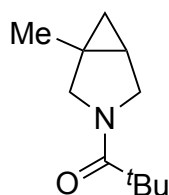
To a flame-dried three-necked round-bottom flask containing LiAlH₄ (0.100 mol, 3.78 g) in anhydrous THF (70 mL) was added dropwise 3-benzyl-1-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione in anhydrous THF (30 mL) under argon atmosphere at 0 °C. After 60 min under reflux (**Note:** *GC analysis after 30 min indicated the full consumption of the substrate*), the reaction mixture was quenched by the slow addition of Rochelle salt (0.200 mol, 56.4 g) and NaOH (0.400 mol, 16.0 g) in H₂O (200 mL) at 0 °C (**Caution:** *gas bubbles vigorously*) and stirred for 30 min at 50 °C. Two layers were separated, and the aqueous layer was extracted with Et₂O (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give the crude yellow oil, which was used in the next step without further purification.

1-Methyl-3-azabicyclo[3.1.0]hexane



To the aforementioned crude mixture in MeOH/AcOH (5:1, 24 mL), 10% Pd/C (0.34 g) was added under argon atmosphere. The reaction vessel was evacuated and backfilled with hydrogen (balloon) three times. After stirring for 60 hours at room temperature, the reaction mixture was filtered through a Celite pad, and the pad cake was washed with AcOEt. Removal of solvents under reduced pressure afforded a faint yellow oil and the crude oil was basified with 10 M NaOH aq. (20 mL) at 0 °C. After the extraction with Et₂O (50 mL × 3), the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give the title compound and directly used in the next step without isolation.

rac-3-Pivaloyl-(1*S*,5*R*)-1-methyl-3-azabicyclo[3.1.0]hexane (1b)

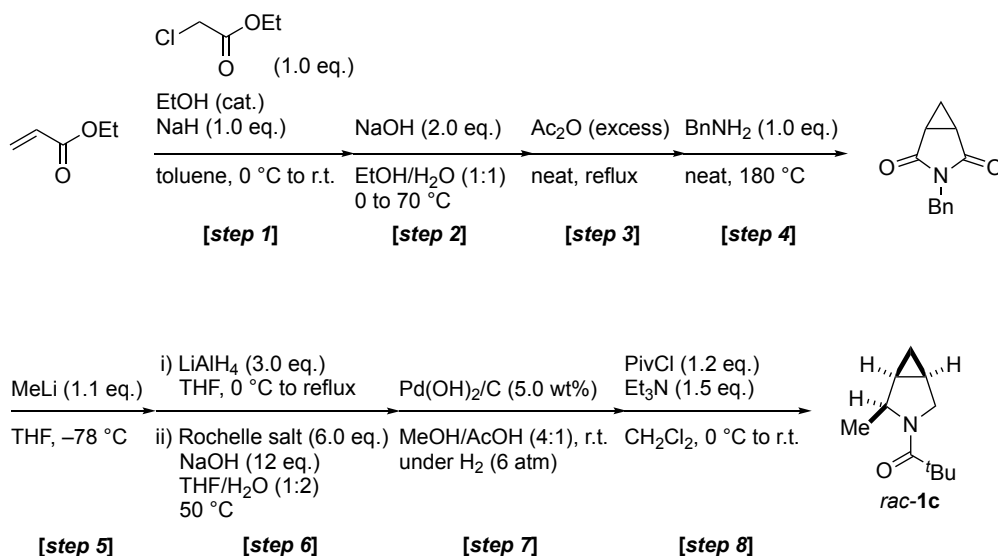


To a round-bottom flask containing the aforementioned crude mixture and Et₃N (71.4 mmol, 9.95 mL) in anhydrous CH₂Cl₂ (100 mL) was added PivCl (35.3 mmol, 4.30 mL) at 0 °C under argon atmosphere. After stirring for 20 hours at room temperature, the reaction was quenched with 3 M HCl aq. (20 mL) and two layers were separated. The organic layer was washed with saturated Na₂CO₃ aq. (30 mL) and brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was purified by MPLC (1st eluent: hexane/AcOEt = 4/1; 2nd hexane/AcOEt = 9/1 to 4/1), followed by vacuum distillation over CaH₂ (0.10 kPa, b.p. 42-44 °C) to afford the title compound in 1.9% yield (9.68 mmol, 1.76 g, over 7 steps) as a colorless oil.

Rf: 0.39 (eluent: hexane/AcOEt = 2/1, PMA); **¹H NMR** (400 MHz, CDCl₃, 50 °C) δ 3.90 (d, *J* = 10.5 Hz, 1H), 3.86 (d, *J* = 11.0 Hz, 1H), 3.50 (br d, *J* = 11.0 Hz, 1H), 3.26 (br d, *J* = 10.5 Hz, 1H), 1.26 (s, 3H), 1.22 (s, 9H), 1.25-1.15 (m, 1H), 0.55-0.49 (m, 1H), 0.31-0.27 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 177.2, 54.7, 50.4, 39.0, 27.6, 18.5,

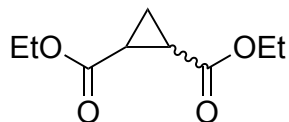
15.2 (Two ^{13}C signals were not detected probably due to peak broadening); **HRMS (ESI)** exact mass calcd. for $\text{C}_{11}\text{H}_{20}\text{ON}$: m/z 182.1539 ($[\text{M}+\text{H}]^+$), found: m/z 182.1534. ($[\text{M}+\text{H}]^+$).

***rac*-3-Pivaloyl-(1*S*,2*S*,5*R*)-2-methyl-3-azabicyclo[3.1.0]hexane (*rac*-1c)**



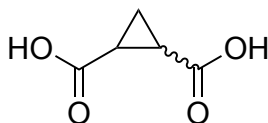
Scheme 5-5 Synthetic route to *rac*-1c

Diethyl cyclopropane-1,2-dicarboxylate



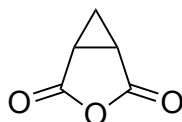
To a flame-dried three-necked round-bottom flask (equipped with a dropping funnel) containing NaH (60% in mineral oil, 0.625 mol, 25.0 g), anhydrous toluene (160 mL) was added under argon atmosphere. After cooling to 0 °C, absolute EtOH (0.50 mL) was slowly added. To this suspension, the mixture of ethyl 2-chloroacetate (0.625 mol, 66.6 mL) and ethyl acrylate (0.625 mol, 66.6 mL) was added over 3 hours at this temperature *via* dropping funnel (**Caution:** gas bubbles vigorously). After the addition, the reaction was further stirred for 14 hours at room temperature. Upon the completion of the reaction, the resulting mixture was quenched with the slow addition of H₂O. The crude reaction mass was filtered through a Celite pad, and the pad cake was washed with AcOEt (200 mL). Removal of solvents under reduced pressure gave a muddy brown oil, and this product was roughly purified by vacuum distillation to afford the title compound (*cis/trans* mixture, 0.293 mol, 54.5 g, considered to be 100% pure) as a pale-yellow oil.

Cyclopropane-1,2-dicarboxylic acid



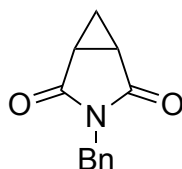
To a round-bottom flask containing NaOH (0.586 mol, 23.4 g) in H₂O (120 mL) was added dropwise the aforementioned oil (293 mmol, 54.5 g, considered to be 100% pure) in EtOH (120 mL) at 0 °C. After stirring for 4 hours at 70 °C, all volatiles were removed under reduced pressure to give a colorless solid. The crude mixture was acidified with 6 M HCl aq. (180 mL), extracted with hot AcOEt (*ca.* 70 °C, 150 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give dicarboxylic acid (*cis/trans* mixture) as an off-white solid, which was directly used in the next step without purification (not weighed).

3-Oxabicyclo[3.1.0]hexane-2,4-dione



The aforementioned crude dicarboxylic acid was treated with acetic anhydride (150 mL) under reflux for 18 hours. Upon cooling to *ca.* 80 °C, an excess amount of acetic anhydride was removed by rotary evaporator (bath temp. 70 °C), and roughly purified by vacuum distillation (0.10 kPa, b.p. 110 °C, bath temp. 140-180 °C) to give the target acid anhydride (106 mmol, 11.9 g, considered to be 100% pure) as a colorless solid and used without further purification.

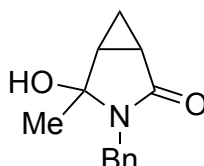
3-Benzyl-3-azabicyclo[3.1.0]hexane-2,4-dione



To a round-bottom flask containing the aforementioned acid anhydride (0.106 mol, 11.9 g) was added benzylamine (0.106 mol, 11.6 mL) at room temperature (**Caution:** *very exothermic*). After stirring for 2 hours at 180 °C, the reaction mixture was cooled to room temperature and solidified by the addition of ⁱPrOH. The resulting slurry was filtered

through a Kiriya filter paper (mother liquid: orange solution), washed with cold *i*PrOH, and dried under a high vacuum at 60 °C to afford the title compound in 11% yield (66.0 mmol, 13.3 g, over 4 steps) as a colorless solid.

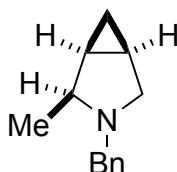
3-Benzyl-4-hydroxy-4-methyl-3-azabicyclo[3.1.0]hexan-2-one



This compound was prepared according to the literature procedure.³⁹

To a flame-dried three-necked round-bottom flask containing the aforementioned *N*-benzylimide (20.0 mmol, 4.02 g) in anhydrous THF (200 mL) was added dropwise MeLi (3.1 M in diethoxymethane, 22.0 mmol, 7.10 mL) at –78 °C under argon atmosphere. After stirring for 20 min at this temperature, saturated NH₄Cl aq. (50 mL) was added to this cold reaction mixture with vigorous stirring. The resulting mixture was warmed to room temperature and further stirred for 10 min. Two layers were separated, and the aqueous layer was extracted with AcOEt (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give the title compound as a colorless solid, which was directly used to the next step without further purification (substrate/product = 3/97).

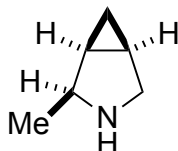
rac-(1*S*,2*S*,5*R*)-3-Benzyl-2-methyl-3-azabicyclo[3.1.0]hexane



To a flame-dried three-necked round-bottom flask containing LiAlH₄ (90.0 mmol, 3.42 g) in anhydrous THF (100 mL) was added portion wise the aforementioned amide (29.5 mmol considered to be 100% purity) at 0 °C. After stirring for 60 min under reflux (**Note:** GC analysis after 30 min indicated the full consumption of the substrate), the reaction mixture was cooled to 0 °C and quenched with the very slow addition of Rochelle salt (0.180 mol, 50.8 g) and NaOH (0.360 mol, 14.4 g) in H₂O (200 mL) (**Caution:** very exothermic and gas bubbles vigorously). After addition, the mixture was stirred for 30

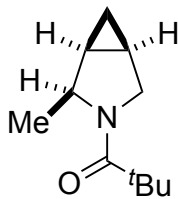
min at 50 °C. Two layers were separated, and the aqueous layer was extracted with Et₂O (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to afford the title compound, which was used without purification.

***rac*-(1*S*,2*S*,5*R*)-2-Methyl-3-azabicyclo[3.1.0]hexane**



To the above-mentioned crude material in MeOH/AcOH (4:1, 37.5 mL) was added Pd(OH)₂/C (0.28 g) at room temperature. The reaction vessel was purged with hydrogen (6 atm). After stirring for 3 days at room temperature under 6 atm of hydrogen gas, the reaction mixture was filtered through a Celite pad, and the pad cake was washed with AcOEt. All volatiles were removed under reduced pressure to give a yellow oil. The crude oil was basified with 10 M NaOH aq. (20 mL) and extracted with Et₂O (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, evaporated under reduced pressure. ¹H NMR analysis indicated full conversion of the substrate and directly used to the next step without further purification.

***rac*-3-Pivaloyl-(1*S*,2*S*,5*R*)-2-methyl-3-azabicyclo[3.1.0]hexane (1c)**

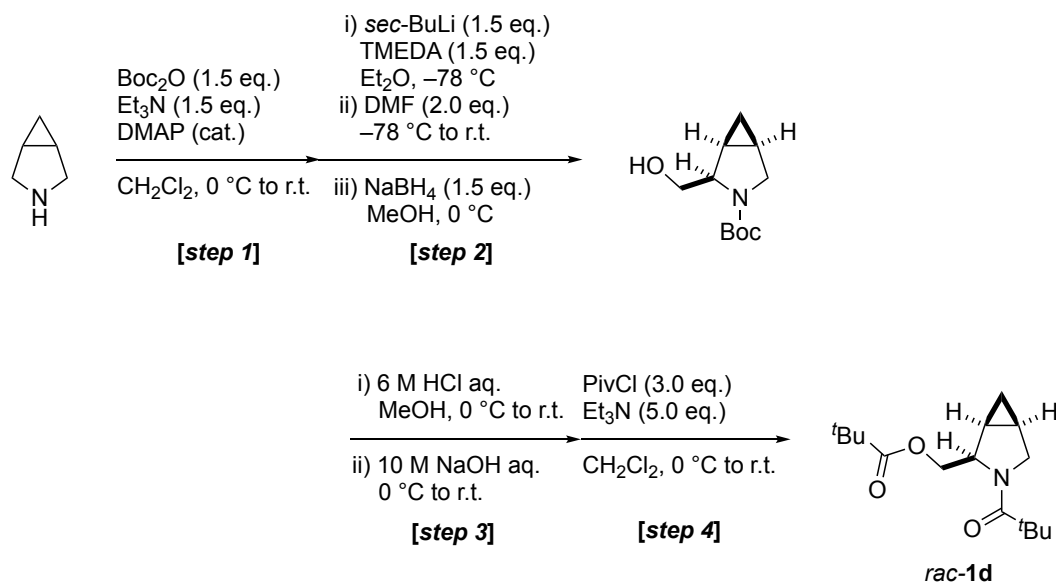


To a round-bottom flask containing the crude amine and Et₃N (44.3 mmol, 6.17 mL) in anhydrous CH₂Cl₂ (100 mL) was dropwise added PivCl (35.4 mmol, 4.31 mL) at 0 °C under argon atmosphere. After stirring for 14 hours at 0 °C to room temperature, the resulting reaction mixture was treated with 1 M HCl aq. (100 mL) and two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (100 mL × 2). The combined organic layers were washed with saturated NaHCO₃ aq. (50 mL × 2), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Purification by MPLC (eluent: hexane/AcOEt = 9/1 to 4/1), followed by vacuum distillation over CaH₂ (0.10 kPa, b.p.

52-53 °C) afforded the title compound in 42% yield (12.5 mmol, 2.27 g, over 4 steps, >20:1 dr) as a colorless oil. Stereochemistry was determined by NOE measurements.

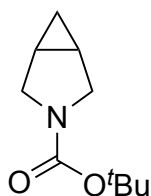
Rf: 0.46 (eluent: hexane/AcOEt = 3/1, PMA); **¹H NMR** (400 MHz, CDCl₃) δ 4.16 (qd, *J* = 6.0, 5.5 Hz, 1H), 3.58 (d, *J* = 9.6 Hz, 1H), 3.68 (dd, *J* = 9.6, 4.6 Hz, 1H), 1.62-1.49 (m, 2H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.18 (s, 9H), 0.55 (ddd, *J* = 8.2, 5.0, 5.0 Hz, 1H), 0.27 (ddd, *J* = 8.2, 4.1, 4.1 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 178.6, 56.5, 51.6, 39.5, 27.7, 21.9, 17.7, 15.7, 7.7; **HRMS (ESI)** exact mass calcd. for C₁₁H₂₀ON: *m/z* 182.1539 ([M+H]⁺), found: *m/z* 182.1535 ([M+H]⁺).

***rac*-((1*S*,2*R*,5*R*)-3-Pivaloyl-3-azabicyclo[3.1.0]hexan-2-yl)methyl pivalate (*rac*-1d)**



Scheme 5-6 Synthetic route to *rac*-1d

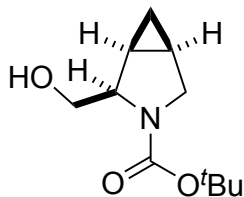
***N*-Boc-3-azabicyclo[3.1.0]hexane**



To a flame-dried round-bottom flask containing 3-azabicyclo[3.1.0]hexane (76.0 mmol, 6.32 g), Et₃N (0.115 mol, 16.0 mL), and a catalytic amount of DMAP in anhydrous CH₂Cl₂ (200 mL) was dropwise added Boc₂O (0.115 mol, 25.1 g) at 0 °C under argon atmosphere. The reaction mixture was gradually warmed up to room temperature and

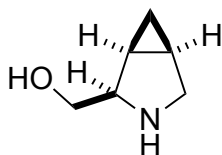
stirred overnight at this temperature. Upon the completion of the reaction, all volatiles were removed by a rotary evaporator. The resulting crude residue was purified by MPLC (eluent: hexane/AcOEt = 100/0 to 80/20) to give the analytically pure title compound in 72% yield (54.9 mmol, 10.1 g) as a colorless oil.

***rac*-(1*S*,2*R*,5*R*)-2-(Hydroxymethyl)-*N*-Boc-3-azabicyclo [3.1.0]hexane**



To a flame-dried two-necked round-bottom flask containing *N*-Boc-3-azabicyclo[3.1.0]hexane (freshly distilled over CaH₂, 25.0 mmol, 4.59 g), TMEDA (distilled over CaH₂, 37.6 mmol, 5.64 mL) in anhydrous Et₂O (50 mL) was dropwise added *sec*-BuLi (1.25 M in *n*-hexane/cyclohexane, 37.6 mmol, 30.1 mL) at –78 °C under argon atmosphere. After stirring for 3 hours at –78 °C to –45 °C, anhydrous DMF (50.0 mmol, 3.87 mL) was quickly added and stirred for 45 min at –45 °C to room temperature, after which the reaction was quenched with saturated NH₄Cl aq. (30 mL). Two layers were separated, and the aqueous layer was extracted with Et₂O (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. To this crude residue in MeOH (50 mL) was portion wise added NaBH₄ (37.6 mmol, 1.42 g) at 0 °C under air. After stirring for 60 min at 0 °C, MeOH was removed under reduced pressure to give an orange viscous oil. The resulting crude mixture was treated with saturated NH₄Cl aq. (20 mL) and extracted with AcOEt (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give a pale-yellow oil (5.57 g), which was used in the next step without further purification.

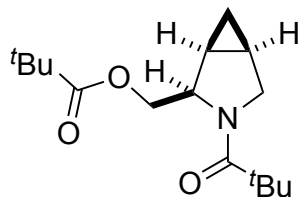
***rac*-(1*S*,2*R*,5*R*)-3-Azabicyclo[3.1.0]hexan-2-yl)methanol**



To a round-bottom flask containing the aforementioned crude mixture (15.5 mmol, 3.30

g, considered to be 100% purity) in MeOH (30 mL) was added 6 M HCl aq. (60 mL) dropwise at 0 °C under air. After the addition, the reaction was gradually warmed up to room temperature and further stirred for 6 hours at this temperature. The reaction mixture was re-cooled down to 0 °C and quenched with 10 M NaOH aq. (pH~10). MeOH was removed under reduced pressure, and the aqueous phase was extracted with Et₂O (30 mL × 6). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to afford a brown oil containing amino alcohol with high purity. The aqueous layer was evaporated under reduced pressure to give pale yellow solid. The solid was treated with TBME (100 mL), filtered to remove solid residue, and the filtrate was evaporated under reduced pressure to afford a colorless solid containing amino alcohol in >95% NMR purity. These two products were combined (1.58 g, yellowish solid) and used in the next step without further purification.

***rac*-((1*S*,2*R*,5*R*)-3-Pivaloyl-3-azabicyclo[3.1.0]hexan-2-yl)methyl pivalate (*rac*-1d)**

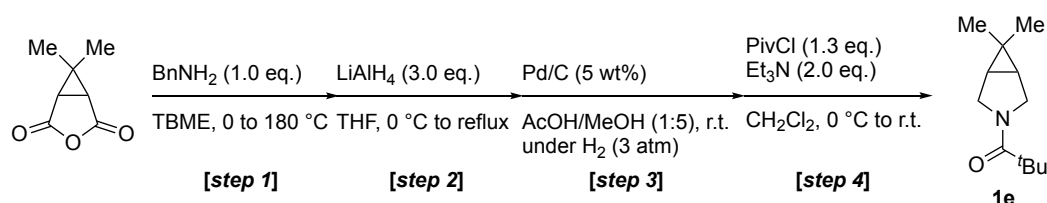


To a round-bottom flask containing the aforementioned amino alcohol and Et₃N (75.0 mmol, 10.5 mL) in anhydrous CH₂Cl₂ (50 mL) was added PivCl (45.0 mmol, 5.48 mL) dropwise at 0 °C under argon atmosphere. After stirring for 23 hours at 0 °C to room temperature, the resulting reaction mixture was treated with 3 M HCl aq. (30 mL) and stirred for 10 min. Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (30 mL × 3). The combined organic layers were washed with saturated NaHCO₃ aq. (50 mL × 1), washed with H₂O (50 mL × 1), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The resulting crude residue was purified by MPLC (eluent: hexane/AcOEt = 9/1 to 7/3) to afford the title compound in 65% yield (9.58 mmol, 2.70 g, over 4 steps) as a colorless solid. Stereochemistry was determined by NOE measurements.

Rf: 0.26 (eluent: hexane/AcOEt = 6/1, *p*-anisaldehyde); **Melting point:** 74-75 °C; **¹H NMR** (400 MHz, CDCl₃) δ 4.58 (dd, *J* = 10.1, 3.7 Hz, 1H), 4.40 (m, 1H), 3.93 (dd, *J* = 10.1, 8.6 Hz, 1H), 3.77 (d, *J* = 2.8 Hz, 2H), 1.73-1.60 (m, 2H), 1.21 (s, 9H), 1.20 (s, 9H), 0.66 (ddd, *J* = 8.0, 5.1, 5.1 Hz, 1H), 0.41 (ddd, *J* = 8.0, 4.1, 4.1 Hz, 1H); **¹³C NMR** (101

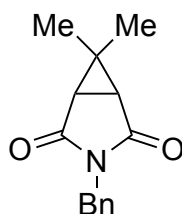
MHz, CDCl₃) δ 179.2, 177.9, 64.1, 59.5, 51.7, 39.6, 38.7, 27.8, 27.2, 18.8, 16.4, 8.4;
HRMS (ESI) exact mass calcd. for C₁₆H₂₇O₃NNa: m/z 304.1883 ([M+Na]⁺), found: m/z 304.1880 ([M+Na]⁺).

3-Pivaloyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane (1e)



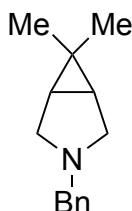
Scheme 5-7 Synthetic route to **1e**

3-Benzyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione



To a round-bottom flask containing caronic anhydride (35.0 mmol, 4.90 g) in TBME (5.0 mL) was added benzylamine (35.0 mmol, 3.83 mL) at 0 °C (**Caution:** *very exothermic*). After stirring for 3 hours at 180 °C, the reaction mixture was cooled to *ca.* 60 °C, and wet ^tPrOH (10 mL containing 5% v/v H₂O) was added. Upon standing at 0 °C, a colorless precipitate was generated, collected by filtration, and washed with a minimal amount of cold ^tPrOH (−78 °C) to give the analytically pure title compound in quantitative yield as a colorless solid in >99% yield (34.8 mmol, 7.98 g).

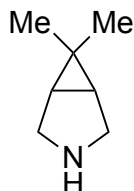
3-Benzyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane



To a flame-dried three-necked round-bottom flask containing LiAlH₄ (105 mmol, 3.98 g) in anhydrous THF (50 mL) was added the aforementioned *N*-benzylimide in anhydrous

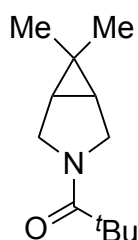
THF (50 mL) at room temperature (**Caution: exothermic**). After stirring for 90 min under reflux (**Note: GC analysis after 60 min indicated the full consumption of the substrate**), the resulting reaction mixture was cooled to 0 °C. To this mixture, a solution containing Rochelle salt (0.210 mol, 59.2 g) and NaOH (0.420 mol, 16.8 g) in H₂O (100 mL) was slowly added. After stirring for 60 min at 45 °C, the reaction mixture was extracted with Et₂O. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give a crude colorless oil, which was used in the next step without purification (not weighed).

6,6-Dimethyl-3-azabicyclo[3.1.0]hexane



To the aforementioned crude mixture in MeOH/AcOH (5:1, 24 mL) was added 10% Pd/C (0.35 g). After stirring for 12 hours at room temperature under 3 atm of hydrogen gas, the reaction mixture was filtered through a Celite pad, and the pad cake was washed with MeOH. All volatiles were removed by evaporation to afford the crude viscous oil. To this crude mixture, 10 M NaOH aq. (20 mL) and TBME (200 mL) were added, and two layers were separated. the organic phase was dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give the crude amine and directly used in the next step (not weighed).

3-Pivaloyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane (1e)

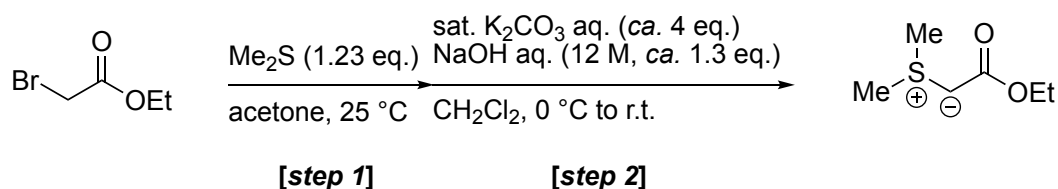


To a round-bottom flask containing the aforementioned crude amine and Et₃N (70.0 mmol, 9.76 mL) in anhydrous CH₂Cl₂ (100 mL) was added PivCl (45.5 mmol, 5.54 mL) at 0 °C under argon atmosphere. After stirring for 12 hours at 0°C to room temperature, the reaction mixture was quenched with 1 M HCl aq. (100 mL) and two layers were separated.

The organic layer was washed with saturated Na₂CO₃ aq. (100 mL × 2), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Purification by MPLC (eluent: hexane/AcOEt = 4/1 to 3/1) afforded the title compound in 66% yield (23.1 mmol, 4.51 g, over 4 steps) as a colorless solid.

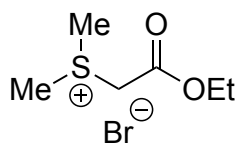
Rf: 0.36 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point:** 55-57 °C; **¹H NMR** (400 MHz, CDCl₃) δ 3.80-3.48 (m, 4H), 1.47-1.27 (m, 2H), 1.22 (s, 9H), 1.02 (s, 3H), 0.89 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.7, 48.5, 47.1, 38.8, 29.1, 27.2, 26.1, 24.8, 18.9, 12.5 (*mixture of rotamers*); **HRMS (ESI)** exact mass calcd. for C₁₂H₂₁ONNa: *m/z* 218.1515 ([M+Na]⁺), found: *m/z* 218.1512 ([M+Na]⁺).

3-Pivaloyl-3-azabicyclo[3.1.0]hexan-6-yl)methyl pivalate (1f)



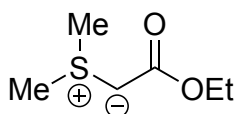
Scheme 5-8 Synthetic route to EDSA

(2-Ethoxy-2-oxoethyl)dimethylsulfonium bromide



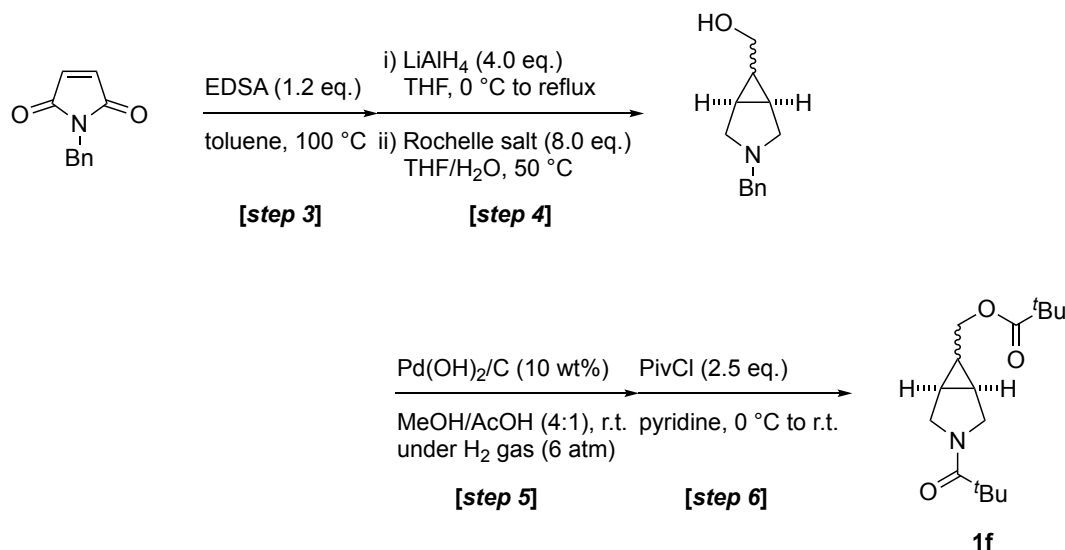
To a round-bottom flask containing ethyl bromoacetate (0.150 mol, 25.3 g) in acetone (25 mL) was added dimethylsulfide (0.184 mol, 13.5 mL) in one portion at 25 °C under argon atmosphere. After stirring for 19 hours at this temperature, the resulting white slurry was filtered and washed with acetone (*ca.* 20 mL). The resulting colorless solid was dried under high vacuum at room temperature to give the target sulfonium bromide in 84% yield (0.127 mmol, 29.1 g).

Ethyl (dimethylsulfanylidene)acetate (EDSA)



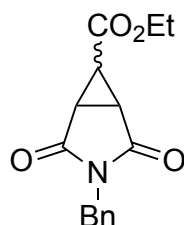
To a round-bottom flask containing the aforementioned sulfonium bromide (50.0 mmol,

11.5 g) in CH_2Cl_2 (50 mL), saturated K_2CO_3 aq. (25.0 mL containing 28 g of K_2CO_3) and 12.5 M NaOH aq. (5.25 mL containing 2.63 g of NaOH) were sequentially added at 0 °C. The resulting mixture was stirred for 10 min at this temperature and then, warmed to room temperature. After stirring for 30 min at this temperature, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The resulting mixture was transferred to a separation funnel, the lower aqueous layer was removed (*Note: the layers are inverted due to the high concentration of salts in the aqueous phase*). The organic layer was filtered through Celite pad, and the pad cake was washed with CH_2Cl_2 (100 mL). The combined organic layers were evaporated under reduced pressure to afford the title compound in 88% yield (44.1 mmol, 6.54 g) as a faint yellow oil. This oil was directly used in the next step without further purification.



Scheme 5-9 Synthetic route to **1f**

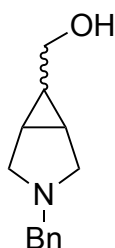
Ethyl 3-benzyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate



A three-necked round-bottom flask (equipped with an addition funnel and a thermometer) containing *N*-benzylmaleimide (36.8 mmol, 6.88 g) in anhydrous toluene (85 mL) was

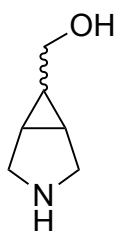
heated to 100 °C (internal temperature, bath temperature was adjusted to 110 °C). To this solution was quickly added EDSA (44.1 mmol, 6.54 g) in anhydrous toluene (85 mL) *via* addition funnel (**Note:** It took 30 sec. The internal temperature dropped down from 100 to 80 °C during this process and it took 4 min to reach back to 100 °C.) After stirring for 3 hours at this temperature, the resulting mixture was evaporated under reduced pressure to afford a highly viscous red oil, which was used in the next step without purification (not weighed).

(3-Benzyl-3-azabicyclo[3.1.0]hexan-6-yl)methanol



To a flame-dried three-necked round-bottom flask containing the aforementioned crude oil in anhydrous THF (120 mL) was added LiAlH₄ (0.147 mol, 5.58 g) portion wise at 0 °C under argon atmosphere. After stirring for 11 hours under reflux, the reaction mixture was cooled to room temperature and quenched with the very slow addition of aqueous Rochelle salt (2 M, 0.294 mol, 82.9 g). The resulting mixture was stirred for 30 min at 50 °C. Upon cooling to room temperature, the resulting mixture was diluted with AcOEt (200 mL) and H₂O (150 mL). Two layers were separated, and the aqueous layer was extracted with AcOEt (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Assay by ¹H NMR indicated a 50:50 *endo/exo* mixture of the title compound, which was used in the next step without purification.

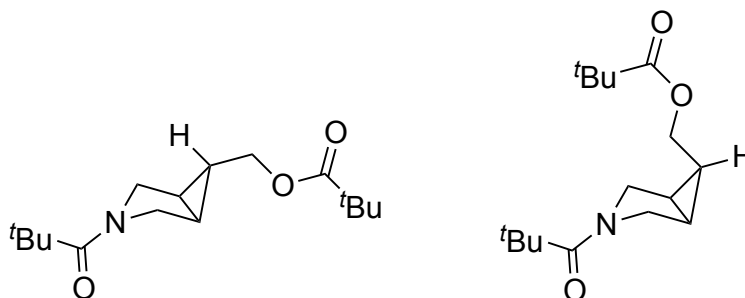
(3-Azabicyclo[3.1.0]hexan-6-yl)methanol



To the aforementioned crude material in MeOH (50 mL) was added Pd(OH)₂/C (0.75 g)

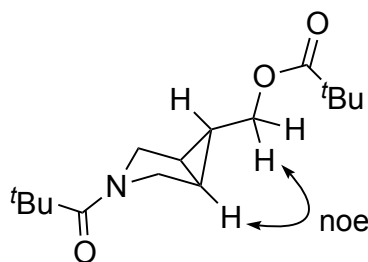
at room temperature. The reaction vessel was purged with hydrogen (6 atm). After stirring for 21 hours at room temperature under 6 atm of hydrogen gas, the reaction mixture was filtered through a Celite pad, and the pad cake was washed with AcOEt (30 mL). Removal of solvents under reduced pressure afforded a yellow oil. ^1H NMR analysis indicated almost no conversion of the substrate. The resulting mixture was roughly purified by MPLC (eluent: hexane/AcOEt = 50/50/ to 0/100). To this residue in MeOH/AcOH (4:1, 50 mL) was added $\text{Pd}(\text{OH})_2/\text{C}$ (0.75 g) at room temperature. The reaction vessel filled with hydrogen (6 atm). After stirring for 24 days at room temperature under 6 atm of hydrogen gas, the reaction mixture was filtered through a Celite pad, and the pad cake was washed with AcOEt (50 mL). Removal of solvents under reduced pressure afforded a yellow oil. ^1H NMR analysis indicated the remaining substrate and directly used in the next step without isolation.

3-Pivaloyl-3-azabicyclo[3.1.0]hexan-6-yl)methyl pivalate (**1f**)



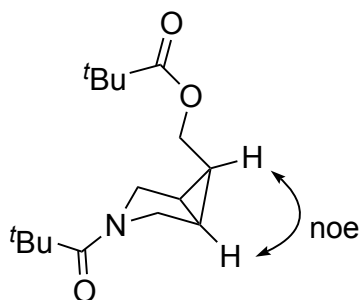
To a round-bottom flask containing the aforementioned crude mixture in pyridine (super-dehydrated, 50 mL) was added PivCl (92.0 mmol, 11.2 mL) at 0 °C under argon atmosphere. After stirring for 19 hours at 0 °C to room temperature, the reaction mixture was quenched with 3 M HCl aq. (50 mL) and extracted with CH_2Cl_2 (100 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 1), dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The resulting crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 3/1) to afford the inseparable *endo/exo* mixture of the title compound. These two products were separated by preparative recycling HPLC (eluent: hexane/ i PrOH = 95/5, flow rate: 20.0 mL/min, λ = 215 nm) to afford *endo*-**1f** in 6.1% yield (2.25 mmol, 632 mg) as a colorless solid and *exo*-**1f** in 3.8% yield (1.39 mmol, 391 mg) as a colorless solid, respectively. The stereochemistry of these products was assigned by NOE analysis respectively.

(1 α ,5 α ,6 α)-3-Pivaloyl-3-azabicyclo[3.1.0]hexan-6-yl)methyl pivalate (*exo*-1f)



Rf: 0.21 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point:** 74-75 °C; **¹H NMR** (400 MHz, CDCl₃, 50 °C) δ 3.96 (d, J = 7.1 Hz, 2H), 3.91 (d, J = 11.3 Hz, 2H), 3.48 (d, J = 11.3 Hz, 2H), 1.57-1.48 (m, 2H), 1.21 (s, 9H), 1.19 (s, 9H), 0.91 (tt, J = 7.1, 3.2 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 178.4, 177.2, 65.1, 49.5, 39.0, 38.8, 27.5, 27.1, 20.9, 20.7 (br); **HRMS (ESI)** exact mass calcd. for C₁₆H₂₇O₃NNa: m/z 304.1883 ([M+Na]⁺), found: m/z 304.1882 ([M+Na]⁺).

(1 α ,5 α ,6 β)-3-Pivaloyl-3-azabicyclo[3.1.0]hexan-6-yl)methyl pivalate (*endo*-1f)



Rf: 0.21 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point:** 64-65 °C; **¹H NMR** (400 MHz, CDCl₃, 50 °C) δ 4.01 (d, J = 7.8 Hz, 2H), 3.81 (d, J = 11.8 Hz, 2H), 3.69 (d, J = 11.8 Hz, 2H), 1.82-1.67 (m, 2H), 1.27 (t, J = 7.8 Hz, 1H), 1.21 (s, 9H), 1.18 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 178.3, 176.0, 59.8, 47.5, 39.0, 38.7, 27.2, 27.2, 19.5, 18.7; **HRMS (ESI)** exact mass calcd. for C₁₆H₂₇O₃NNa: m/z 304.1883 ([M+Na]⁺), found: m/z 304.1881 ([M+Na]⁺).

HPLC analysis

Separation conditions for the *endo/exo* mixture were investigated using an analytical HPLC apparatus (COSMOSIL 5SL-II packed column, eluent: hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, λ = 210 nm, t_R (*exo*) = 9.00 min and t_R (*endo*) = 10.44 min).

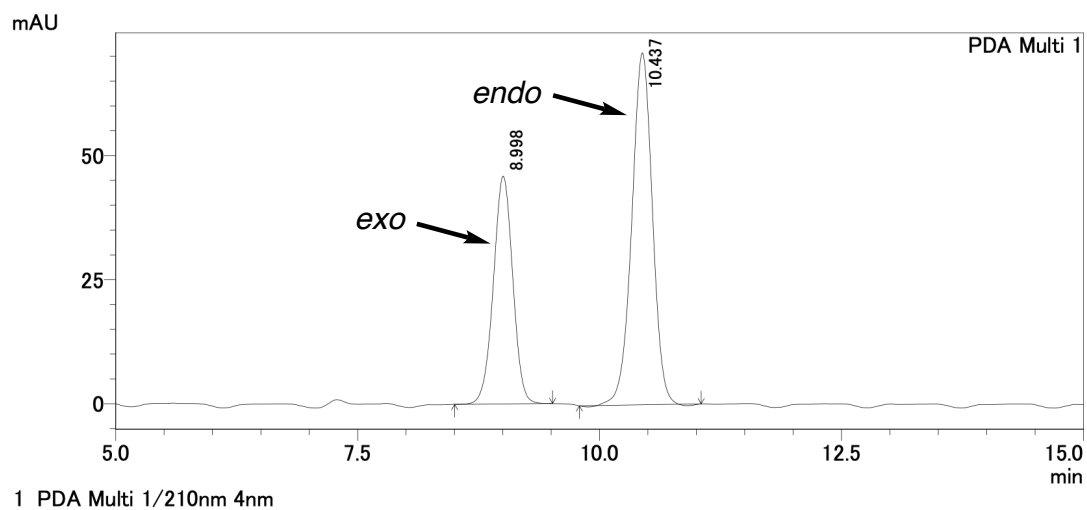
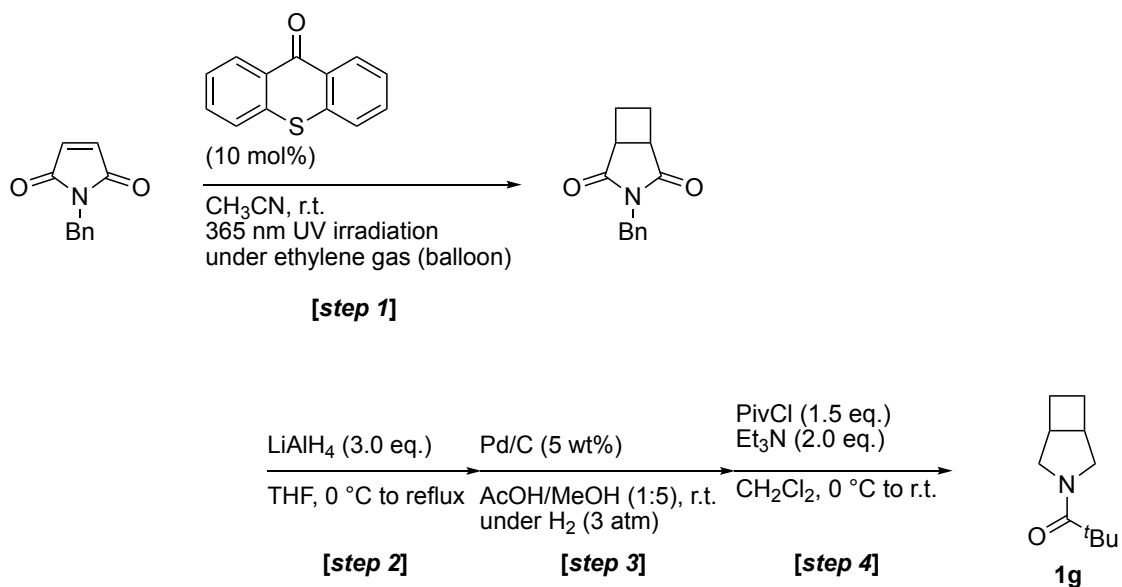


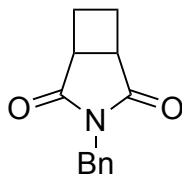
Figure 5-4 HPLC traces of the mixture of *exo*-**1f** and *endo*-**1f**

3-Pivaloyl-3-azabicyclo[3.2.0]heptane (**1g**)



Scheme 5-10 Synthetic route to **1g**

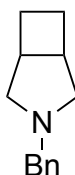
3-Benzyl-3-azabicyclo[3.2.0]heptane-2,4-dione



This compound was prepared according to modified literature procedures.^{43,44} To a stirred

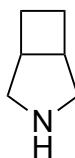
solution of *N*-benzylmaleimide (12.2 mmol, 2.28 g) and 9*H*-thioxanthen-9-one (1.2 mmol, 0.26 g) in CH₃CN (distilled over MS4Å, 100 mL), ethylene gas was bubbled for 3 min at room temperature. After stirring for 4 days under photoirradiation with UV light (365 nm) under an ethylene gas atmosphere (**Note:** *The reaction was monitored by GC*), all volatiles were evaporated under reduced pressure. The crude residue was purified by MPLC (eluent: hexane/AcOEt = 9/1 to 7/3) to give an analytically pure title compound in 84% yield (8.41 mmol, 1.81 g) as a faint yellow solid (3 batches).

3-Benzyl-3-azabicyclo[3.2.0]heptane



To a flame-dried three-necked round-bottom flask containing LiAlH₄ (70.1 mmol, 2.66 g) in anhydrous THF (70 mL) was added dropwise the aforementioned *N*-benzylamide (23.4 mmol, 5.03 g) in anhydrous THF (30 mL) at room temperature (**Caution:** *exothermic*). After stirring for 60 min under reflux (**Note:** *GC analysis after 30 min indicated the full consumption of the substrate*), the reaction mixture was cooled to 0 °C and quenched with the solution containing Rochelle salt (0.140 mol, 39.5 g) and NaOH (0.280 mol, 11.2 g) in H₂O (100 mL). After stirring for 60 min at 45 °C, the reaction mass was extracted with Et₂O, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give a crude mixture, which was directly used without further purification (not weighed).

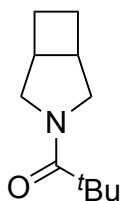
3-Azabicyclo[3.2.0]heptane



To the aforementioned crude *N*-benzylamine in MeOH (50 mL) was added Pd(OH)₂/C (0.33 g) at room temperature. The reaction vessel was substituted with hydrogen (6 atm). After stirring for 2 days at room temperature under 6 atm of hydrogen gas, the reaction mixture was filtered through Celite pad, and the pad cake was washed with AcOEt.

Removal of solvents under reduced pressure afforded a yellow oil. ^1H NMR analysis indicated *ca.* 40% conversion of the substrate. To this residue in MeOH/AcOH (4:1, 38 mL) was added $\text{Pd}(\text{OH})_2/\text{C}$ (0.44 g) at room temperature. The reaction vessel was substituted with hydrogen (6 atm). After stirring for 2 days at room temperature under 6 atm of hydrogen gas, the reaction mixture was filtered through a Celite pad, and the pad cake was washed with AcOEt. All volatiles were removed under reduced pressure to give a yellow oil. The crude oil was basified with 10 M NaOH aq. (20 mL) and extracted with Et_2O (50 mL $\times$ 4). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. ^1H NMR analysis indicated full conversion of the substrate and directly used in the next step without isolation (not weighed).

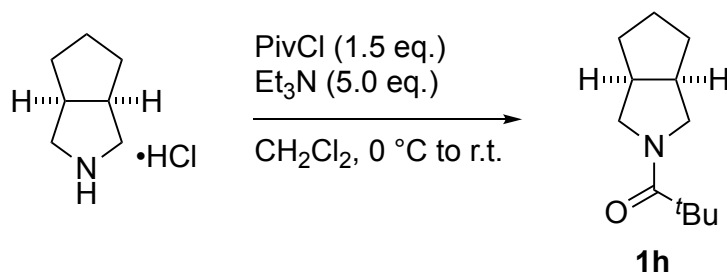
3-Pivaloyl-3-azabicyclo[3.2.0]heptane (1g)



To the crude mixture obtained in step 3 in anhydrous CH_2Cl_2 (60 mL), Et_3N (46.8 mmol, 6.52 mL) and PivCl (35.1 mmol, 4.28 mL) were sequentially added at 0 °C under argon atmosphere. After stirring for 20 hours at room temperature, the reaction was quenched with 3 M HCl aq. (20 mL). Two layers were separated and the organic layer was washed with saturated Na_2CO_3 aq. (30 mL $\times$ 1), dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure to give a crude colorless solid. Purification by MPLC (eluent: hexane/AcOEt = 3/1) afforded the title compound in 60% yield (14.0 mmol, 2.54 g, over 3 steps) as a colorless solid.

Rf: 0.40 (eluent: hexane/AcOEt = 2/1, *p*-anisaldehyde); **Melting point:** 58-60 °C; **^1H NMR** (400 MHz, CDCl_3) δ 3.90 (d, J = 11.9 Hz, 2H), 3.31 (dd, J = 11.9, 6.9 Hz, 2H), 2.98-2.82 (m, 2H), 2.24-2.13 (m, 2H), 1.72-1.62 (m, 2H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, CDCl_3) δ 177.3, 54.1, 39.0, 36.8 (br), 27.8, 24.1; **HRMS (ESI)** exact mass calcd. for $\text{C}_{11}\text{H}_{20}\text{ON}$: m/z 182.1539 ($[\text{M}+\text{H}]^+$), found: m/z 182.1536 ($[\text{M}+\text{H}]^+$).

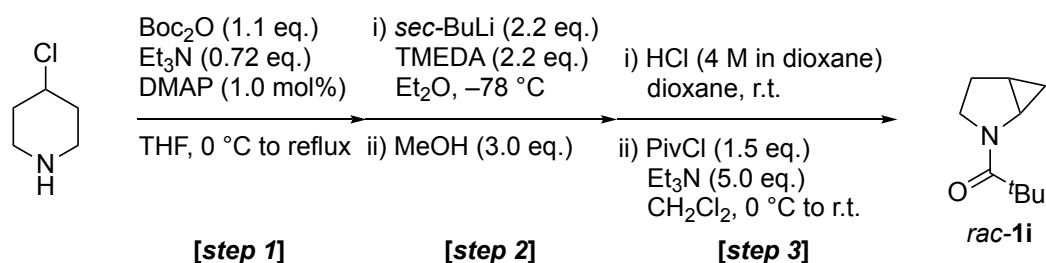
2-Pivaloyl-(3*R*,6*aS*)-octahydrocyclopenta[*c*]pyrrole (**1h**)



To a round-bottom flask containing (3*R*,6*aS*)-octahydrocyclopenta[*c*]pyrrole hydrochloride (20.0 mmol, 2.95 g) and Et₃N (0.100 mol, 13.9 mL) in anhydrous CH₂Cl₂ (60 mL) was added dropwise PivCl (30.0 mmol, 3.65 mL) at 0 °C under argon atmosphere. After stirring for 4 hours at room temperature, the reaction was quenched with 3 M HCl aq. (50 mL) and two layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were sequentially washed with saturated Na₂CO₃ aq. (50 mL × 2) and brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to afford a crude pale yellow solid, which was purified by MPLC (eluent: hexane/AcOEt = 4/1 to 3/1) to give the title compound in 87% yield (17.5 mmol, 3.41 g) as a colorless solid.

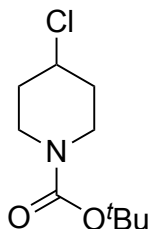
Rf: 0.28 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point:** 43-44 °C; **¹H NMR** (400 MHz, CDCl₃) δ 3.76-3.63 (m, 2H), 3.39 (dd, *J* = 11.9, 3.5 Hz, 2H), 2.84-2.38 (m, 2H), 1.88-1.76 (m, 2H), 1.76-1.66 (m, 1H), 1.65-1.53 (m, 1H), 1.51-1.39 (m, 2H), 1.25 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃, 60 °C) δ 176.2, 53.6, 42.4, 38.8, 32.1, 27.6, 25.5; **HRMS (ESI)** exact mass calcd. for C₁₂H₂₂ON: *m/z* 196.1696 ([*M*+*H*]⁺), found: *m/z* 196.1692 ([*M*+*H*]⁺).

rac-2-Pivaloyl-(1*R*,5*S*)-2-azabicyclo[3.1.0]hexane (*rac*-**1i**)^{27b}



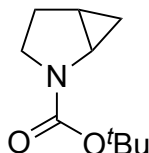
Scheme 5-11 Synthetic route to *rac*-**1i**

***N*-Boc-4-chloropiperidine**



To a round-bottom flask containing 4-chloropiperidine (50.0 mmol, 5.49 mL) in anhydrous THF (100 mL) were sequentially added Et₃N (35.9 mmol, 5.00 mL) and DMAP (0.500 mmol, 61.1 mg) at room temperature under argon atmosphere. The resulting mixture was cooled to 0 °C and Boc₂O (55.0 mmol, 12.0 g) was added dropwise. Upon the completion of the addition, the reaction mixture was heated to 65 °C and stirred for 12 hours at this temperature. The resulting mixture was cooled to room temperature, diluted with AcOEt (400 mL), and washed with 10% aqueous citric acid (100 mL). Two layers were separated and the organic layer was dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was purified by MPLC (eluent: hexane/AcOEt = 9/1) to afford the title compound in 90% yield (45.2 mmol, 9.93 g) as a colorless oil.

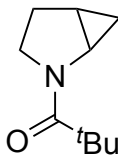
***N*-Boc-2-azabicyclo[3.1.0]hexane**



To a flame-dried three-necked round-bottom flask containing *N*-Boc-4-chloropiperidine (30.0 mmol, 6.59 g) in anhydrous Et₂O (180 mL) was added TMEDA (distilled over CaH₂, 66.0 mmol, 9.90 mL) at room temperature under argon atmosphere. The resulting mixture was cooled to –78 °C and *sec*-BuLi (1.25 M in *n*-hexane/cyclohexane, 66.0 mmol, 52.8 mL) was added dropwise. After stirring for 90 min at this temperature, the reaction was quenched with MeOH (90.0 mmol, 3.64 mL) at –78 °C and gradually warmed up to room temperature. To the resulting mixture was added H₂O (50 mL) and two layers were separated. The aqueous layer was extracted with Et₂O (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to afford crude oil, which was directly used for the next step without further purification.

(not weighed).

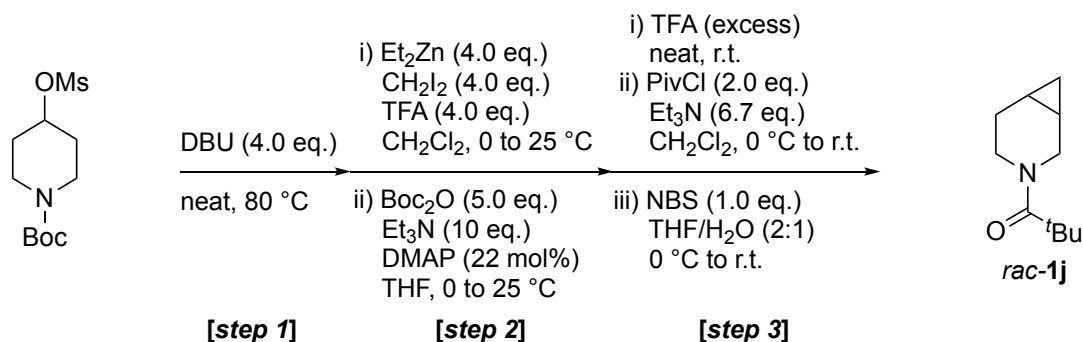
***rac*-2-Pivaloyl-(1*R*,5*S*)-2-azabicyclo[3.1.0]hexane (1i)**



To a round-bottom flask containing the aforementioned crude oil was added HCl (4 M in dioxane, 60 mL) at room temperature under argon atmosphere (**Caution:** *gas bubbles vigorously*). After stirring for 30 min at room temperature, all volatiles were removed under reduced pressure to afford a yellowish solid. The solid was suspended in CH₂Cl₂ (100 mL) and Et₃N (0.150 mol, 20.9 mL) was added dropwise under argon atmosphere at 0 °C (**Caution:** *exothermic*), followed by the slow addition of PivCl (45.0 mmol, 5.48 mL). The resulting mixture was warmed to room temperature and stirred for 9 hours at this temperature before being quenched with 3 M HCl aq. (50 mL). Two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (100 mL × 3). The combined organic layers were washed with saturated NaHCO₃ aq. (100 mL × 1), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Purification by flash column chromatography (eluent: hexane/AcOEt = 4/1), followed by vacuum distillation over CaH₂ (0.10 kPa, b.p. 60-62 °C) afforded the title compound in 76% yield (22.7 mmol, 3.79 g, over 2 steps) as a colorless solid (colorless oil at 25 °C).

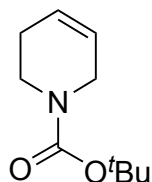
Rf: 0.32 (eluent: hexane/AcOEt = 2/1, *p*-anisaldehyde); **¹H NMR** (400 MHz, CDCl₃) δ 3.90 (ddd, *J* = 12.8, 10.3, 3.2 Hz, 1H), 3.65-3.45 (m, 1H), 3.16 (ddd, *J* = 12.8, 8.7, 8.7 Hz, 1H), 2.14-1.97 (m, 1H), 1.89 (ddd, *J* = 12.3, 8.7, 3.2 Hz, 1H), 1.80-1.65 (m, 1H), 1.32 (s, 9H), 0.83 (ddd, *J* = 8.7, 6.0, 5.5 Hz, 1H), 0.54 (ddd, *J* = 5.5, 5.3, 2.7 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 177.2, 46.8, 38.8, 36.6, 27.6, 24.3, 18.8, 13.6; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₇ONNa: *m/z* 190.1202 ([M+Na]⁺), found: *m/z* 190.1200 ([M+Na]⁺).

***rac*-3-Pivaloyl-(1*R*,6*R*)-3-azabicyclo[4.1.0]heptane (*rac*-1j)^{28,35}**



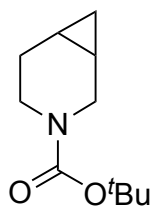
Scheme 5-12 Synthetic route to *rac*-1j

***N*-Boc-1,2,3,6-tetrahydropyridine**



To a round-bottom flask containing commercial *N*-Boc-4-((methylsulfonyl)oxy)piperidine (50.0 mmol, 14.0 g) was added DBU (0.200 mol, 29.9 mL) at room temperature in one portion. The resulting mixture was stirred for 16 hours at 80 °C. Upon cooling to room temperature, H₂O (100 mL) and AcOEt (200 mL) were sequentially added. Two layers were separated and the aqueous layer was extracted with AcOEt (100 mL × 3). The combined organic layers were sequentially washed with 1 M HCl aq. (100 mL × 3), saturated NaHCO₃ aq. (100 mL × 2), and brine (50 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to afford a faint yellow oil, which was used to the next step without further purification.

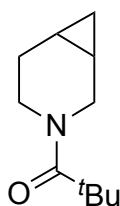
***N*-Boc-3-azabicyclo[4.1.0]heptane**



To a flame-dried three-necked round-bottom flask containing anhydrous CH₂Cl₂ (75 mL)

was added Et₂Zn (1.0 M in hexanes, 60.0 mmol, 60.0 mL) at 0 °C under argon atmosphere. To this solution, TFA (60.0 mmol, 4.59 mL) in anhydrous CH₂Cl₂ (15 mL) was added dropwise *via* syringe and the reaction mixture was stirred for 40 min at 0 °C. After that, CH₂I₂ (60.0 mmol, 4.84 mL) in anhydrous CH₂Cl₂ (15 mL) was added dropwise *via* syringe, followed by the injection of air (15 mL) *via* syringe. The resulting mixture was stirred for 40 min at 0 °C to form a colorless solution. *N*-Boc-1,2,3,6-tetrahydropyridine (15.0 mmol, 2.75 g) in anhydrous CH₂Cl₂ (45.0 mL) was added dropwise *via* syringe, and the reaction was allowed to warm to room temperature. After stirring for 12 hours at room temperature, the crude mixture was partially concentrated to one-quarter volume. Anhydrous THF (100 mL) was added and the solution was cooled to 0 °C, followed by the sequential addition of Et₃N (0.150 mol, 20.9 mL), DMAP (3.25 mmol, 0.397 g), and Boc₂O (75.0 mmol, 16.4 g). After stirring for 9 hours at 25 °C, the reaction was quenched with saturated NH₄Cl aq. (60 mL) and diluted with AcOEt (300 mL) and H₂O (300 mL). Two layers were separated and the aqueous layer was extracted with AcOEt (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give a deep bloody-red oil. This oil was roughly purified by flash column chromatography (eluent: hexane/AcOEt = 2/1) to afford the title compound (containing *ca.* 9% of the unreacted substrate) as a yellow oil and used to the next step without further purification.

1-(3-Azabicyclo[4.1.0]heptan-3-yl)-2,2-dimethylpropan-1-one (1j)



To a round-bottom flask containing the aforementioned yellow oil was added TFA (20 mL) and the mixture was stirred for 20 min at room temperature under air (**Caution:** *gas bubbles vigorously*). An excess amount of TFA was removed under reduced pressure and diluted with anhydrous CH₂Cl₂ (100 mL). The mixture was allowed to cool to 0 °C, followed by the sequential addition of Et₃N (0.100 mol, 13.9 mL) and PivCl (30.0 mmol, 3.65 mL). After stirring for 13 hours at 0 °C to room temperature, the reaction mixture was quenched with 3 M HCl aq. (50 mL) and two layers were separated. the aqueous

layer was extracted with CH_2Cl_2 (100 mL $\times$ 3). The combined organic layers were washed with saturated NaHCO_3 aq. (50 mL), dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure to give a crude yellow oil. We found that contaminating olefin prohibited clean isolation of the title compound. Therefore, the olefin was removed by hydroxy bromination of the crude oil. To a round-bottom flask containing the crude oil in THF/ H_2O (2:1, 60 mL) was added NBS (freshly recrystallized from hot water (*vide infra*), 15.0 mmol, 2.67 g,) at 0 °C under argon atmosphere. After that, the reaction was allowed to warm to room temperature and further stirred for 60 min. The reaction mixture was diluted with AcOEt (200 mL) and quenched with saturated NaHCO_3 aq. (50 mL). two layers were separated, and the aqueous layer was extracted with AcOEt (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. the crude residue was purified by flash column chromatography (eluent: hexane/AcOEt = 8/1), followed by vacuum distillation over CaH_2 (0.10 kPa, b.p. 60-62 °C) to afford the title compound in 48% yield (7.22 mmol, 1.31 g, over 3 steps) as a colorless oil.

Rf: 0.26 (eluent: hexane/AcOEt = 4/1, *p*-anisaldehyde); **^1H NMR** (400 MHz, CDCl_3) δ 4.05 (d, J = 13.3 Hz, 1H), 3.66 (ddd, J = 14.0, 5.6, 5.1 Hz, 1H), 3.61 (dd, J = 13.3, 3.2 Hz, 1H), 3.00 (ddd, J = 14.0, 9.9, 5.1 Hz, 1H), 1.95 (dddd, J = 14.5, 7.9, 5.1, 5.1 Hz, 1H), 1.72 (ddd, J = 14.5, 9.9, 5.6 Hz, 1H), 1.25 (s, 9H), 1.09-0.96 (m, 2H), 0.64 (ddd, J = 8.7, 8.7, 5.0 Hz), 0.14 (ddd, J = 5.2, 5.2, 5.0 Hz, 1H); **^{13}C NMR** (101 MHz, CDCl_3) δ 176.6, 44.0, 42.1, 38.5, 28.3, 23.1, 10.2, 9.2, 7.3; **HRMS (ESI)** exact mass calcd. for $\text{C}_{11}\text{H}_{20}\text{ON}$: m/z 182.1539 ($[\text{M}+\text{H}]^+$), found: m/z 182.1536 ($[\text{M}+\text{H}]^+$).

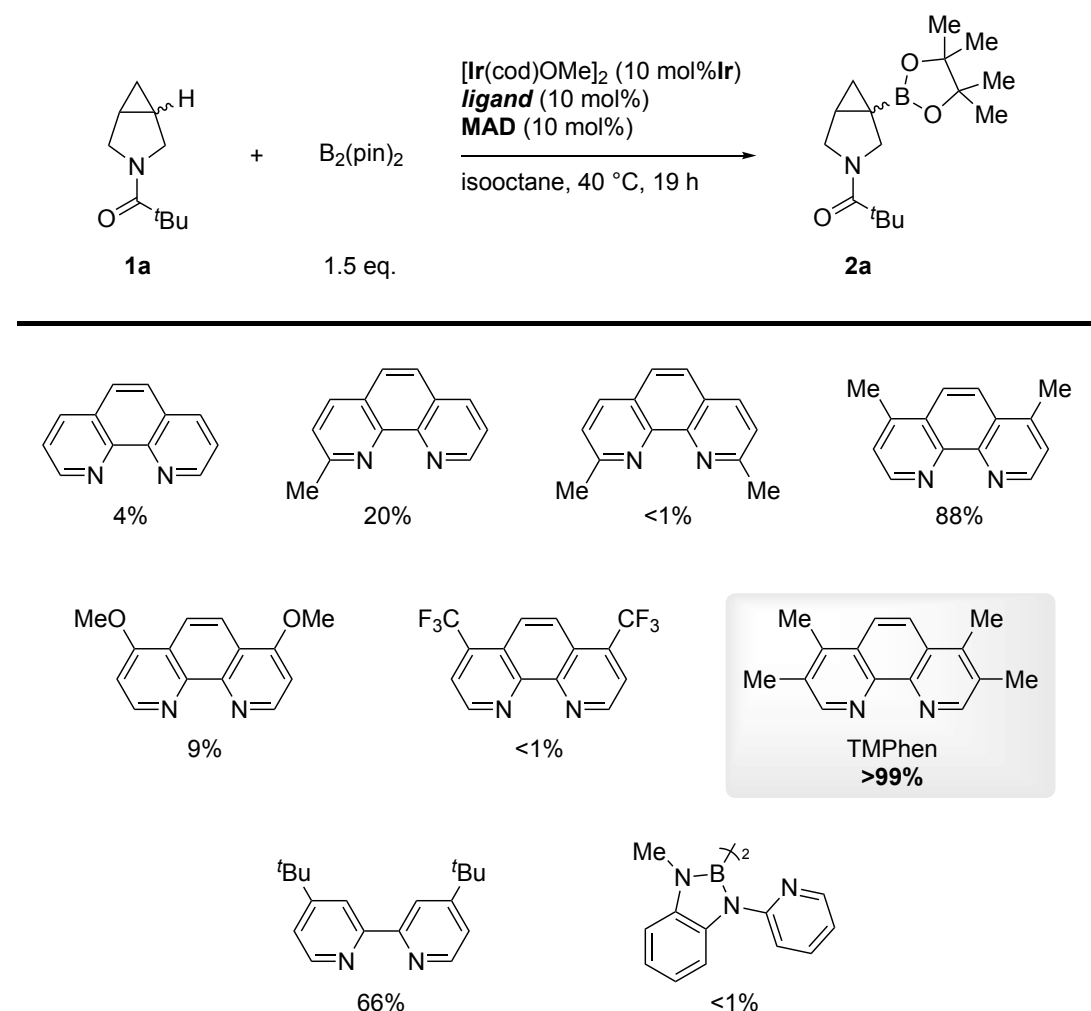
Note: recrystallization of *N*-bromosuccinimide was performed as follows.

To an Erlenmeyer flask containing 40 mL of pre-heated (90 °C) distilled water was added NBS (4.0 g) with stirring to dissolve completely. The flask was placed in an ice bath without stirring to give a colorless crystalline solid. The solid was collected by filtration, washed with a minimal amount of cold distilled water, and dried under high vacuum at 30 °C to afford 3.0 g of pure NBS, which was immediately used in the aforementioned reaction.

5.5.2 Racemic C–H borylation of bicyclic amines

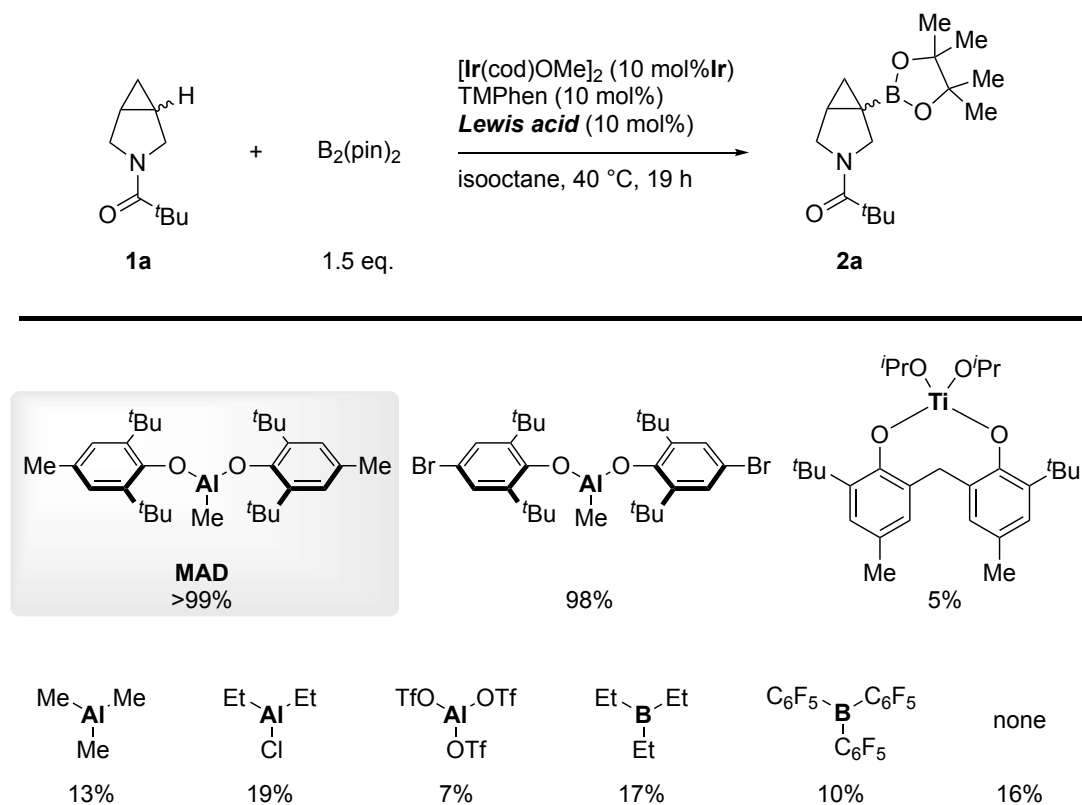
5.5.2.1 Optimization of reaction conditions

Table 5-3 Ligand screening^{a,b}



^aReaction conditions: **1a** (0.100 mmol), $\text{B}_2(\text{pin})_2$ (0.150 mmol), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.00500 mmol), ligand (0.0100 mmol), and MAD (0.0100 mmol) in isooctane (0.50 mL) at 40 °C for 19 h. ^bYield was determined by GC-FID analysis using n-dodecane as an internal standard.

Table 5-4 Lewis acid screening^{a,b}



^aReaction conditions: **1a** (0.100 mmol), $\text{B}_2(\text{pin})_2$ (0.150 mmol), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.00500 mmol), TMPhen (0.0100 mmol), and Lewis acid (0.0100 mmol) in isooctane (0.50 mL) at 40 °C for 19 h. ^bYield was determined by GC-FID analysis using *n*-dodecane as an internal standard.

5.5.2.2 General procedure

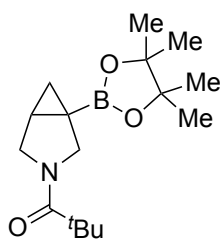
In a nitrogen-filled glovebox, a 15 mL vial charged with $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), TMAPhen (0.10 mmol, 23.6 mg), and $\text{B}_2(\text{pin})_2$ (1.50 mmol, 381 mg) in isooctane (5.0 mL) was sealed with a Teflon-lined cap, placed into a pre-heated aluminum block (70 °C) and stirred for 30 min to prepare an iridium complex (*Note: generally, the reaction mixture turns into dark green color*). Upon cooling to room temperature, MAD (0.100 mmol, 48.0 mg) and substrate (1.00 mmol) were sequentially added to this solution. The 15 mL vial was then sealed with a Teflon-lined cap and removed from the glovebox. After stirring under the designated conditions, the reaction mixture was cooled to room temperature and exposed to the air to quench the reaction. The resulting crude mixture was purified by silica gel flash column chromatography.

Notes:

Borylated products are unstable on silica gel column chromatography should be done very quickly (≤ 10 min) to prevent the decomposition or over-adsorption of the product. If pinacol still remains after column chromatography, it can be removed under high vacuum in a desiccator at 70-80 °C.

In many cases, isolated borylation products are first obtained as a very viscous oil, which can be solidified by standing them under high vacuum for 1-2 days at room temperature.

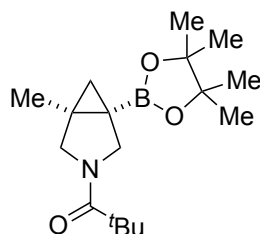
rac-3-Pivaloyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane (*rac*-2a)



This reaction was performed with **1a** (1.00 mmol, 167 mg), $\text{B}_2(\text{pin})_2$ (1.50 mmol, 381 mg), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), TMAPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 40 °C for 20 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 5/1) to afford the title compound in 89% yield (0.891 mmol, 261 mg) as a colorless solid.

R_f: 0.40 (eluent: hexane/AcOEt = 2/1, *p*-anisaldehyde); **Melting point**: 68-70 °C; **¹H NMR** (400 MHz, CDCl₃): δ 3.98 (d, *J* = 11.1 Hz, 1H), 3.84 (d, *J* = 11.1 Hz, 1H), 3.55 (*virt* brs, 1H), 3.42 (*virt* brs, 1H), 1.73-1.60 (m, 1H), 1.23 (s, 12H), 1.21 (s, 9H), 0.96-0.87 (m, 1H), 0.39-0.31 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃): δ 177.4, 83.4, 50.7, 49.3, 39.0, 27.5, 24.6, 21.5, 14.0 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **HRMS (ESI)** exact mass calcd. for C₁₆H₂₉O₃NB: *m/z* 294.2235 ([M+H]⁺), found: *m/z* 294.2232 ([M+H]⁺).

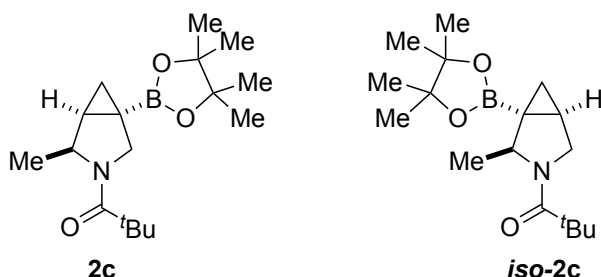
***rac*-3-Pivaloyl-(1*S*,5*R*)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane (*rac*-2b)**



This reaction was performed with *rac*-**1b** (1.00 mmol, 181 mg), B₂(pin)₂ (1.50 mmol, 381 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 60 °C for 20 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 5/1) to afford the title compound in 93% yield (0.934 mmol, 287 mg) as a colorless solid.

R_f: 0.31 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point**: 78-79 °C; **¹H NMR** (400 MHz, CDCl₃) δ 3.99 (d, *J* = 11.2 Hz, 1H), 3.82 (d, *J* = 11.2 Hz, 1H), 3.62 (br, 1H), 3.20 (br, 1H), 1.30 (s, 3H), 1.25 (s, 6H), 1.23 (s, 6H), 1.21 (s, 9H), 0.86 (d, *J* = 4.0 Hz, 1H), 0.49 (d, *J* = 4.0 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 177.0, 83.4, 54.9, 52.1, 38.9, 27.6, 25.1, 24.6, 20.2, 16.7 (*One ¹³C signal was not detected probably due to peak broadening*); **HRMS (ESI)** exact mass calcd. for C₁₇H₃₀O₃NBNa: *m/z* 330.2211 ([M+Na]⁺), found: *m/z* 330.2212 ([M+Na]⁺).

rac-3-Pivaloyl-(1*R*,4*S*,5*S*)-4-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane (*rac*-**2c**) and *rac*-3-Pivaloyl-(1*S*,2*S*,5*R*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane (*rac*-*iso*-**2c**)



This reaction was performed with *rac*-**1c** (1.00 mmol, 181 mg), B₂(pin)₂ (1.50 mmol, 381 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 80 °C for 20 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 5/1) to afford the title compound in 60% yield (0.599 mmol, 184 mg) as a colorless solid [**2c/iso-2c** = 86/14].

Rf: 0.46 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **¹H NMR** (400 MHz, CDCl₃) δ 4.25 (q, *J* = 5.9 Hz, 0.14H), 4.16 (qd, *J* = 6.0, 4.7 Hz, 0.86H), 3.88 (d, *J* = 9.8 Hz, 0.14H), 3.78 (d, *J* = 10.2 Hz, 0.86H), 3.71 (d, *J* = 10.2 Hz, 0.86H), 3.66 (dd, *J* = 9.8, 5.0 Hz, 0.14H), 1.77 (ddd, *J* = 7.6, 4.8, 4.7 Hz, 0.86H), 1.73-1.67 (m, 0.14H), 1.29 (d, *J* = 6.0 Hz, 2.58H), 1.24 (d, *J* = 5.9 Hz, 0.42H), 1.25-1.16 (m, 21H), 0.89 (dd, *J* = 7.8, 4.1 Hz, 0.86H), 0.83 (dd, *J* = 7.6, 4.2 Hz, 0.14H), 0.58-0.48 (m, 1H). **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 178.71, 178.66, 83.3, 83.2, 58.0, 56.4, 52.8, 51.3, 39.6, 39.5, 29.5, 27.8, 24.7, 24.6, 24.5, 22.8, 18.0, 17.9, 14.1, 12.8 (the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation); **HRMS (ESI)** exact mass calcd. for C₁₇H₃₀O₃NBNa: *m/z* 330.2211 ([M+Na]⁺), found: *m/z* 330.2212 ([M+Na]⁺).

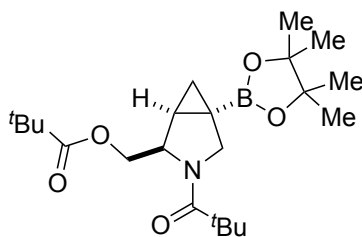
For data collection, the major isomer was isolated by recycling gel permeation chromatography (**Note**: all the attempts for the isolation of the minor isomer were in failure)

<Data for the major isomer>

Melting point: 127–128 °C; **¹H NMR** (400 MHz, CDCl₃) δ 4.14 (qd, *J* = 6.0, 4.7 Hz, 1H), 3.76 (d, *J* = 10.1 Hz, 1H), 3.69 (d, *J* = 10.1 Hz, 1H), 1.75 (ddd, *J* = 7.6, 4.7, 4.7 Hz, 1H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.20 (s, 12H), 1.19 (s, 9H), 0.87 (dd, *J* = 7.6, 4.1 Hz, 1H),

0.51 (dd, $J = 4.7, 4.1$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3 , 50 °C) δ 178.9, 83.5, 56.5, 52.9, 39.7, 29.6, 27.9, 24.7, 18.1, 14.2 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **HRMS (ESI)** exact mass calcd. for $\text{C}_{17}\text{H}_{30}\text{O}_3\text{NBNa}$: m/z 330.2211 ($[\text{M}+\text{Na}]^+$), found: m/z 330.2216 ($[\text{M}+\text{Na}]^+$).

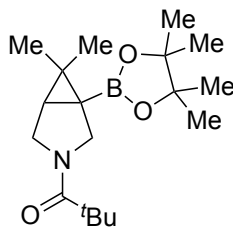
***rac*-((1*S*,2*R*,5*R*)-3-Pivaloyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexan-2-yl)methyl pivalate (*rac*-2d)**



This reaction was performed with **1d** (1.00 mmol, 281 mg), $\text{B}_2(\text{pin})_2$ (2.00 mmol, 508 mg), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 100 °C for 12 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 5/1) to afford the title compound in 39% yield (0.387 mmol, 158 mg) as a colorless solid.

Rf: 0.36 (eluent: hexane/AcOEt = 3/1, KMnO_4 w/o heating); **Melting point**: 131-135 °C; **^1H NMR** (400 MHz, CDCl_3) δ 4.57 (dd, $J = 10.1, 3.7$ Hz, 1H), 4.41 (ddd, $J = 8.6, 4.4, 3.7$ Hz, 1H), 3.93 (dd, $J = 10.1, 8.6$ Hz, 1H), 3.85 (d, $J = 10.0$ Hz, 1H), 3.69 (d, $J = 10.0$ Hz, 1H), 1.86 (ddd, $J = 7.8, 4.4, 4.4$ Hz, 1H), 1.231 (s, 6H), 1.228 (s, 6H), 1.21 (s, 9H), 1.20 (s, 9H), 0.95 (dd, $J = 7.8, 4.4$ Hz, 1H), 0.65 (dd, $J = 4.4, 4.4$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3 , 50 °C) δ 179.3, 177.9, 83.7, 64.4, 59.5, 53.1, 39.6, 38.7, 27.8, 27.2, 26.4, 24.73, 24.66, 14.9; **HRMS (ESI)** exact mass calcd. for $\text{C}_{22}\text{H}_{38}\text{O}_5\text{NBNa}$: m/z 430.2735 ($[\text{M}+\text{Na}]^+$), found: m/z 430.2738 ($[\text{M}+\text{Na}]^+$).

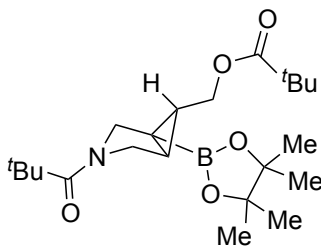
***rac*-3-Pivaloyl-6,6-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane (*rac*-2e)**



This reaction was performed with **1e** (1.00 mmol, 195 mg), B₂(pin)₂ (1.50 mmol, 381 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 100 °C for 15 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 3/1) to afford an inseparable mixture of the title compound and the unreacted substrate. These compounds could be separable by recycling gel permeation chromatography (eluent: CHCl₃ only) to give the analytically pure title compound in 42% yield (0.422 mmol, 136 mg, 71% brsm) as a colorless solid and the recovered substrate in 41% yield (0.409 mmol, 79.8 mg) as a colorless solid.

Rf: 0.26 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point:** 95-97 °C; **¹H NMR** (400 MHz, CDCl₃) δ 3.85-3.48 (m, 4H), 1.30-1.19 (m, 22H), 1.17 (s, 3H), 0.95 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 175.5, 83.4, 48.6 (br), 38.8, 27.3, 25.3 (br), 25.1, 24.3, 24.1, 14.0 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation and the carbon directly attached to the nitrogen atom was not detected due to peak broadening, which could be attributed to amide rotation*); **HRMS (ESI)** exact mass calcd. for C₁₈H₃₂O₃NBNa: *m/z* 344.2367 ([M+Na]⁺), found: *m/z* 344.2368 ([M+Na]⁺).

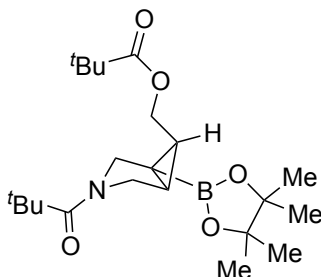
***rac*-((1*R*,5*R*,6*R*)-3-Pivaloyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)methyl pivalate (*rac-exo*-2f)**



This reaction was performed with *exo*-**1f** (1.00 mmol, 281 mg), B₂(pin)₂ (1.50 mmol, 381 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 80 °C for 3 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 4/1) to afford the title compound in 94% yield (0.942 mmol, 384 mg) as a colorless solid.

Rf: 0.35 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point**: 117-118 °C; **¹H NMR** (400 MHz, CDCl₃, 50 °C) δ 4.32 (dd, *J* = 11.5, 7.2 Hz, 1H), 4.03 (dd, *J* = 11.5, 7.9 Hz, 1H), 3.98 (d, *J* = 11.4 Hz, 1H), 3.84 (d, *J* = 11.4 Hz, 1H), 3.52 (d, *J* = 11.4 Hz, 1H), 3.43 (dd, *J* = 11.4, 4.1 Hz, 1H), 1.68 (dd, *J* = 4.1, 3.9 Hz, 1H), 1.24 (s, 6H), 1.22 (s, 6H), 1.20 (s, 9H), 1.18 (s, 9H), 1.08 (ddd, *J* = 7.9, 7.2, 3.9 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 178.4, 177.2, 83.7, 63.9, 51.7, 49.4, 39.0, 38.7, 27.5, 27.2, 26.7, 25.0, 24.4 (the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation); **HRMS (ESI)** exact mass calcd. for C₂₂H₃₈O₅NBNa: *m/z* 430.2735 ([M+Na]⁺), found: *m/z* 430.2745 ([M+Na]⁺).

***rac*-((1*R*,5*R*,6*S*)-3-Pivaloyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)methyl pivalate (*rac*-endo-2f)**

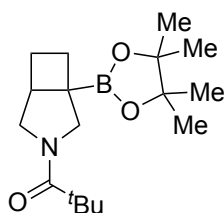


This reaction was performed with *endo*-**1f** (1.00 mmol, 281 mg), B₂(pin)₂ (1.50 mmol, 381 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 60 °C for 3 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 3/1) to afford the title compound in 93% yield (0.925 mmol, 377 mg) as a colorless solid.

Rf: 0.32 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point**: 104-105 °C; **¹H NMR** (400 MHz, CDCl₃, 50 °C) δ 4.09 (dd, *J* = 11.8, 7.6 Hz, 1H), 4.01 (dd, *J* = 11.8, 7.9 Hz, 1H), 3.85 (d, *J* = 12.1 Hz, 1H), 3.82 (d, *J* = 11.8 Hz, 1H), 3.74 (d, *J* = 11.8 Hz, 1H),

3.69 (dd, $J = 12.1, 5.2$ Hz, 1H), 1.86 (dd, $J = 7.8, 5.2$ Hz, 1H), 1.56 (ddd, $J = 7.9, 7.8, 7.6$ Hz, 1H), 1.22 (s, 9H), 1.21 (s, 12H), 1.18 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3 , 50 °C) δ 178.2, 176.0, 83.8, 59.8, 48.6, 47.7, 39.0, 38.7, 27.3, 27.2, 24.9, 24.7, 24.6, 24.3; **HRMS (ESI)** exact mass calcd. for $\text{C}_{22}\text{H}_{38}\text{O}_5\text{NBNa}$: m/z 430.2735 ($[\text{M}+\text{Na}]^+$), found: m/z 430.2744 ($[\text{M}+\text{Na}]^+$).

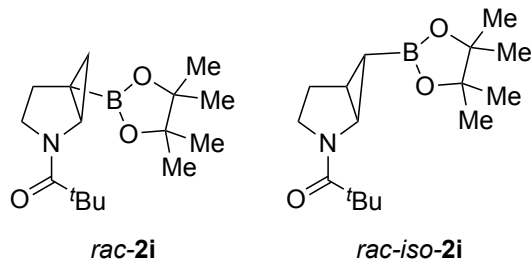
***rac*-3-Pivaloyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.2.0]heptane (*rac*-2g)**



This reaction was performed with **1g** (1.00 mmol, 181 mg), $\text{B}_2(\text{pin})_2$ (1.50 mmol, 381 mg), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 80 °C for 12 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 3/1) to afford the title compound in 77% yield (0.766 mmol, 236 mg) as a colorless solid.

Rf: 0.23 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point**: 70-73 °C; ^1H NMR (400 MHz, CDCl_3) δ 4.03-3.86 (m, 2H), 3.39-3.26 (m, 2H), 2.95-2.74 (m, 1H), 2.29-2.14 (m, 2H), 1.76-1.64 (m, 2H), 1.31 (s, 9H), 1.27 (s, 12H); ^{13}C NMR (101 MHz, CDCl_3 , 50 °C) δ 177.0, 83.4, 55.9, 54.3, 54.1, 39.8 (br), 38.9, 27.8, 25.7, 24.6, 24.1; **HRMS (ESI)** exact mass calcd. for $\text{C}_{17}\text{H}_{30}\text{O}_3\text{NBNa}$: m/z 330.2211 ($[\text{M}+\text{Na}]^+$), found: m/z 330.2212 ($[\text{M}+\text{Na}]^+$).

***rac*-2-Pivaloyl-(1*R*,5*S*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[3.1.0]hexane (*rac*-2*i*)** and ***rac*-2-Pivaloyl-(1*R*,5*S*,6*S*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[3.1.0]hexane (*rac*-*iso*-2*i*)**



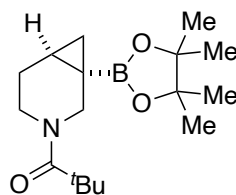
rac-2*i* : *rac*-*iso*-2*i* = 60 : 40

This reaction was performed with *rac*-1*i* (1.00 mmol, 167 mg), B₂(pin)₂ (1.50 mmol, 381 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 40 °C for 20 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 5/1) to afford the title compound in 96% yield (0.962 mmol, 282 mg) as a colorless solid.

Rf: 0.19 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **¹H NMR** (400 MHz, CDCl₃) δ 3.98-3.83 (m, 1H), 3.80-3.46 (m, 1H), 3.28-3.05 (m, 1H), 2.18-1.80 (m, 2.4H), 1.32 (s, 3.6H), 1.31 (s, 3.6H), 1.27-1.24 (m, 9H), 1.22 (s, 2.4H), 1.21 (s, 2.4H), 1.08 (t, *J* = 5.0 Hz, 0.6H), 0.74 (dd, *J* = 5.0, 3.0 Hz, 0.6H), 0.14 (dd, *J* = 5.5, 3.0 Hz, 0.4H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 177.2, 176.9, 83.6, 83.3, 47.6, 46.1, 42.8, 42.3, 38.84, 38.79, 27.6, 25.7, 24.7, 24.6, 24.5, 18.6 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation and the carbon directly attached to the nitrogen atom was not detected due to peak broadening, which could be attributed to amide rotation*); **HRMS (ESI)** exact mass calcd. for C₁₆H₂₈O₃NBNa: *m/z* 316.2054 ([M+Na]⁺), found: *m/z* 316.2058 ([M+Na]⁺).

Note: all the attempts for the isolation of these isomers as B(pin) form were in failure. The conversion of Alkyl–B(pin) into Alkyl–B(dan) made it possible to isolate these isomers (Scheme 5-13).

***rac*-3-Pivaloyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[4.1.0]heptane (*rac*-2j)**

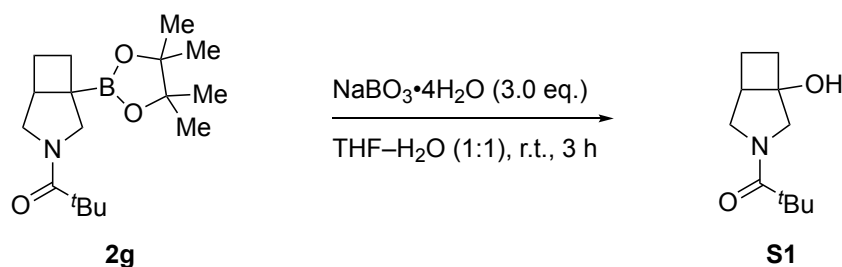


This reaction was performed with *rac*-1j (1.00 mmol, 181 mg), B₂(pin)₂ (1.50 mmol, 381 mg), [Ir(cod)OMe]₂ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), and MAD (0.100 mmol, 48.0 mg) in isooctane (5.0 mL) at 70 °C for 20 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 5/1 to 3/1) to afford the title compound in 68% yield (0.677 mmol, 208 mg) as a faint yellow solid.

Rf: 0.27 (eluent: hexane/AcOEt = 3/1, *p*-anisaldehyde); **Melting point:** 106-108 °C; **¹H NMR** (400 MHz, CDCl₃) δ 3.86 (br d, *J* = 13.6 Hz, 1H), 3.81 (br d, *J* = 13.6 Hz, 1H), 3.46 (ddd, *J* = 13.2, 5.6, 5.6 Hz, 1H), 3.08 (ddd, *J* = 13.2, 8.9, 5.4 Hz, 1H), 1.93 (dddd, *J* = 16.4, 7.1, 5.6, 5.4, 1H), 1.77 (dddd, *J* = 16.4, 8.9, 5.6, 2.3 Hz, 1H), 1.24 (s, 9H), 1.23-1.19 (m, 1H), 1.185 (s, 6H), 1.177 (s, 6H), 0.85 (dd, *J* = 8.6, 3.9 Hz, 1H), 0.43 (dd, *J* = 5.6, 3.9 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 176.7, 83.3, 45.7, 41.2, 38.6, 28.5, 24.7, 24.6, 22.6, 15.5, 14.9; **HRMS (ESI)** exact mass calcd. for C₁₇H₃₁O₃NB: *m/z* 308.2392 ([M+H]⁺), found: *m/z* 308.2397 ([M+H]⁺).

5.5.2.3 Determination of site selectivity

***rac*-3-Pivaloyl-1-hydroxy-3-azabicyclo[3.2.0]heptane (S1)**



To a 15 mL vial containing **2g** (0.280 mmol, 85.9 mg) in THF/H₂O (1:1, 2.0 mL) was added NaBO₃·4H₂O (0.840 mmol, 129 mg) at room temperature. The resulting mixture was stirred for 3 hours at this temperature, after which water (10 mL) and Et₂O (10 mL) were added. Two layers were separated, and the aqueous layer was extracted with Et₂O

(10 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude mixture was purified by MPLC (eluent: hexane/AcOEt = 50/50 to 0/100) to afford **S1** in 58% yield (0.164 mmol, 32.3 mg) as a colorless solid.

Rf: 0.28 (eluent: AcOEt only, PMA); **Melting point**: 72-74 $^\circ\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 4.11 (d, J = 12.5 Hz, 1H), 3.82 (d, J = 11.8 Hz, 1H), 3.58 (dd, J = 11.8, 6.0 Hz, 1H), 3.47 (d, J = 12.5 Hz, 1H), 2.71 (m, 1H), 2.40-2.10 (m, 3H), 2.03 (m, 1H), 1.34-1.23 (m, 1H), 1.28 (s, 9H); **^{13}C NMR** (101 MHz, CDCl_3 , 50 $^\circ\text{C}$) δ 177.0, 79.5 (br), 60.5, 52.9, 45.9 (br), 38.9, 33.7, 27.7, 17.0; **HRMS (ESI)** exact mass calcd. for $\text{C}_{11}\text{H}_{19}\text{O}_2\text{NNa}$: m/z 220.1308 ($[\text{M}+\text{Na}]^+$), found: m/z 220.1307 ($[\text{M}+\text{Na}]^+$).

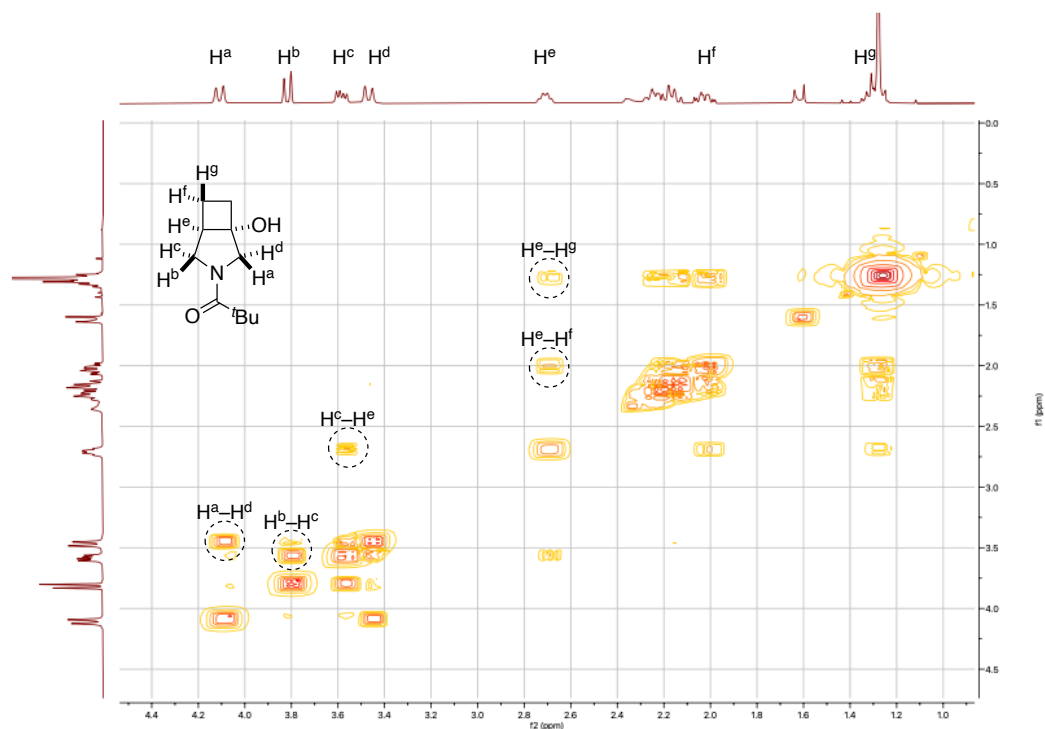


Figure 5-5 ^1H - ^1H COSY analysis of **S1**

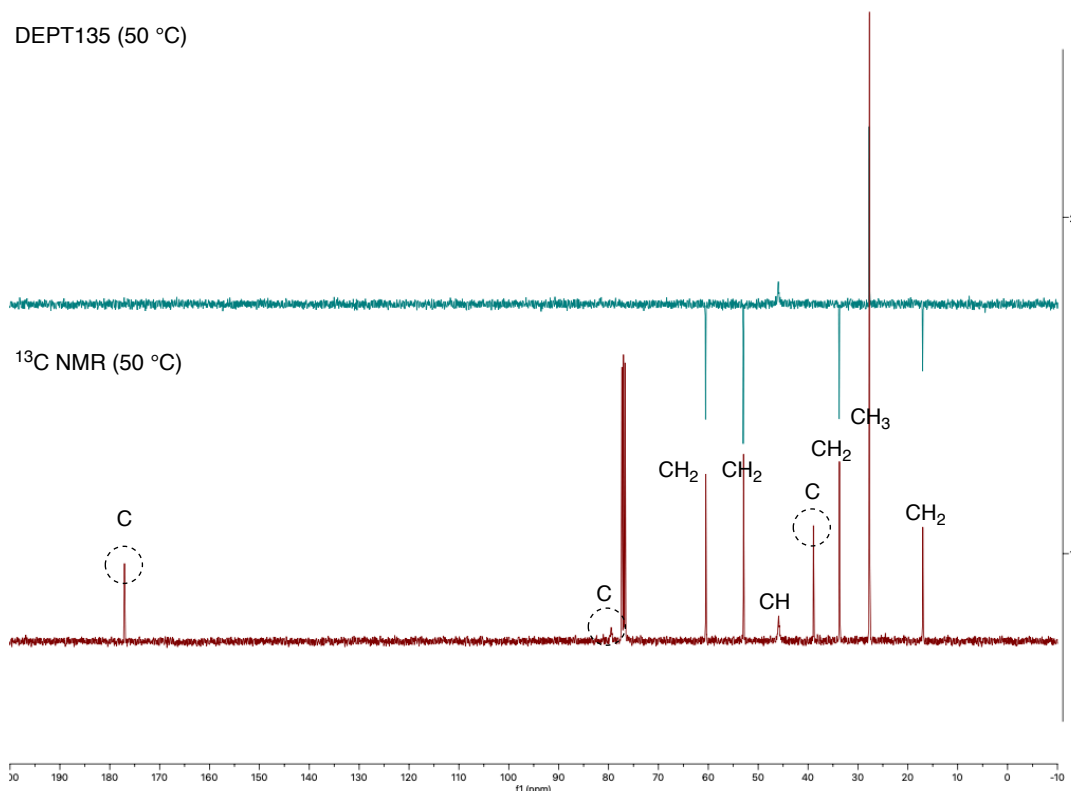
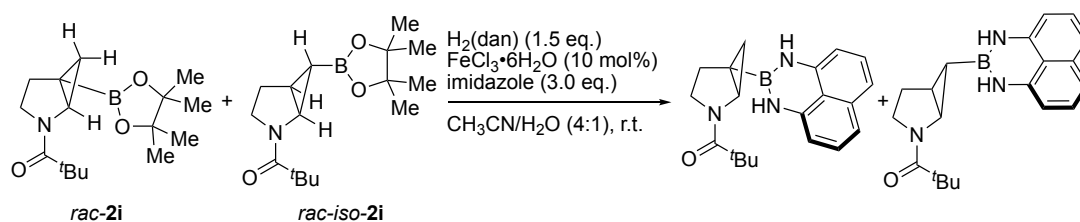


Figure 5-6 ¹³C NMR and DEPT135 analysis of S1

***rac*-2-(2-Pivaloyl-(1*R*,5*S*)-2-azabicyclo[3.1.0]hexan-5-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine** and ***rac*-2-(2-Pivaloyl-(1*R*,5*S*,6*S*)-2-azabicyclo[3.1.0]hexan-6-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine**



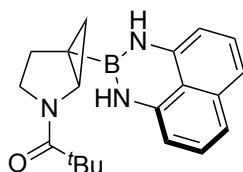
Scheme 5-13 Conversion of boron functionality and product identification

Prepared according to literature procedure (slightly modified).^{45,46}

To a round-bottom flask containing FeCl₃•6H₂O (0.100 mmol, 27.0 mg), 1,8-diaminonaphthalene (1.50 mmol, 0.237 g) and imidazole (3.00 mmol, 0.204 g) in CH₃CN/H₂O (4:1, 20 mL) was added the mixture of *rac*-**2i** and *rac*-*iso*-**2i** (1.00 mmol in total, 0.293 g) at room temperature under argon atmosphere. After stirring for 22 hours, all volatiles were removed under reduced pressure. The resulting crude residue was

purified by MPLC (eluent: hexane/AcOEt = 75/35 to 30/70) to afford the title compounds in 73% yield (combined).

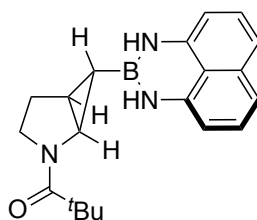
***rac*-2-(2-Pivaloyl-(1*R*,5*S*)-2-azabicyclo[3.1.0]hexan-5-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine**



0.141 g (0.422 mmol) as a pinkish solid

Rf: 0.39 (eluent: hexane/AcOEt = 1/1, *p*-anisaldehyde); **Melting point:** 220 °C (decomp.); **¹H NMR** (400 MHz, CDCl₃) δ 7.11 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.03 (dd, *J* = 8.2, 0.9 Hz, 2H), 6.34 (dd, *J* = 7.3, 0.9 Hz, 2H), 5.49 (br, 2H), 4.02 (ddd, *J* = 12.5, 9.7, 3.1 Hz, 1H), 3.79-3.60 (m, 1H), 3.25 (ddd, *J* = 12.5, 8.6, 8.5 Hz, 1H), 2.12 (m, 1H), 1.99 (m 1H), 1.34 (s, 9H), 0.97 (dd, *J* = 5.9, 5.7 Hz, 1H), 0.89 (dd, *J* = 5.7, 3.0 Hz); **¹³C NMR** (101 MHz, DMSO-*d*₆, 50 °C) δ 175.4, 141.9, 135.7, 127.3, 119.1, 115.9, 105.1, 46.2, 42.3, 38.2, 27.3, 26.1 (br), 17.7 (br); **HRMS (ESI)** exact mass calcd. for C₂₀H₂₄ON₃BNa: *m/z* 356.1905 ([M+Na]⁺), found: *m/z* 356.1907 ([M+Na]⁺).

***rac*-2-(2-Pivaloyl-(1*R*,5*S*,6*S*)-2-azabicyclo[3.1.0]hexan-6-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine**



0.104 g (0.312 mmol) as a pinkish solid

Rf: 0.30 (eluent: hexane/AcOEt = 1/1, *p*-anisaldehyde); **Melting point:** 225 °C (decomp.); **¹H NMR** (400 MHz, CDCl₃) δ 7.10 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.02 (dd, *J* = 8.2, 0.7 Hz, 2H), 6.31 (dd, *J* = 7.3, 0.7 Hz, 2H), 5.41 (br, 2H), 3.95 (ddd, *J* = 12.8, 10.2, 3.0 Hz, 1H), 3.78-3.57 (m, 1H), 3.21 (ddd, *J* = 12.8, 8.8, 8.7 Hz, 1H), 2.23-2.10 (m, 1H), 2.05-1.96 (m, 1H), 1.96-1.83 (m, 1H), 1.32 (s, 9H), 0.22 (dd, *J* = 5.8, 3.0 Hz, 1H); **¹³C NMR** (101 MHz, DMSO-*d*₆, 50 °C) δ 175.8, 141.9, 135.8, 127.3, 119.1, 115.8, 104.9,

45.7, 41.9, 38.2, 27.3, 24.3 (br), 13.7 (br); **HRMS (ESI)** exact mass calcd. for $C_{20}H_{24}ON_3BNa$: m/z 356.1905 ($[M+Na]^+$), found: m/z 356.1905 ($[M+Na]^+$).

5.5.2.4 Proposed Catalytic Cycle

According to the author's previous work (*Angew. Chem. Int. Ed.* **2023**, e202300704.), we proposed the following catalytic cycle (Methyl groups on the phenanthroline ligand were omitted for clarity).

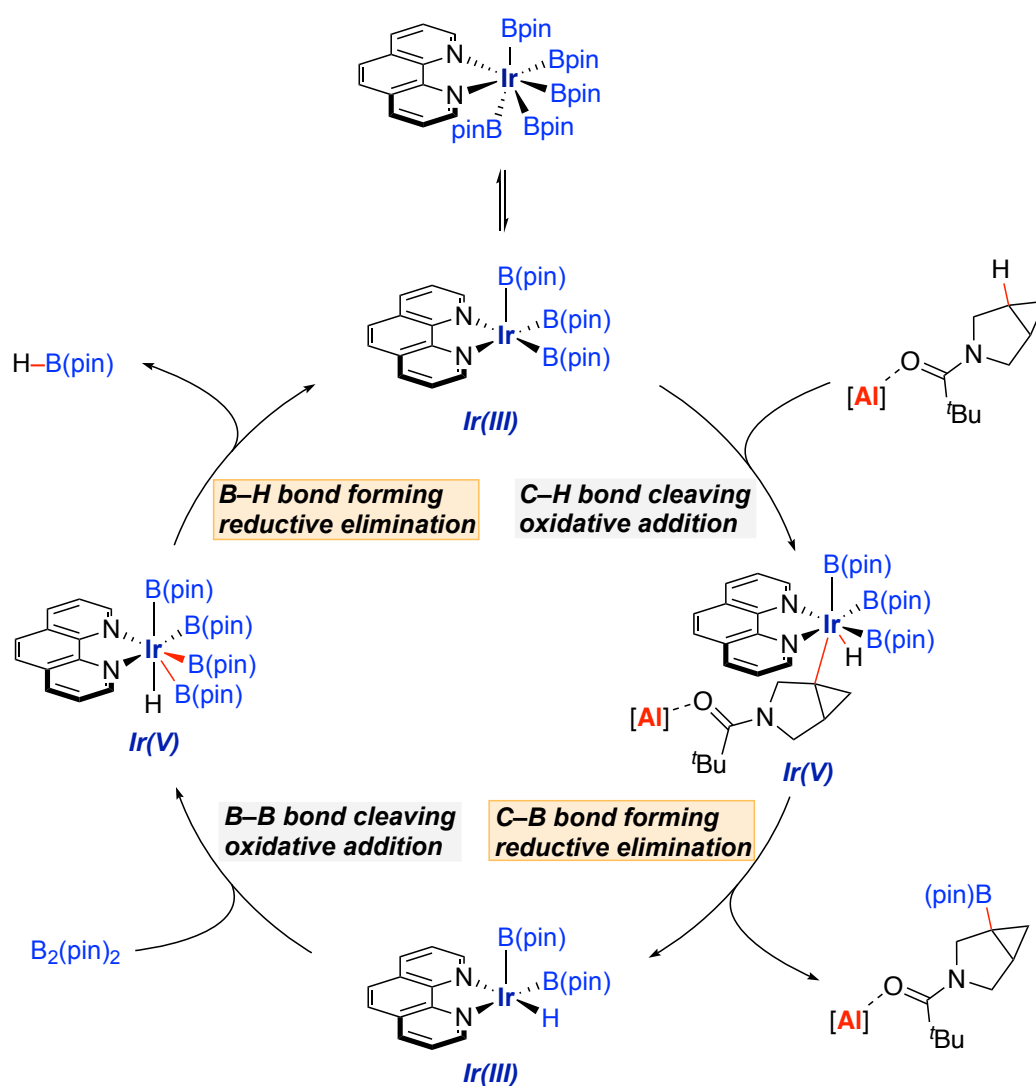


Figure 5-7 Proposed catalytic cycle

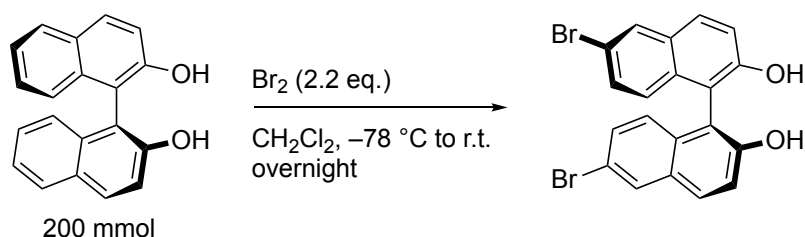
5.5.3 Catalytic asymmetric C–H borylation of bicyclic amines

5.5.3.1 Catalyst preparations

<scalable column-chromatography-free preparation of catalyst precursor>

These catalyst precursors were prepared according to the literature procedure (modified).³⁰

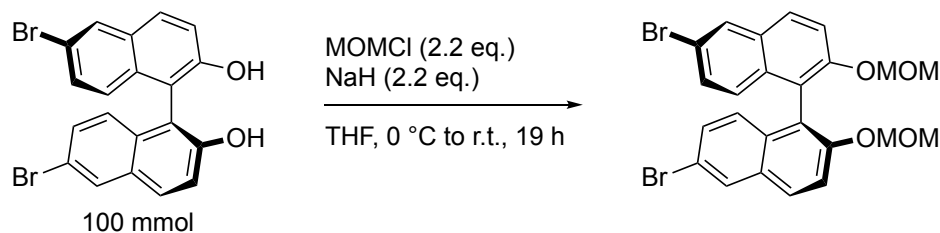
(S)-6,6'-Dibromo-[1,1'-binaphthalene]-2,2'-diol



To a three-necked round-bottom flask containing (*S*)-BINOL (0.200 mol, 57.3 g) in anhydrous CH_2Cl_2 (500 mL) was dropwise added bromine (0.440 mol, 22.6 mL) at -78°C under argon atmosphere. After stirring overnight at -78°C to room temperature, the reaction was quenched with saturated Na_2SO_3 aq. (10 mL), followed by the addition of Na_2SO_3 and NaHCO_3 as solid. After stirring for 30 min at room temperature, the reaction mass was filtered and the pad cake was washed with hexane. All volatiles were evaporated under reduced pressure and further dried under a high vacuum. The obtained solid was triturated with hexane (250 mL) under reflux for 2 hours. Upon cooling to room temperature, the solid was collected by filtration and dried under a high vacuum at 50°C for 2 hours to afford the title compound in quantitative yield as an off-white solid (>95% NMR purity).

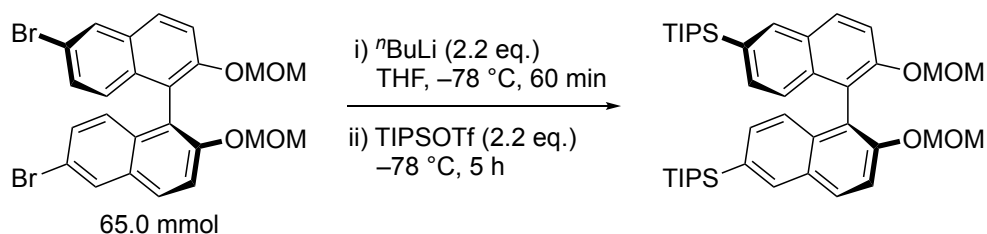
^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 2H), 7.90 (d, $J = 8.9$ Hz, 2H), 7.43–7.33 (m, 4H), 6.96 (d, $J = 8.9$ Hz, 2H), 5.02 (s, 2H).

(S)-6,6'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene



To a flame-dried three-necked round-bottom flask containing (*S*)-6,6'-dibromo-[1,1'-binaphthalene]-2,2'-diol (0.100 mol, 44.4 g) in anhydrous THF (300 mL) was added portion wise NaH (0.220 mol, 8.80 g) at 0 °C under argon atmosphere. After stirring for 15 min at 0 °C, MOMCl (0.220 mol, 16.7 mL) was added dropwise at this temperature and the reaction was further stirred for 19 hours at 0 °C to room temperature. The resulting reaction mixture was quenched with saturated NH₄Cl aq. (50 mL), and THF was removed by a rotary evaporator. To the resulting viscous oil, H₂O (200 mL) and CH₂Cl₂ (200 mL) were sequentially added. Two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (200 mL × 3). The combined organic layers were washed with H₂O (twice), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Trituration with distilled water, followed by drying under high vacuum at 70 °C afforded the analytically pure title compound in 94% yield (94.3 mmol, 50.2 g) as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 1.9 Hz, 2H), 7.86 (d, *J* = 9.1 Hz, 2H), 7.59 (d, *J* = 9.1 Hz, 2H), 7.29 (dd, *J* = 9.0, 1.9 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 5.09 (d, *J* = 6.9 Hz, 2H), 4.98 (d, *J* = 6.9 Hz, 2H), 3.16 (s, 6H).

(*S*)-(2,2'-Bis(methoxymethoxy)-[1,1'-binaphthalene]-6,6'-diyl)bis(triisopropylsilane)



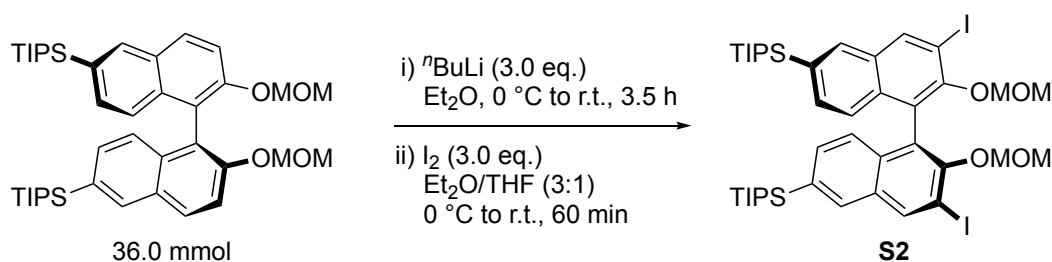
To a flame-dried three-necked round-bottom flask containing (*S*)-6,6'-dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (65.0 mmol, 34.6 g) in anhydrous THF (450 mL) was dropwise added ⁿBuLi (1.57 M in hexanes, 0.143 mol, 91.0 mL) at -78 °C under argon atmosphere. After stirring for 60 min at -78 °C (**Note:** full conversion was confirmed in 20 min), TIPSOTf (freshly distilled over CaH₂, 0.143 mol, 43.8 g) was added dropwise and stirred for 5 hours at this temperature. The reaction was quenched with saturated NaHCO₃ aq. (ca. 200 mL) at -78 °C and gradually warmed up to room temperature with vigorous stirring. To this mixture, AcOEt (500 mL) was added and two layers were separated. The aqueous layer was extracted with AcOEt (300 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated

under reduced pressure to afford a yellow viscous oil. This oil was solidified with MeOH (*ca.* 50 mL), followed by the removal of all volatiles. The resulting yellow solid was triturated with MeOH (400 mL) for 8 h under gentle refluxing, and the solid was collected by filtration. Dryness under a high vacuum at 70 °C afforded the analytically pure title compound in 89% yield (57.5 mmol, 39.5 g) as a colorless solid.

Note: With non-distilled TIPSOTf, the author observed mono-TIPS introduction and MOM deprotection, which prohibit the clean isolation of the target compound.

¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 2H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.55 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.11 (d, *J* = 6.8 Hz, 2H), 4.99 (d, *J* = 6.8 Hz, 2H), 3.12 (s, 6H), 1.45 (hept, *J* = 7.5 Hz, 6H), 1.08 (d, *J* = 7.5 Hz, 36H).

(*S*)-(3,3'-Diiodo-2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-6,6'-diyl)bis(triisopropylsilane) (S2)



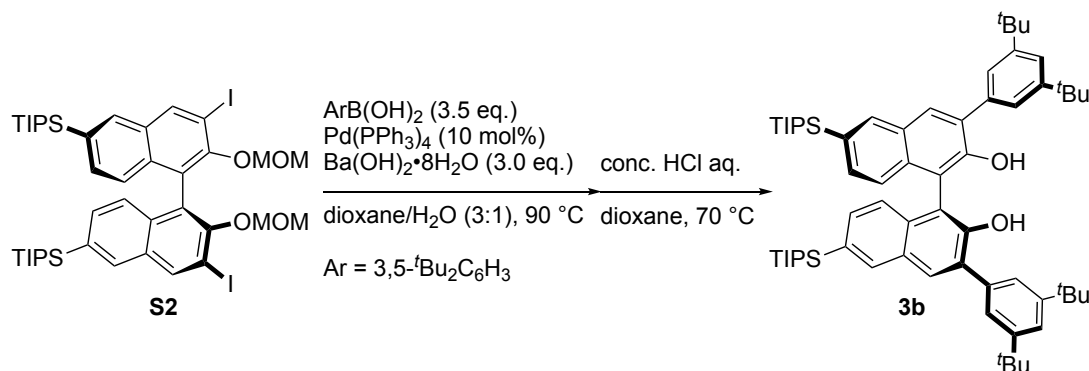
To a flame-dried three-necked round-bottom flask containing (*S*)-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-6,6'-diyl)bis(triisopropylsilane) (36.0 mmol, 24.7 g) in anhydrous Et₂O (600 mL) was dropwise added *n*-BuLi (1.57 M in hexanes, 108 mmol, 68.8 mL) at 0 °C under argon atmosphere. After stirring for 3.5 hours at room temperature (**Note:** full conversion was confirmed in 3 hours), the reaction mixture was cooled to 0 °C, diluted with anhydrous THF (200 mL), and treated with I₂ (108 mmol, 27.4 g) in one portion. The reaction mixture was stirred for 5 min and warmed up to room temperature. After stirring for 60 min at room temperature, the reaction mixture was re-cooled down to 0 °C and quenched with saturated Na₂SO₃ aq. (200 mL) and saturated NaHCO₃ aq. (200 mL). After the vigorous stirring for 15 min at room temperature, two layers were separated and the aqueous layer was extracted with AcOEt (300 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The resulting solid was further dried under high vacuum at 60 °C overnight to afford the title compound (containing some impurities) in 82% yield (29.4

mmol, 27.6 g, considered to be 100% purity), which had sufficient purity to be used in the next step without further purification.

For the data collection, the title compound was isolated by semi-preparative recycling HPLC resolution (COSMOSIL, eluent: hexane/AcOEt = 40/1, flow rate: 4.0 mL/min, λ = 254 nm).

Rf: 0.23 (eluent: hexane/AcOEt = 15/1, UV); **Melting point:** 174-176 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.54 (s, 2H), 7.90 (s, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 4.79 (d, J = 5.6 Hz, 2H), 4.76 (d, J = 5.6 Hz, 2H), 2.52 (s, 6H), 1.45 (hept, J = 7.5 Hz, 6H), 1.09 (d, J = 7.5 Hz, 18H), 1.08 (d, J = 7.5 Hz, 18H); **¹³C NMR** (101 MHz, CDCl₃) δ 152.1, 140.2, 134.4, 133.7, 132.9, 132.8, 131.7, 126.1, 125.2, 99.3, 91.8, 56.4, 18.6, 10.8; **HRMS (ESI)** exact mass calcd. for C₄₂H₆₀O₄I₂NaSi₂: m/z 961.2012 ([M+Na]⁺), found: m/z 961.2039 ([M+Na]⁺); **Optical rotation:** $[\alpha]_D^{23}$ = -14.5 (c = 1.0, CH₂Cl₂).

(S)-3,3'-Bis(3,5-di-*tert*-butylphenyl)-6,6'-bis(triisopropylsilyl)-[1,1'-binaphthalene]-2,2'-diol (3b)

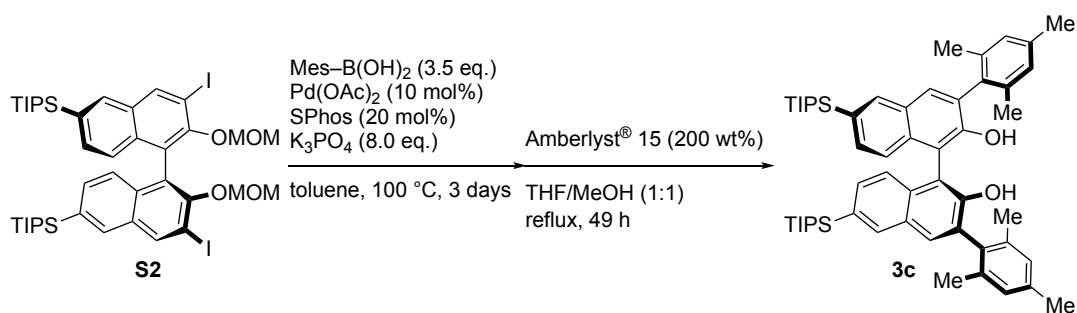


To a flame-dried Schlenk flask were added **S2** (1.00 mmol, 0.939 g), 3,5-di-*tert*-butylphenylboronic acid (3.50 mmol, 0.820 g), Ba(OH)₂•8H₂O (3.00 mmol, 0.946 g) and Pd(PPh₃)₄ (0.100 mmol, 0.116 g) in wet dioxane (10 mL, dioxane/H₂O = 3/1, *deoxygenated by argon bubbling just before use*), and the resulting solution was further degassed by three freeze-pump-thaw cycles. The flask was sealed and stirred for 113 hours at 90 °C. Upon cooling to room temperature, the resulting reaction mixture was diluted with CH₂Cl₂ (30 mL) and water (30 mL). The crude mixture was filtered through Celite pad, and the pad cake was washed with CH₂Cl₂ (30 mL). Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (30 mL × 3). The combined organic layers were washed with water (30 mL × 1), dried over anhydrous Na₂SO₄, filtered, and

evaporated under reduced pressure. The resulting crude mixture was roughly purified by MPLC (eluent: hexane/AcOEt = 40/1), which was used in the next step without further purification. To the mixture in dioxane (20 mL) was added concentrated HCl aq. (1.0 mL) at room temperature. The resulting mixture was heated to 70 °C and stirred for 7.5 hours at this temperature under air. Upon cooling to room temperature, the reaction was quenched with saturated NaHCO₃ aq. (10 mL) and extracted with AcOEt (20 mL × 3). The combined organic layers were washed with brine (20 mL × 1), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The resulting crude mixture was purified by MPLC (SiO₂, eluent: hexane/AcOEt = 40/1) to afford **3b** in 80% yield (0.802 mmol, 0.782 g, over 2 steps) as a pale yellow solid.

Rf: 0.13 (eluent: hexane/AcOEt = 40/1, UV and/or basic KMnO₄); **Melting point**: 178–184 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.05 (s, 2H), 8.00 (s, 2H), 7.58 (d, *J* = 1.8 Hz, 4H), 7.47 (t, *J* = 1.8 Hz, 2H), 7.40 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 5.51 (s, 2H), 1.47 (hept, *J* = 2.8 Hz, 6H), 1.39 (s, 36H), 1.11 (d, *J* = 2.8 Hz, 18H), 1.09 (d, *J* = 2.8 Hz, 18H); **¹³C NMR** (101 MHz, CDCl₃) δ 150.9, 150.3, 136.6, 136.3, 133.0, 132.9, 131.3, 131.2, 130.2, 129.0, 123.9, 123.1, 121.8, 112.6, 35.0, 31.6, 18.6, 10.9; **HRMS (ESI)** exact mass calcd. for C₆₆H₉₃O₂Si₂: *m/z* 973.6709 ([M–H][–]), found: *m/z* 973.6718 ([M–H][–]); **Optical rotation** [α]_D²³ = –53.5 (*c* = 1.0, CH₂Cl₂);

(S)-3,3'-Dimesityl-6,6'-bis(triisopropylsilyl)-[1,1'-binaphthalene]-2,2'-diol (3c)



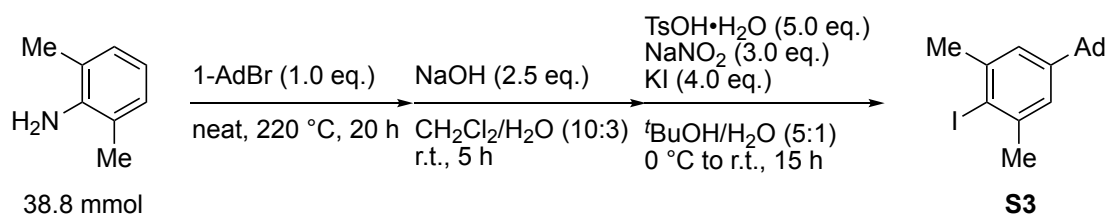
This compound was prepared according to the literature procedures (modified).^{47,48}

An 80 mL Schlenk flask charged with **S2** (1.00 mmol, 939 mg), mesitylboronic acid (3.50 mmol, 574 mg), Pd(OAc)₂ (0.100 mmol, 22.5 mg), SPhos (0.200 mmol, 82.1 mg), and K₃PO₄ (8.00 mmol, 1.70 g) was carefully evacuated and backfilled with argon for three times. After the addition of toluene (10 mL), the vessel was heated to 100 °C for 3 days. The resulting mixture was cooled to room temperature and diluted with AcOEt (20 mL),

filtered through Celite pad, and the pad cake was washed with AcOEt (20 mL). Then silica gel was added to the solution and the mixture was concentrated by a rotary evaporator. The resulting mixture was further dried under high vacuum. The crude residue was purified by MPLC (eluent: hexane/AcOEt = 40/1) to afford the target intermediate in 87% yield, which was dissolved in THF/MeOH (1:1, 14 mL), and Amberlyst 15 (800 mg) was added to the solution at room temperature. The resulting mixture was stirred at 70 °C and held at this temperature. After 41 hours, Amberlyst 15 (800 mg) was added and stirred at the same temperature for 8 h. The reaction mixture was cooled to room temperature, filtered through a filter paper, and evaporated under reduced pressure. The crude residue was purified by MPLC (eluent: hexane/AcOEt = 30/1) to afford **3c** in 53% yield (0.462 mmol, 386 mg) as a colorless solid.

R_f: 0.21 (eluent: hexane/AcOEt = 20/1, UV and/or KMnO₄); **Melting point**: 192 °C (decomp.); **¹H NMR** (400 MHz, CDCl₃): δ 7.99 (s, 2H), 7.73 (s, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.02 (s, 4H), 5.06 (s, 2H), 2.36 (s, 6H), 2.20 (s, 6H), 2.11 (s, 6H), 1.46 (hept, *J* = 7.6 Hz, 6H), 1.12 (d, *J* = 7.6 Hz, 36H).; **¹³C NMR** (101 MHz, CDCl₃): δ 150.3, 137.5, 137.1, 136.2, 133.4, 133.2, 132.7, 131.0, 129.8, 129.1, 128.4, 128.4, 123.2, 112.6, 21.1, 20.7, 18.7, 11.0; **HRMS (ESI)** exact mass calcd. for C₅₆H₇₃O₂Si₂: *m/z* 833.5144 ([M-H]⁻), found: *m/z* 833.5153 ([M-H]⁻); **Optical rotation** [α]_D²³ = -56.7 (*c* = 1.0, CH₂Cl₂).

1-(4-Iodo-3,5-dimethylphenyl)adamantane (S3)

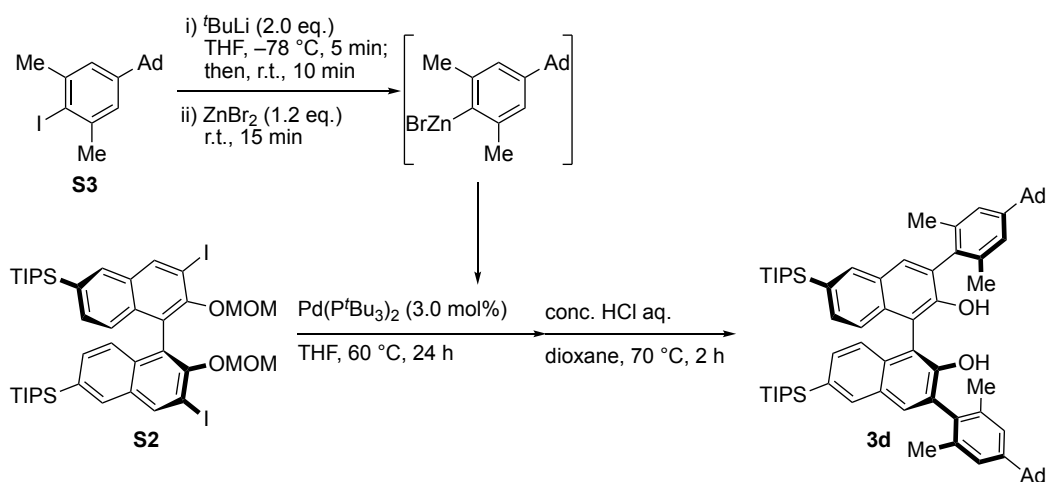


A 15 mL vial containing 2,6-xylydine (38.8 mmol, 4.79 mL) and 1-bromoadamantane (38.8 mmol, 8.34 g) was sealed and heated at 220 °C for 20 hours without stirring. After being cooled to room temperature, the 15 mL vial was crushed with a hammer, and a brown solid was collected. This brown solid was dissolved with CH₂Cl₂ (100 mL) and H₂O (30 mL). To this solution was added NaOH (0.100 mol, 4.00 g) in one portion at room temperature. After stirring for 5 hours at this temperature, two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (30 mL × 3). The combined organic

layers were washed with brine (30 mL $\times$ 1), dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. To this crude residue in $t\text{-BuOH}$ (240 mL) and H_2O (10 mL) was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (0.200 mol, 38.0 g) at room temperature. After cooling to 0 $^\circ\text{C}$, a solution of KI (0.160 mol, 26.6 g) and NaNO_2 (0.120 mol, 8.28 g) in H_2O (36 mL) was added dropwise. After the addition, the cooling bath was removed and the reaction was further run for 15 hours at room temperature before quenched with saturated Na_2SO_3 aq. To the resulting mixture, were added hexane (100 mL) and H_2O (100 mL), and two layers were separated. The aqueous layer was extracted with hexane (100 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 1), dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. Purification by MPLC (eluent: hexane/ CH_2Cl_2 = 1/1) afforded the title compound in 73% yield (28.4 mmol, 10.4 g, over 3 steps) as an off-white solid.

Rf: 0.63 (eluent: hexane only, UV); **Melting point:** 137-139 $^\circ\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 7.05 (s, 2H), 2.47 (s, 6H), 2.09 (br, 3H), 1.88 (br, 6H), 1.82-1.70 (m, 6H); **^{13}C NMR** (101 MHz, CDCl_3 , 50 $^\circ\text{C}$) δ 150.8, 141.4, 123.8, 104.7, 43.0, 36.7, 35.7, 29.8, 28.9; **HRMS (EI)** exact mass calcd. for $\text{C}_{18}\text{H}_{23}\text{I}$: m/z 366.0844 ($[\text{M}]^+$), found: m/z 366.0836 ($[\text{M}]^+$).

(S)-3,3'-Bis(4-(adamantan-1-yl)-2,6-dimethylphenyl)-6,6'-bis(triisopropylsilyl)-[1,1'-binaphthalene]-2,2'-diol (3d)



This compound was prepared according to the literature procedure (modified).⁴⁹

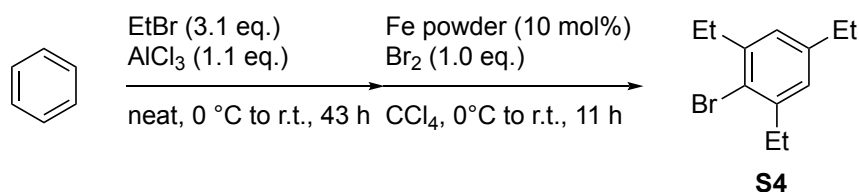
To a flame-dried two-necked round-bottom flask containing **S3** (4.00 mmol, 1.47 g) in anhydrous THF (4.0 mL) was added $t\text{-BuLi}$ (1.60 M in pentane, 8.0 mmol, 5.0 mL) at -78

°C under argon atmosphere. After stirring for 5 min at this temperature, the cooling bath was removed and the reaction mixture was further stirred for 10 min. After that, ZnBr₂ (flame dried under high vacuum just before use, 4.80 mmol, 1.08 g) in anhydrous THF (4.0 mL) was added at room temperature *via* syringe. The reaction mixture was stirred for 15 min at this temperature. To another flame-dried Schlenk flask containing Pd(P^{*i*}Bu₃)₂ (0.0300 mmol, 15.3 mg) and **S2** (1.00 mmol, 0.939 g) in anhydrous THF (10 mL) was added the aforementioned freshly prepared zinc reagent *via* syringe. The solution was thoroughly degassed by three freeze-pump-thaw cycles. The solution was heated to 60 °C for 24 hours under argon atmosphere. Upon the completion of the reaction, the reaction mixture was cooled to room temperature, and quenched by the slow addition of saturated NH₄Cl aq. (10 mL) and H₂O (20 mL). Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (15 mL × 4). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was roughly purified by MPLC (eluent: hexane/AcOEt = 40/1). To this residue in dioxane (10 mL) was added concentrated HCl aq. (0.50 mL) and heated to 70 °C for 2 hours under air. The resulting reaction mixture was cooled to room temperature and quenched with saturated NaHCO₃ aq. (10 mL). After adding CH₂Cl₂ (20 mL), two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. ¹H NMR analysis indicated that the substrate was not fully converted. To this residue in dioxane (20 mL) was added concentrated HCl aq. (0.50 mL) and heated to 70 °C for 12 hours under air. The resulting reaction mixture was cooled to room temperature and quenched with saturated NaHCO₃ aq. (10 mL). After adding CH₂Cl₂ (40 mL), two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Purification by MPLC (eluent: hexane/CH₂Cl₂ = 4/1) afforded **3d** in 43% yield (0.428 mmol, 0.461 g, over 2 steps) as a colorless solid.

Rf: 0.26 (eluent: hexane/CH₂Cl₂ = 3/1, UV and/or basic KMnO₄); **Melting point**: 295 °C (decomp.); **¹H NMR** (400 MHz, CDCl₃) δ 7.96 (s, 2H), 7.73 (s, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 2.3 Hz, 2H), 7.15 (d, *J* = 2.3 Hz, 2H), 5.04 (s, 2H), 2.23 (s, 6H), 2.14 (s, 6H), 2.11 (m, 6H), 1.96 (m, 12H), 1.79 (m, 12H), 1.46 (hept, *J* = 7.3 Hz, 6H), 1.113 (d, *J* = 7.3 Hz, 18H), 1.105 (d, *J* = 7.3 Hz, 18H); **¹³C NMR** (101 MHz, CDCl₃) δ 150.9, 150.3, 136.7, 136.2, 133.4, 133.2, 132.6, 130.9, 129.7, 129.2,

129.0, 124.2, 123.2, 112.7, 43.2, 36.9, 36.0, 29.0, 21.0, 18.7, 11.0; **HRMS (ESI)** exact mass calcd. for $C_{74}H_{97}O_2Si_2$: m/z 1073.7022 ($[M-H]^-$), found: m/z 1073.7041 ($[M-H]^-$); **Optical rotation** $[\alpha]_D^{23} = -44.3$ ($c = 1.0$, CH_2Cl_2).

2-Bromo-1,3,5-triethylbenzene (S4)



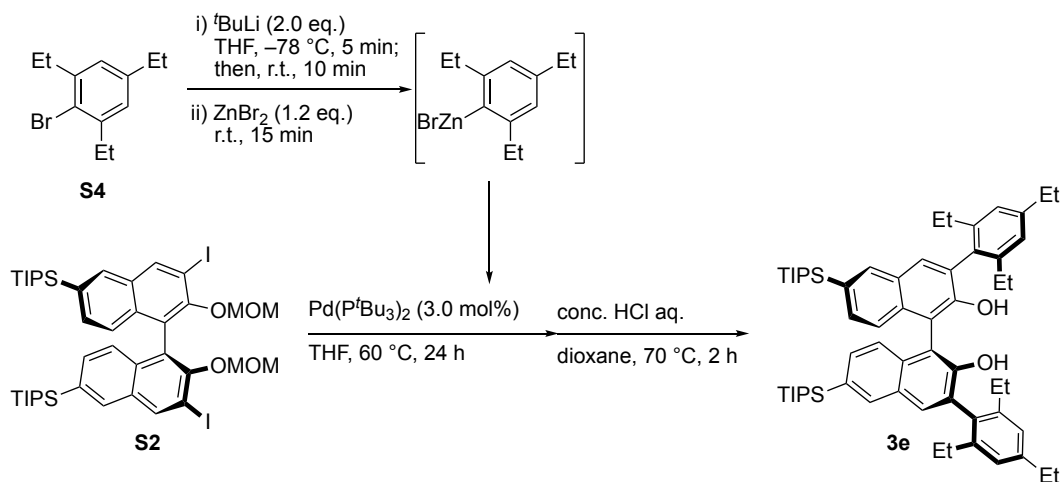
This compound was prepared according to the literature procedure (slightly modified).⁵⁰ To a flame-dried three-necked round-bottom flask (fitted with a reflux condenser which was connected to a tube that was submerged into a saturated $NaHCO_3$ aq. to quench the evolved gases) containing $AlCl_3$ (0.340 mol, 45.3 g) was added EtBr (0.590 mol, 50.0 mL) at 0 °C under argon atmosphere *via* a syringe pump (rate: 100 mL/h). Upon the completion of the addition, anhydrous benzene (0.320 mol, 28.6 mL) was added dropwise *via* a syringe pump (rate: 86 mL/h), after which EtBr (0.390 mol, 32.5 mL) was added dropwise *via* a syringe pump (rate: 86 mL/h) whilst maintaining a reaction temperature at 0 °C. After stirring for 43 hours at 0 °C to room temperature, the reaction mixture was slowly added into a 1L beaker containing ice to quench the reaction. To the resulting mixture was added Et_2O (250 mL). Two layers were separated and the aqueous layer was further extracted with Et_2O (100 mL $\times$ 2). The combined organic layers were sequentially washed with H_2O (100 mL $\times$ 1), 1 M NaOH aq. (100 mL $\times$ 1), and H_2O (100 mL $\times$ 1). The resulting organic layer was dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. the crude mixture was purified by vacuum distillation (b.p. 50–52 °C, 2 torr) to afford 1,3,5-triethylbenzene in 96% yield (0.307 mol, 49.8 g) as a colorless oil.

To a three-necked round-bottom flask (fitted with a reflux condenser and an addition funnel) containing 1,3,5-triethylbenzene (0.100 mol, 16.2 g) and Fe powder (10.0 mmol, 0.558 g) in CCl_4 (10 mL) was added Br_2 (0.100 mol, 5.15 mL) in CCl_4 (10 mL) dropwise *via* the addition funnel over 2.5 hours at 0 °C under air in the absence of light. After the addition, the resulting mixture was further stirred for 11 hours at 0 °C to room temperature, after which CH_2Cl_2 (40 mL) and H_2O (40 mL) were added. Two layers were separated and the organic layer was sequentially washed with H_2O (40 mL $\times$ 1), 15% NaOH aq. (40

mL $\times$ 1), and H₂O (40 mL $\times$ 3, *until the aqueous layer became neutral, which was checked by pH test paper*). The organic layer was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure. the resulting crude mixture was purified by vacuum distillation (b.p. 72-74 °C, 1 torr) to afford the title compound in 80% yield (80.1 mmol, 19.3 g) as a colorless oil. The spectral data was matched with the reported values.⁵¹

¹H NMR (400 MHz, CDCl₃): δ 6.93 (s, 2H), 2.79 (q, J = 7.3 Hz, 4H), 2.59 (q, J = 7.3 Hz, 2H), 1.28-1.21 (m, 9H); ¹³C NMR (101 MHz, CDCl₃): δ 143.6, 143.2, 126.6, 123.3, 30.2, 28.3, 15.4, 14.4.

(S)-3,3'-Bis(2,4,6-triethylphenyl)-6,6'-bis(triisopropylsilyl)-[1,1'-binaphthalene]-2,2'-diol (3e)



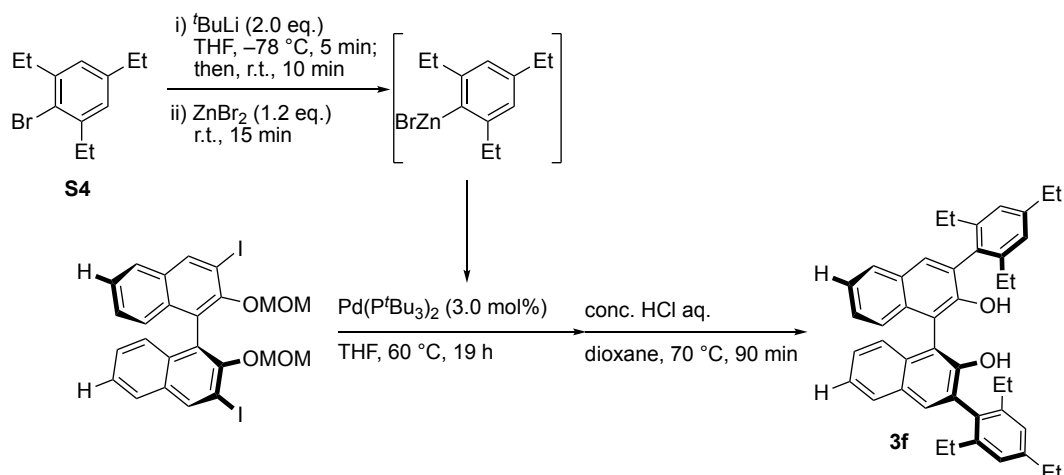
This compound was prepared according to the literature procedure (modified).⁵³

To a flame-dried Schlenk flask containing **S4** (20.0 mmol, 4.82 g) in anhydrous THF (20 mL) was added *t*-BuLi (1.60 M in pentane, 40.0 mmol, 25.0 mL) at -78 °C under argon atmosphere. After stirring for 5 min at this temperature, the cooling bath was removed and the reaction was further stirred for 10 min. After that, ZnBr₂ (flame dried under high vacuum before use, 24.0 mmol, 5.40 g) in anhydrous THF (20 mL) was added at room temperature *via* syringe. The reaction mixture was stirred for 15 min at this temperature. To another flame-dried Schlenk flask containing Pd(P^{*t*}Bu₃)₂ (0.150 mmol, 76.7 mg) and **S2** (5.00 mmol, 4.70 g) in anhydrous THF (50 mL) was added the aforementioned freshly prepared zinc reagent *via* syringe. The solution was thoroughly degassed by three freeze-pump-thaw cycles. The solution was heated to 60 °C for 36 hours. After cooling to 0 °C, the reaction was quenched by the slow addition of saturated NH₄Cl aq. (50 mL). Two

layers were separated, and the aqueous layer was extracted with hexane (100 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The resulting crude residue was roughly purified by flash column chromatography (eluent: hexane/AcOEt = 100/0 to 100/1 to 50/1) to afford the title compound in *ca.* 85% yield (4.26 mmol, 4.29 g, considered to be 100% purity) as a brown solid, which was used in the next step without further purification. (*Note: We found that the contamination of 1,3,5-triethylbenzene at this stage prohibited the clean isolation of the target BINOL derivative after the next step, so the complete removal is necessary.*) To the aforementioned mixture in dioxane (100 mL) was added concentrated HCl aq. (3.0 mL) and heated to 70 °C for 3 hours under air. Upon cooling to room temperature, the reaction was diluted with water (100 mL) and CH₂Cl₂ (200 mL). Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (100 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The resulting crude residue was purified by flash column chromatography (eluent: hexane/AcOEt = 100/0 to 40/1) to afford **3e** in 59% yield (2.95 mmol, 2.71 g, over 2 steps) as a pale-yellow powder.

Rf: 0.12 (eluent: hexane/AcOEt = 40/1, UV/KMnO₄); **Melting point:** 126-136 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.00 (s, 2H), 7.77 (s, 2H), 7.45 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 1.8 Hz, 2H), 7.08 (d, *J* = 1.8 Hz, 2H), 5.04 (s, 2H), 2.72 (q, *J* = 7.6 Hz, 4H), 2.65-2.33 (m, 8H), 1.50 (hept, *J* = 7.5 Hz, 6H), 1.33 (t, *J* = 7.5 Hz, 6H), 1.15 (d, *J* = 7.6 Hz, 3H), 1.13 (d, *J* = 7.5 Hz, 18H), 1.12 (d, *J* = 7.5 Hz, 18H), 1.06 (t, *J* = 7.5 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 150.6, 144.2, 143.3, 143.3, 136.1, 133.5, 132.7, 131.9, 131.2, 129.7, 128.8, 128.5, 125.6, 123.2, 112.6, 28.8, 27.0, 18.7, 15.4, 15.2, 10.9 (*One aromatic ¹³C signal was overlapped with others*); **HRMS (ESI)** exact mass calcd. for C₆₂H₈₅O₂Si₂: *m/z* 917.6083 ([M-H]⁻), found: *m/z* 917.6088 ([M-H]⁻); **Optical rotation:** $[\alpha]_D^{23} = -52.7$ (*c* = 1.0, CH₂Cl₂).

(S)-3,3'-Bis(2,4,6-triethylphenyl)-[1,1'-binaphthalene]-2,2'-diol (3f)

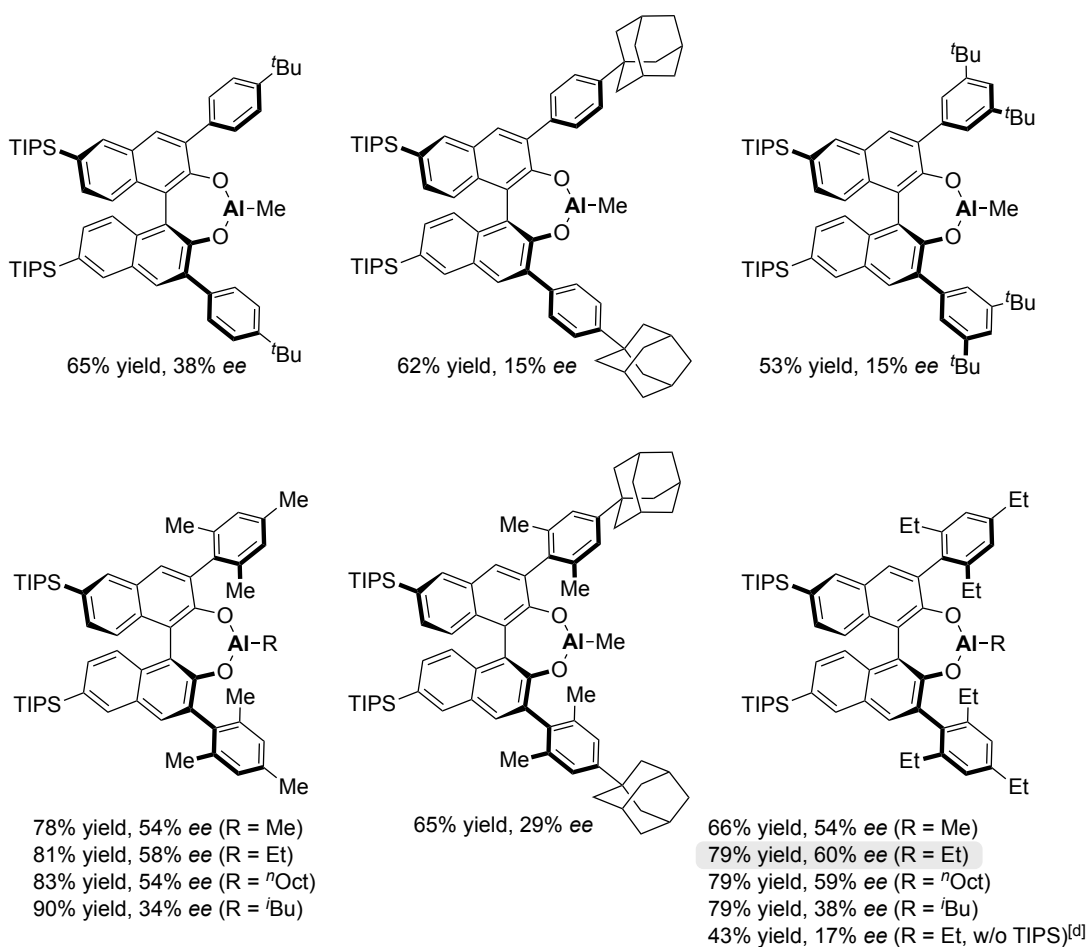
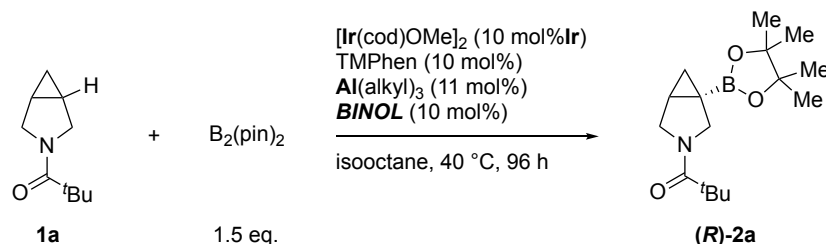


This compound was prepared following the procedure analogous to that for the preparation of **3e** with (S)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene.⁵³ Purification was performed by flash column chromatography (eluent: hexane/AcOEt = 100/0 to 30/1) to afford **3f** in 72% yield (0.717 mmol, 435 mg, over 2 steps) as a colorless solid.

Rf: 0.43 (eluent: hexane/AcOEt = 10/1, UV and/or basic KMnO_4); **Melting point**: $74\text{--}76\text{ }^{\circ}\text{C}$; **^1H NMR** (400 MHz, CDCl_3 , $50\text{ }^{\circ}\text{C}$) δ 7.87 (d, $J = 8.0\text{ Hz}$, 2H), 7.78 (s, 2H), 7.42–7.35 (m, 2H), 7.35–7.29 (m, 2H), 7.24 (d, $J = 8.5\text{ Hz}$, 2H), 7.06 (s, 4H), 4.97 (s, 2H), 2.69 (q, $J = 7.5\text{ Hz}$, 4H), 2.58–2.29 (m, 8H), 1.30 (t, $J = 7.5\text{ Hz}$, 6H), 1.09 (t, $J = 7.5\text{ Hz}$, 6H), 1.01 (t, $J = 7.5\text{ Hz}$, 6H); **^{13}C NMR** (101 MHz, CDCl_3 , $50\text{ }^{\circ}\text{C}$) δ 150.5, 144.5, 143.4, 133.7, 131.8, 130.9, 129.3, 129.1, 128.2, 126.7, 125.80, 125.75, 124.6, 123.8, 113.4, 28.8, 27.0, 15.3, 15.2 (One aromatic ^{13}C signal was overlapped with others); **HRMS (ESI)** exact mass calcd. for $\text{C}_{44}\text{H}_{45}\text{O}_2$: m/z 605.3414 ($[\text{M}-\text{H}]^-$), found: m/z 605.3414 ($[\text{M}-\text{H}]^-$); **Optical rotation**: $[\alpha]_{\text{D}}^{23} = -57.4$ ($c = 1.0$, CH_2Cl_2).

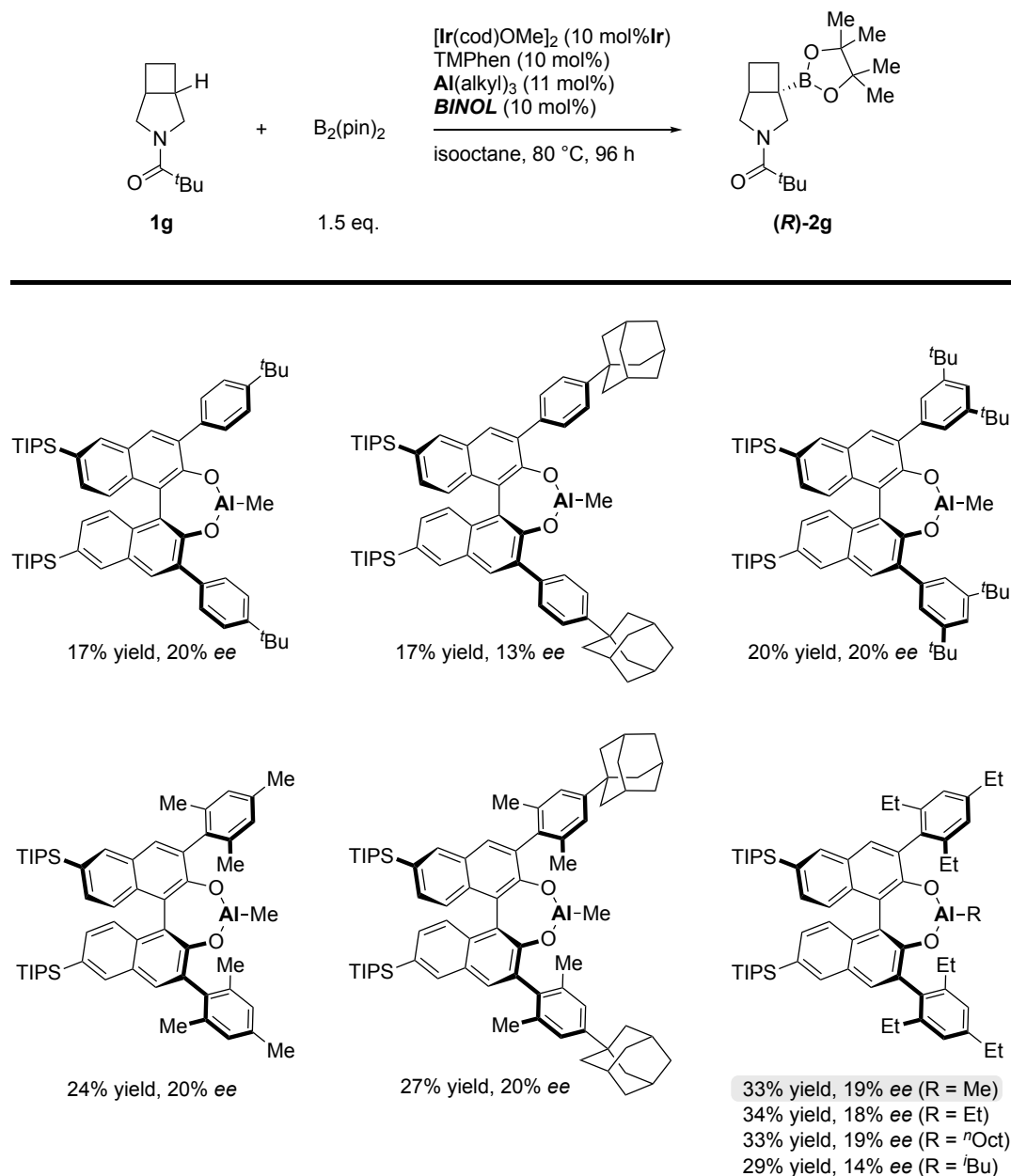
5.5.3.2 Optimization of chiral Al-BINOLate

Table 5-5 Chiral Al-BINOLate screening for the asymmetric borylation of **1a**^{a,b,c}



^aTypical reaction conditions: **1a** (0.300 mmol), B₂(pin)₂ (0.450 mmol), [Ir(cod)OMe]₂ (0.01500 mmol), TMPhen (0.0300 mmol), Al(alkyl)₃ (0.0330 mmol), and BINOL (0.0300 mmol) in isooctane (1.50 mL) at 40 °C for 96 h. ^bYield was determined by GC-FID analysis using *n*-dodecane as an internal standard. ^cEe was determined after the conversion B(pin) moiety into B(dan) for clear measurement (see also §5.5.3.3). ^d**3f** was used instead of **3e**.

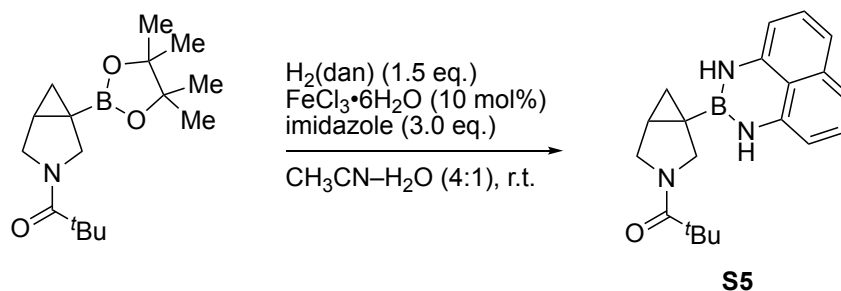
Table 5-6 Chiral Al-BINOLate screening for the asymmetric borylation of **1g**^{a,b,c}



^aTypical reaction conditions: **1g** (0.300 mmol), $B_2(\text{pin})_2$ (0.450 mmol), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.01500 mmol), TMPhen (0.0300 mmol), $\text{Al}(\text{alkyl})_3$ (0.0330 mmol), and BINOL (0.0300 mmol) in isooctane (1.50 mL) at 80 °C for 96 h. ^bYield was determined by GC-FID analysis using *n*-dodecane as an internal standard. ^cEe was determined after the conversion B(pin) moiety into B(dan) for clear measurement (see also §5.5.3.3).

5.5.3.3 Preparation of racemic samples for the investigation of enantio-separation conditions

rac-2-(3-Pivaloyl-(1*S*,5*R*)-3-azabicyclo[3.1.0]hexan-5-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (**S5**)



Scheme 5-14 Synthetic scheme for the preparation of **S5**

This compound was prepared according to literature procedure using *rac*-**2a** on 0.200 mmol scale (slightly modified, see also Scheme 5-13).^{48,49} Purification was performed by MPLC (eluent: hexane/AcOEt = 3/1 to 1/1) to afford **S5** in 92% yield (0.183 mmol, 61.1 mg) as a faint pinkish solid.

Rf: 0.14 (eluent: hexane/AcOEt = 2/1, *p*-anisaldehyde); **Melting point**: 101-104 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.11 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.03 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.32 (dd, *J* = 7.2, 1.0 Hz, 2H), 5.47 (brs, 2H), 4.07 (d, *J* = 10.9 Hz, 1H), 3.97 (d, *J* = 10.9 Hz, 1H), 3.60–3.45 (m, 2H), 1.68 (br, 1H), 1.26 (s, 9H), 0.83 (dd, *J* = 7.5, 4.9 Hz, 1H), 0.49 (t, *J* = 4.6 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 177.6, 140.6, 136.3, 127.5, 119.5, 117.9, 105.8, 51.3, 49.6, 39.1, 27.6, 23.0 (br), 13.9 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation*); **HRMS (ESI)** exact mass calcd. for C₂₀H₂₄ON₃BNa: *m/z* 356.1905 ([M+Na]⁺), found: *m/z* 356.1901 ([M+Na]⁺).

The enantiomers could be separable by HPLC analysis (Daicel COSMOSIL® 5SL-II + Daicel CHIRALPAK® IA-3, eluent: hexane/*i*PrOH = 90/10, flow rate: 1.0 mL/min, *t_R* = 18.8 min and 20.9 min, λ = 333 nm, ambient temperature).

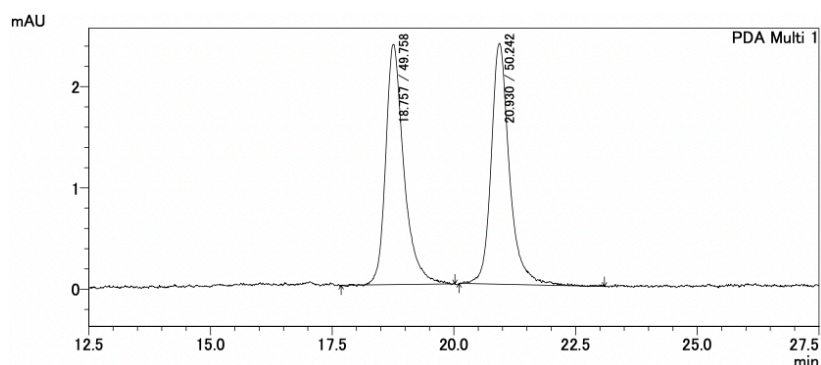
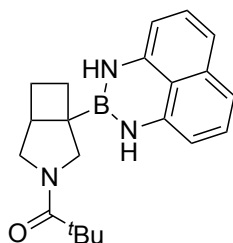


Figure 5-8 Chiral HPLC trace of **S5**

***rac*-2-(3-Pivaloyl-(1*S*,5*R*)-3-azabicyclo[3.2.0]heptan-5-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (*rac*-4)**



This compound was prepared using *rac*-**2g** following the procedure analogous to that for the preparation of **S5** on 0.100 mmol scale. Purification was performed by MPLC (eluent: hexane/AcOEt = 100/0 to 1/1) to afford the title compound in 60% yield (0.0596 mmol, 20.7 mg) as an off-white solid.

Rf: 0.37 (eluent: hexane/AcOEt = 1/1, *p*-anisaldehyde); **Melting point**: 61-63 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.12 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.04 (dd, *J* = 8.3, 0.8 Hz, 2H), 6.36 (dd, *J* = 7.2, 0.8 Hz, 2H), 5.69 (br, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.43 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.31 (d, *J* = 12.0 Hz, 1H), 2.95-2.78 (m, 1H), 2.33-2.21 (m, 1H), 2.21-2.11 (m, 1H), 1.95-1.84 (m, 1H), 1.83-1.74 (m, 1H), 1.34 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.4, 140.6, 136.2, 127.5, 119.5, 117.9, 105.9, 56.7, 54.5, 39.0, 27.8, 26.5, 24.0 (*the carbon directly attached to the boron atom was not detected due to quadrupolar relaxation and one ¹³C signal was not detected due to peak broadening, which could be attributed to amide rotation*); **HRMS (ESI)** exact mass calcd. for C₂₁H₂₇ON₃B: *m/z* 348.2242 ([M+H]⁺), found: *m/z* 348.2242 ([M+H]⁺).

The enantiomers could be separable by HPLC analysis (Daicel CHIRALPAK® IB N-3, hexane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, *t_R* = 18.0 min and 20.1 min, λ = 333 nm, ambient temperature).

5.5.3.4 General procedure for an asymmetric C–H borylation

(Preparation of chiral Al-BINOLate complex) In a nitrogen-filled glovebox, a 4 mL vial containing **3e** (0.100 mmol, 92.0 mg) in isooctane (2.0 mL) was vigorously stirred at room temperature to dissolve the BINOL derivative completely. The resulting solution was cooled to $-35\text{ }^{\circ}\text{C}$, and AlMe_3 (1.4 M in hexanes, 0.110 mmol, 78.6 μL) or AlEt_3 (1.0 M in hexanes, 0.110 mmol, 110 μL) was added at this temperature with vigorous stirring (**Caution:** gas bubbles vigorously). The resulting clear solution was warmed to room temperature and stirred for 30 min. Upon completion, substrate (1.00 mmol) was added at room temperature and stirred for 5 min at this temperature.

(Preparation of iridium complex) A 15 mL vial containing $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), TPhen (0.100 mmol, 23.6 mg), $\text{B}_2(\text{pin})_2$ (1.50 mmol, 381 mg) in isooctane (2.5 mL) was stirred at $70\text{ }^{\circ}\text{C}$ for 30 min. Upon cooling to room temperature, the aforementioned Al-BINOLate solution was transferred into the iridium solution *via* pipette. The 4 mL vial was rinsed with isooctane (0.50 mL) and the resulting solution was also added to the iridium solution. The 15 mL vial was then sealed with a Teflon-lined cap and removed from the glovebox. After stirring under the designated conditions, the reaction mixture was cooled to room temperature and exposed to the air to quench the reaction. The resulting crude mixture was purified by silica gel flash column chromatography. Enantiomeric excess (ee) was measured by an analytical HPLC resolution.

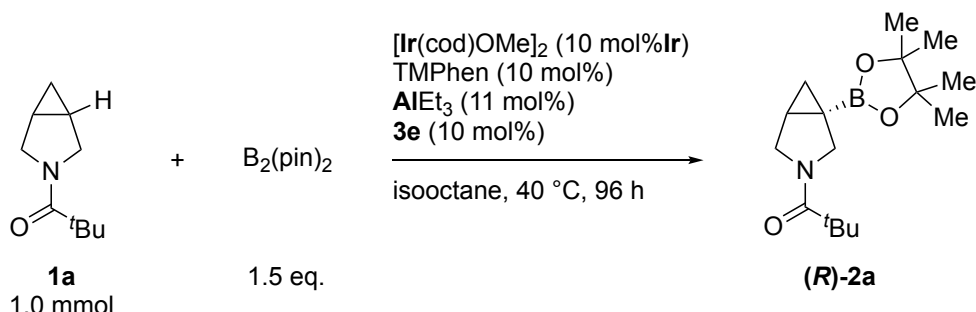
Notes:

Borylated products are unstable on silica gel column chromatography should be done very quickly (≤ 10 min) to prevent the decomposition or over-adsorption of the product. If pinacol still remains after column chromatography, it can be removed under high vacuum in a desiccator at $70\text{--}80\text{ }^{\circ}\text{C}$.

In many cases, isolated borylation products are first obtained as a very viscous oil, which can be solidified by standing them under high vacuum for 1-2 days at room temperature.

5.5.3.5 Product data

3-Pivaloyl-(1*R*,5*S*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane ((*R*)-2a)

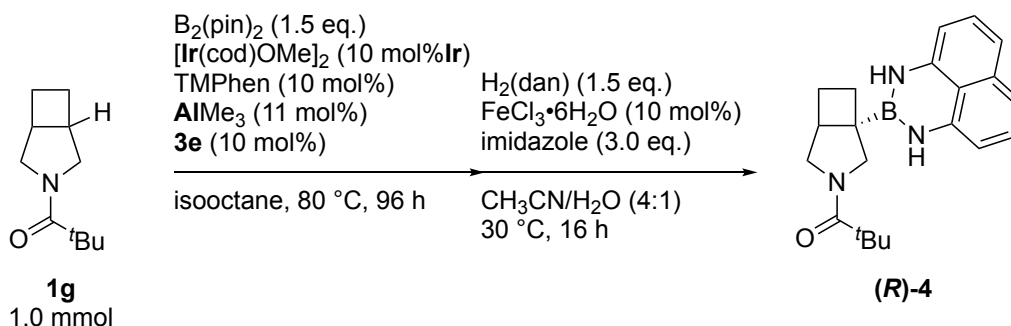


This reaction was performed with **1a** (1.00 mmol, 167 mg), $\text{B}_2(\text{pin})_2$ (1.50 mmol, 381 mg), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), **3e** (0.100 mmol, 92.0 mg), and AlEt_3 (1.0 M in hexanes, 0.110 mmol, 0.110 mL) in isooctane (5.0 mL) at 40 °C for 96 hours. The crude residue was purified by flash column chromatography (eluent: hexane only, then hexane/AcOEt = 8/1 to 3/1) to afford the title compound as a colorless solid in 78% yield (0.781 mmol, 229 mg) [62% ee]. The spectroscopic data were in agreement with those reported above.

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/ i PrOH = 2/1, flow rate = 0.5 mL/min, retention time; 11.1 min (minor) and 12.4 min (major)).

Optical rotation: $[\alpha]_{\text{D}}^{23} = +35.7$ ($c = 1.0$, CH_2Cl_2)

2-(3-Pivaloyl-(1*S*,5*R*)-3-azabicyclo[3.2.0]heptan-5-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine ((*R*)-4)



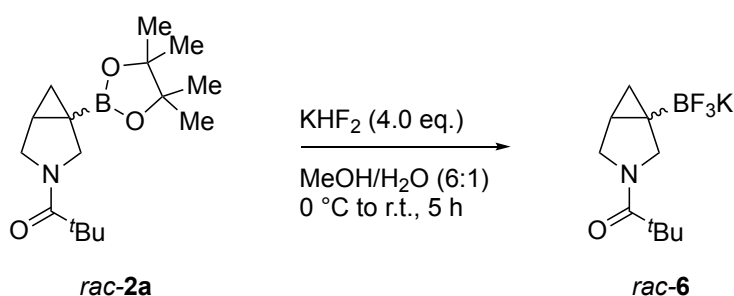
This reaction was performed with **1g** (1.00 mmol, 181 mg), $\text{B}_2(\text{pin})_2$ (1.50 mmol, 381 mg), $[\text{Ir}(\text{cod})\text{OMe}]_2$ (0.0500 mmol, 33.1 mg), TMPhen (0.100 mmol, 23.6 mg), **3e** (0.100

by PLC (eluent: AcOEt only) to afford the title compound in 62% yield (0.0622 mmol, 11.4 mg) as a colorless solid [62% ee].

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OJ-H, hexane/*i*PrOH = 98/2, flow rate = 1.0 mL/min, retention time; 16.4 min (major) and 18.6 min (minor)).

Rf: 0.29 (eluent: AcOEt only, PMA); **Melting point:** 74-75 °C; **¹H NMR** (400 MHz, CDCl₃) δ 4.19 (d, *J* = 10.5 Hz, 1H), 3.71 (d, *J* = 11.5 Hz, 1H), 3.74-3.42 (m, 2H), 3.06 (brs, 1H), 1.62 (m, 1H), 1.21 (s, 9H), 1.15 (ddd, *J* = 9.3, 5.5, 1.8 Hz, 1H), 0.52 (dd, *J* = 5.5, 4.6 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 177.3, 61.1, 53.6, 49.9, 39.0, 27.5, 22.1, 16.9; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₇O₂NNa: *m/z* 206.1152 ([M+Na]⁺), found: *m/z* 206.1148 ([M+Na]⁺); **Optical rotation** [α]_D²³ = +2.5 (*c* = 0.20, CH₂Cl₂).

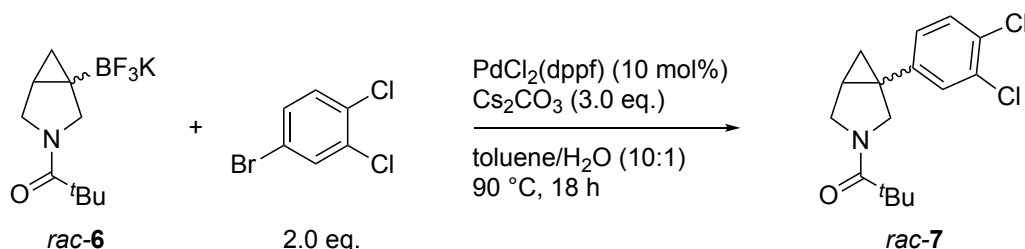
***rac*-Potassium (3-pivaloyl-3-azabicyclo[3.1.0]hexan-1-yl)trifluoroborate (*rac*-6)**



To a 15 mL vial containing *rac*-2a (1.00 mmol, 0.293 g) in MeOH (6.0 mL) was added potassium hydrogen fluoride (4.00 mmol, 0.312 g) in H₂O (1.0 mL) at 0 °C. After 5 hours at room temperature, all volatiles were removed by rotary evaporator and further dried under high vacuum at room temperature. The resulting yellow solid was triturated in hexanes and filtered to remove pinacol. After that, the solid was extracted with hot acetone and evaporated under reduced pressure to afford the title compound in >99% yield (1.00 mmol, 0.271 g) as a faint yellow solid.

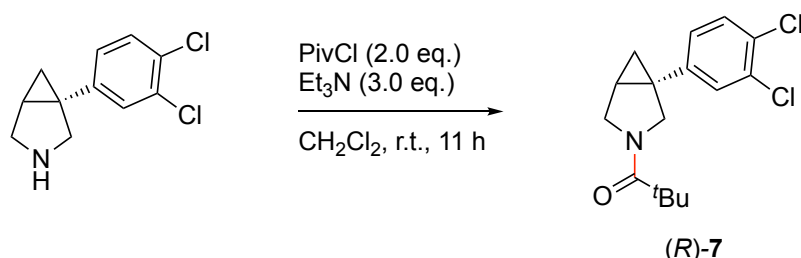
Melting point: 120 °C; **¹H NMR** (400 MHz, acetone-*d*₆) δ 3.78 (d, *J* = 11.0 Hz, 4H), 3.64 (d, *J* = 10.5 Hz, 1H), 3.59-3.09 (m, 2H), 1.19 (s, 9H), 1.11-1.00 (m, 1H), 0.43 (dd, *J* = 6.8, 2.7 Hz, 1H), -0.35 (*virt* s, 1H); **¹³C NMR** (101 MHz, acetone-*d*₆) δ 176.7, 53.9, 51.4, 39.4, 30.6, 28.0, 25.2, 11.9; **¹⁹F NMR** (376 MHz, acetone-*d*₆) δ -143.4; **HRMS (ESI)** exact mass calcd. for C₁₀H₁₆ONBF₃: *m/z* 234.1272 ([M-K]⁻), found: *m/z* 234.1283 ([M-K]⁻).

***rac*-3-Pivaloyl-(1*R*,5*S*)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane** (*rac*-*N*-Piv-Amitifadine, *rac*-7)



Prepared according to literature procedure.⁴⁷ To a 15 mL vial containing *rac*-6 (0.100 mmol, 27.3 mg), 1-bromo-3,4-dichlorobenzene (0.200 mmol, 45.2 mg), PdCl₂(dppf) (0.010 mmol, 7.3 mg) and Cs₂CO₃ (0.300 mmol, 97.7 mg) in toluene (2.4 mL) and H₂O (0.24 mL), argon gas was bubbled for 10 min. After being sealed, the mixture was heated at 90 °C for 17 hours with vigorous stirring. After cooling to room temperature, the reaction mixture was filtered through a Celite pad, and the pad cake was washed with AcOEt. Removal of all volatiles and purification by MPLC (eluent: hexane/AcOEt = 4/1 to 2/1) afforded the title compound in 78% yield (0.0778 mmol, 24.3 mg) as a brown oil. **Rf**: 0.43 (eluent: hexane/AcOEt = 3/1, UV and/or PMA); **¹H NMR** (400 MHz, CDCl₃, 70 °C) δ 7.37 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 2.2 Hz, 1H), 7.04 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.26 (d, *J* = 11.0 Hz, 1H), 4.06 (d, *J* = 11.0 Hz, 1H), 3.66 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.63 (d, *J* = 11.2 Hz, 1H), 1.84 (ddd, *J* = 8.1, 4.7, 4.1, 1H), 1.27 (s, 9H), 1.05 (dd, *J* = 8.1, 5.1 Hz, 1H), 0.84 (dd, *J* = 5.1, 4.7 Hz, 1H); **¹³C NMR** (101 MHz, benzene-*d*₆, 60 °C) δ 176.3, 141.9, 133.0, 130.8, 130.6, 129.3, 126.8, 53.4, 49.8, 39.1, 29.8, 27.8, 24.1, 17.3; **HRMS (ESI)** exact mass calcd. for C₁₆H₁₉ONCl₂Na: *m/z* 334.0736, 336.0707, 338.0677 ([M+Na]⁺), found: *m/z* 334.0741, 336.0711, 338.0682 ([M+Na]⁺). The intensity ratio was *ca.* 10:6:1, which was identical with theoretical isotopic ratio.

3-Pivaloyl-(1*R*,5*S*)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane



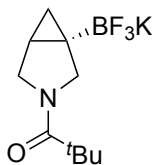
(*R*)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane was prepared according to the

literature procedure.⁵² To a round-bottom flask containing (*R*)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane (1.0 mmol, 0.23 g) in anhydrous CH₂Cl₂ (10 mL), Et₃N (3.0 mmol, 0.42 mL) and PivCl (2.0 mmol, 0.24 mL) were added at room temperature under argon atmosphere. After stirring for 11 hours at this temperature, the reaction was quenched with 1 M HCl aq. (20 mL). Two layers were separated and the organic layer was washed with saturated Na₂CO₃ aq. (20 mL × 2), dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Purification by MPLC (eluent: hexane/AcOEt = 9/1 to 3/1) afforded the title compound in 29% yield (0.293 mmol, 91.5 mg) as a colorless oil [94% ee]. The spectroscopic data were in agreement with those reported above.

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK® IA-3, hexane/*i*PrOH = 95/5, flow rate: 0.75 mL/min, retention time; 12.6 min (minor) and 14.0 min (major)).

Optical rotation $[\alpha]_{\text{D}}^{23} = +101.5$ ($c = 0.60$, CH₂Cl₂);

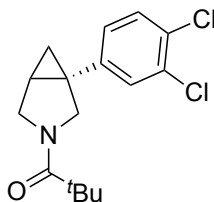
Potassium (1*R*,5*S*)-(3-pivaloyl-3-azabicyclo[3.1.0]hexan-1-yl)trifluoroborate ((*R*)-6)



This compound was prepared using (*R*)-**2a** (62% ee) following the procedure analogous to that for the preparation of *rac*-**6** on 0.500 mmol scale. The title compound was obtained in 88% yield (0.439 mmol, 120 mg) as a faint yellow solid. The spectroscopic data were in agreement with those reported above.

Optical rotation: $[\alpha]_{\text{D}}^{23} = +7.0$ ($c = 0.20$, acetone)

3-Pivaloyl-(1*R*,5*S*)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane ((*R*)-7)



This compound was prepared using (*R*)-**6** following the procedure analogous to that for the preparation of *rac*-**7** on 0.100 mmol scale. The resulting crude mixture was purified

by PLC (eluent: hexane/AcOEt = 3/1) to afford the title compound in 91% yield (0.0913 mmol, 28.5 mg) as a yellow oil [61% ee]. The spectroscopic data were in agreement with those reported above.

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IA-3, hexane/PrOH = 95/5, flow rate = 0.75 mL/min, retention time; 12.6 min (minor) and 14.2 min (major)).

Optical rotation $[\alpha]_{\text{D}}^{23} = +56.3$ ($c = 0.60$, CH_2Cl_2)

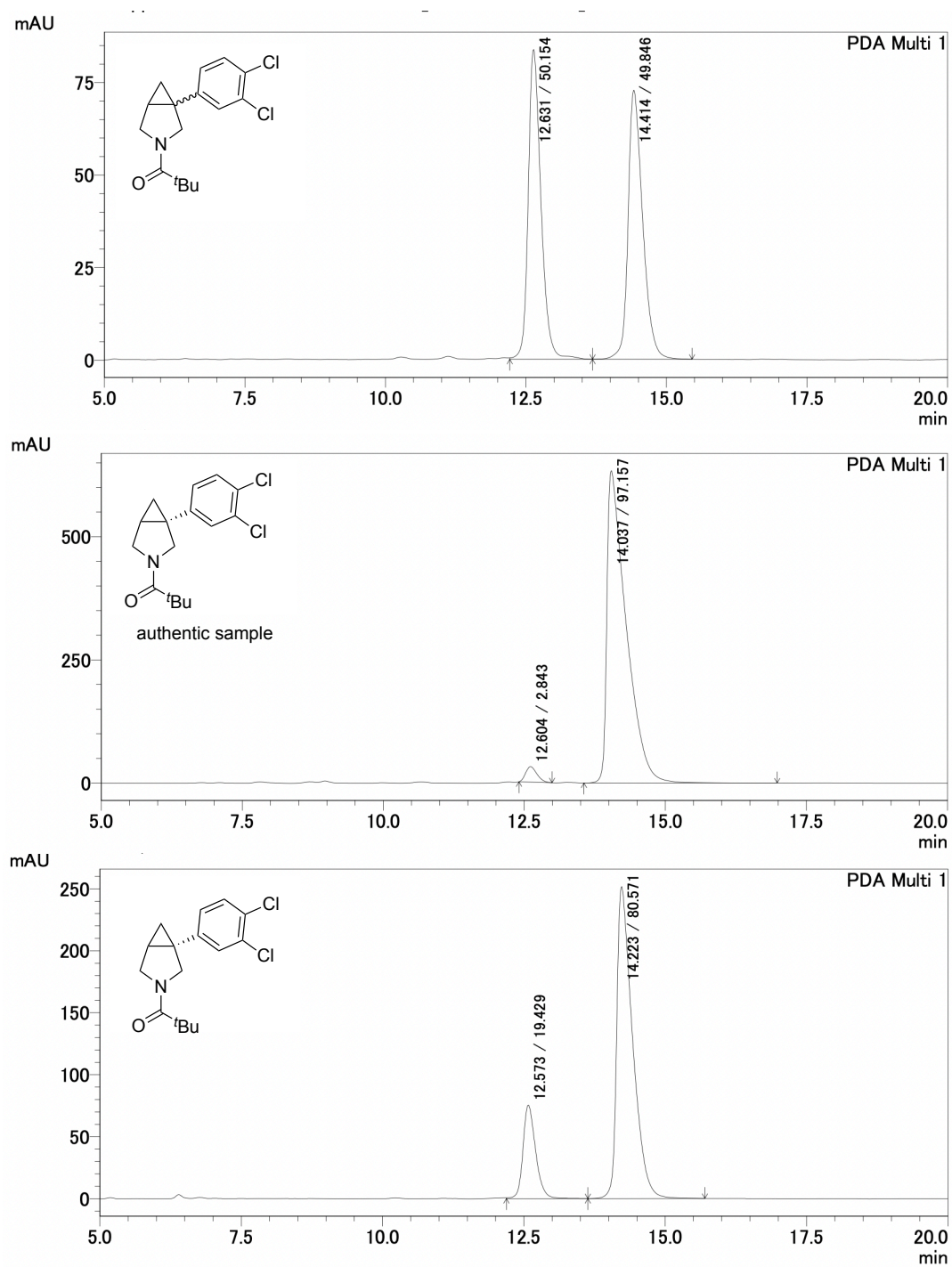
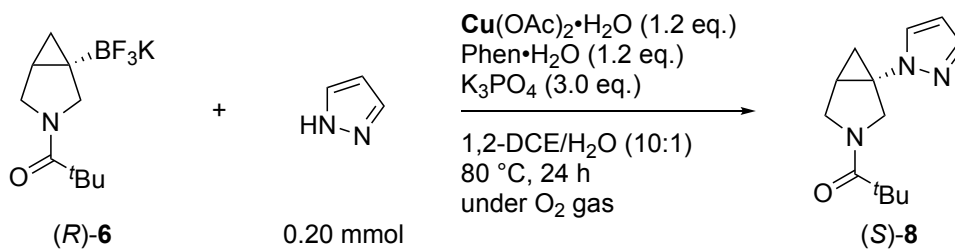


Figure 5-9 Chiral HPLC traces (**up**) *rac*-7. (**middle**) authentic sample. (**bottom**) (*R*)-7

(1*S*,5*R*)-3-PSivaloyl-1-(1*H*-pyrazol-1-yl)-3-azabicyclo[3.1.0]hexane ((*R*)-8)



This compound was prepared according to the literature procedure (modified).⁴⁷

A 15 mL vial containing Cu(OAc)₂•H₂O (0.120 mmol, 24.0 mg) and Phen•H₂O (0.120 mmol, 21.6 mg) in 1,2-DCE (1.8 mL) was vigorously stirred at 80 °C for 20 min under air. Upon cooling to room temperature, (*R*)-**6** (0.100 mmol, 27.3 mg), pyrazole (0.200 mmol, 13.6 mg), aqueous K₃PO₄ (1 M, 0.300 mmol, 63.7 mg), and 1,2-DCE (1.4 mL) were sequentially added. To the resulting mixture, O₂ gas was bubbled for 2 min. The 15 mL vial was sealed with a Teflon-lined cap and stirred for 24 hours at 80 °C. Upon cooling to room temperature, the resulting reaction mixture was filtered through a Celite pad, and the pad cake was washed with AcOEt (20 mL). The filtrate was evaporated under reduced pressure. The resulting crude mixture was purified by PLC (eluent: hexane/AcOEt = 1/3) to afford the title compound in 48% yield (0.476 mmol, 11.1 mg) as a colorless oil [58% ee].

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IA-3, hexane/PrOH = 90/10, flow rate = 1.0 mL/min, retention time; 10.1 min (major) and 11.7 min (minor)).

Rf: 0.64 (eluent: hexane/AcOEt = 1/3, UV and/or KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 6.28 (dd, *J* = 2.4, 2.0 Hz, 1H), 4.39 (d, *J* = 10.6 Hz, 1H), 3.99 (d, *J* = 11.2 Hz, 1H), 3.82 (brs, 2H), 2.04 (m, 1H), 1.51 (ddd, *J* = 8.9, 5.9, 1.6 Hz, 1H), 1.24 (s, 9H), 1.04 (t, *J* = 5.3 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃, 50 °C) δ 177.4, 140.1, 129.9, 106.0, 52.9, 49.3, 39.0, 27.4, 16.0; **HRMS (ESI)** exact mass calcd. for C₁₃H₁₉ON₃Na: *m/z* 256.1420 ([M+Na]⁺), found: *m/z* 256.1418 ([M+Na]⁺); **Optical rotation** [α]_D²³ = +68.5 (*c* = 0.20, CH₂Cl₂);

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Publication List

All the present Thesis have been published in the following journals.

The following parts of the accepted materials were modified:

- (a) A word 'we' is replaced to 'the author'.
- (b) Words 'see supporting information' and similar expressions are deleted and corresponding materials (text, figures, tables, and/or schemes) are moved from supporting information of accepted works to the main text of the Thesis or the experimental section.
- (c) Subtitles are inserted to the section heads.
- (d) Parts of the introduction, results and discussion, and conclusion are modified according to the context of the Thesis.

Chapter 2

- (1) Hashimoto, T.; Shimazaki, Y.; Omatsu, Y.; Maruoka, K.: Indanol-based Chiral Organoiodine Catalysts for Enantioselective *para*-Hydrative Dearomatization. *Angew. Chem. Int. Ed.* **2018**, *57*, 7200–7204. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Chapter 3

- (2) Shimazaki, Y.; Wata, C.; Hashimoto, T.; Maruoka, K.: Enantioselective Hydrative *para*-Dearomatization of Sulfonanilides by an Indanol-based Chiral Organoiodine Catalyst. *Asian J. Org. Chem.* **2021**, *10*, 1638–1642. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Chapter 4

- (3) Kuroda, Y.; Park, K.; Shimazaki, Y.; Zhong, R.-L.; Sakaki, S.; Nakao, Y.: An Iridium/Aluminum Cooperative Strategy for the β -C(sp³)-H Borylation of Saturated Cyclic Amines. *Angew. Chem. Int. Ed.* **2023**, *62*, e202300704. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Chapter 5

(4) Shimazaki, Y.; Osawa, M.; Nakao, Y.: Site-Selective C(sp³)-H Borylation of 3-Azabicyclo[3.1.0]hexanes by Cooperative Iridium/Aluminum Catalysis. *Asian J. Org. Chem.* **2023**, *12*, e202300487. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

The following publications are not included in this Thesis.

(5) Pawliczek, M.; Shimazaki, Y.; Kimura, H.; Oberg, K. M.; Zakpur, S.; Hashimoto, T.; Maruoka, K. Phase-transfer-catalysed asymmetric synthesis of 2,2-disubstituted 1,4-benzoxazin-3-ones. *Chem. Commun.* **2018**, *54*, 7078–7080.

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